Table 2. Mean blank concentrations and method detection limits (ng/g wet weight)

	Mean blank concentrations	Method detection limits
As_{tot}	4.57	3.6
As_i	1.96	2
As^{+3}	< 1	1
As^{+5}	1.96	2
MMA	< 1	1
DMA	< 2	2

Note: As_{tot}-total arsenic
As_i-inorganic arsenic
MMA-monomethylarsonic acid
DMA-dimethylarsinic acid.

Consequently, the data for all four samples of each commodity were averaged.

Total arsenic was detected in two or more samples of 35 of the 40 commodities, that is, all of the commodities except butter, soybean/vegetable oil, salt, whole milk and green beans. Inorganic arsenic was detected in two or more samples of 34 of the 40 commodities, that is, all commodities except soybean/vegetable oil, whole and skim milk, chicken, tuna and orange juice. Inorganic arsenic concentrations were either undetected or "*J*" qualified in approximately one-half of the samples, suggesting that the detection limits achieved in this study are just sufficient to characterize inorganic arsenic concentrations in a wide variety of foods.

Consistent with earlier studies, total arsenic concentrations (all concentrations reported as elemental arsenic per tissue wet weight) were highest in the four kinds of seafood sampled (means ranged from 160 ng/g in freshwater fish to 2360 ng/g in saltwater fish). In contrast, average inorganic arsenic mean concentrations in seafood ranged from less than 1 ng/g to 2 ng/g. Marked variation in total arsenic concentrations observed in finfish samples may reflect variations among species (Table 4). Concentrations were more consistent among canned tuna samples.

The next highest total arsenic concentrations occurred in rice (303 ng/g), which also had the highest concentrations of inorganic arsenic (Table 3). Other foods with relatively high (i.e. greater than 10 ng/g) total arsenic concentrations included foods high in protein (i.e. beef, chicken, pork, eggs and peanut butter) or sugar (i.e. beet sugar, cane sugar, grapes and grape juice), and grains (i.e. corn meal and flour).

The inorganic arsenic concentrations in raw rice (74 ng/g) were much higher than concentrations in other foods. The next highest concentrations of inorganic arsenic were in flour (11 ng/g), grape juice (9 ng/g), cooked spinach (6 ng/g), peanut butter (5 ng/g), peas (5 ng/g), as well as cane sugar, corn meal, cucumber and beet sugar (all 4 ng/g). Inorganic arsenic concentrations were low enough in most foods that it was not clear what arsenic forms predominated (i.e. As^{3+} or As^{5+}); however, in rice, flour, grape juice, spinach, peanut butter and cucumber, the concentrations of As^{3+} were generally more than twice the concentration of As^{5+}. In contrast, cane sugar and beet sugar appeared to have more As^{5+} than As^{3+} (data not shown).

In fruits and vegetables, inorganic arsenic accounted for approximately one-half of the total arsenic (Table 3). In grains, sugars and oil, inorganic arsenic accounted for approximately one-quarter of the total arsenic, while only a small fraction of the total was inorganic in meat, poultry, fish and eggs. With a few exceptions, both MMA and DMA concentrations were undetected or very low. Rice and shellfish (shrimp) were the commodities with the highest DMA concentrations, with mean concentrations of 91 and 34 ng/g, respectively (Table 4). The next highest concentrations of DMA were in beet sugar and cane sugar, with concentrations of 7 and 8 ng/g, respectively (data not shown). DMA was also detected at low concentrations in seafood (Table 4), meat and fruits and fruit juices (data not shown). MMA was repeatedly detected only in samples of apple juice (data not shown) and rice (Table 4).

DISCUSSION

Inorganic arsenic was found at ng/g concentrations in most foods tested. Concentrations for inorganic arsenic reported in the present study were generally lower than those previously reported for seafood, meat and poultry, even though total arsenic concentrations were similar among studies. For example, while inorganic arsenic concentrations in saltwater finfish (cod, halibut, orange roughy, canned tuna) were less than 1 ng/g in the present study, three previous studies reported values from 5 to 28 ng/g for similar fish species (Buchet *et al.*, 1994, Mohri *et al.*, 1990; Yost *et al.*, 1998). Similarly, inorganic arsenic concentrations in shrimp ranged from 1 to 3 ng/g in the four samples tested in the present study, compared to values of 37 ng/g (Mohri *et al.*, 1990) and 100 ng/g (Yost *et al.*, 1998) in two samples tested previously. Meat and poultry products tested in the present study (N = 12) also contained 1 ng/g or less of inorganic arsenic, compared to 9 to 24 ng/g reported in a previous study (Yost *et al.*, 1998).

Inorganic arsenic concentrations in other foods were generally consistent with previously reported values. Inorganic arsenic concentrations have been notably consistent among rice samples tested by several methods, with average values ranging from 74 to 110 ng/g (Table 5). In particular, similar concentrations were reported for split samples analysed by hydride AA after HCl digestion or by ICP–MS after a water-based extraction (Table 5). Given these findings, it is unclear why lower inorganic arsenic concentrations were reported for seafood, meat and poultry in the present study compared to

Table 3. Mean concentrations of total and inorganic arsenic in food

	Total arsenic (ng/g wet weight)		Inorganic arsenic (ng/g wet weight)	
	mean	(se)	mean	(se)
Fats, oils, sweets				
Beet sugar	12.2	(1.3)	3.5	(0.25)
Cane sugar	23.8	(2.7)	4.4	(1.1)
Corn syrup	6.0	(2.2)	0.4 *J*	(0.11)
Butter	1.8 *U*	(0)	1.1 *J*	(0.22)
Soybean oil	1.5 *J*	(0.32)	0.8 *J*	(0.20)
Salt	4.8	(3.0)	0.8 *J*	(0.27)
Beer	2.7 *J*	(1.1)	1.8 *J*	(1.2)
Milk, yogurt, cheese				
Milk, skim (non-fat)	2.6 *J*	(1.2)	1 *U*	(0)
Milk, whole	1.8 *J*	(0.047)	1 *U*	(0)
Meat, poultry, fish, eggs, nuts				
Beef	51.5	(11)	0.4 *J*	(0.23)
Chicken	86.4	(5.6)	0.9 *J*	(0.10)
Pork	13.5	(0.99)	0.6 *J*	(0.025)
Eggs	19.9	(1.5)	1 *J*	(0.27)
Saltwater finfish	2,360	(1,311)	0.5 *J*	(0.20)
Tuna	512	(131)	1 *U*	(0)
Freshwater finfish	160	(132)	1 *J*	(0.33)
Shrimp	1,890	(566)	1.9 *J*	(0.26)
Peanut butter	43.6	(21)	4.7	(1.2)
Vegetables				
Beans (green)	2.1 *J*	(0.26)	1.2 *J*	(0.19)
Carrots	7.3	(2.5)	3.9	(1.4)
Corn (kernel)	1.6 *J*	(0.12)	1.1 *J*	(0.20)
Cucumber	9.6	(1.4)	4.1	(1.2)
Lettuce	1.4 *J*	(0.25)	1.5 *J*	(0.13)
Onions	9.6	(1.9)	3.3	(0.74)
Peas	4.3	(1.1)	4.5	(2.1)
Potatoes	2.8 *J*	(0.62)	0.8 *J*	(0.36)
Spinach	5.1	(1.8)	6.1	(1.4)
Tomato	9.9	(2.6)	0.9 *J*	(0.35)
Fruit				
Apple, raw	4.8	(3.1)	1.8 *J*	(1.3)
Apple, juice	7.6	(2.3)	2.8	(0.44)
Banana	2.3 *J*	(0.74)	0.6 *J*	(0.14)
Grapes	10.2	(3.1)	3.6	(1.2)
Grape juice	~~68.3~~ 19.1	(3.0)	9.2	(1.7)
Orange	1.6 *J*	(1.0)	2.4	(0.83)
Orange juice	4.8	(1.3)	1 *U*	(0)
Peaches	3.4 *J*	(1.2)	2.3	(0.26)
Watermelon	~~40.2~~ 6.7	(2.8)	~~8.9~~ 2.1	(0.52)
Bread				
Corn (meal)	38.6	(6.1)	4.4	(0.90)
Flour	39.1	(6.0)	10.9	(2.6)
Rice	303	(61)	73.7	(9.6)
Water				
Tap water	1.8 *U*	(0)	0.8 *J*	(0.18)

Note: Mean values are the average of four samples—three individual sample values and the average of the replicate samples of the fourth individual sample.

All mean values were computed as follows: One-half the method detection limit was used for all "*U*" qualified values. If all values to be averaged were "*U*" qualified, the mean value was also "*U*" qualified. If the mean value was equivalent to or less than the method detection limit, a "*J*" qualifier was assigned.

J-value reported is above blank concentration but less than the method detection limit

se-standard error

U-not detected; value reported is one-half of the method detection limit.

earlier studies. Buchet *et al.* (1994) also used HCl digestion and hydride AA analysis, while Mohri *et al.* (1990) used an alkaline (NaOH) digestion prior to hydride AA analysis. As in the present study, fish samples were collected at markets in the country in which the study was conducted. Additional studies will be necessary to confirm the observed differences in inorganic arsenic concentrations reported in studies of seafood from different countries.

The results of the present study confirm that rice has higher inorganic arsenic concentrations than most other foods. Consequently, diets that rely heavily on rice may contain the most inorganic arsenic. In addition to rice, the data presented suggest that grains and produce are likely to be significant contributors to dietary inorganic arsenic intake. Food consumption data will be combined with inorganic arsenic concentrations to explore the variation in arsenic intake within the United States

Table 4. Arsenic concentrations in individual samples of selected foods (ng/g wet weight)

Sample	Total arsenic	Inorganic arsenic	MMA	DMA
Saltwater finfish				
Orange roughy	568	1 *U*	0.5 *U*	1 *J*
Cod—sample 1	6080	0.3 *J*	0.5 *U*	5
Cod—sample 2	2320	0.1 *J*	0.5 *U*	4 *J*
Halibut	466	0.7*J*	0.5 *U*	0.7 *J*
Mean	2360	0.5 *J*	0.5 *U*	3
Canned tuna				
Sample 1	770	1 *U*	0.5 *U*	1 *J*
Sample 2	156	1 *U*	0.5 *U*	6
Sample 3	500	1 *U*	0.5 *U*	3
Sample 4	621	1 *U*	0.5 *U*	2 *J*
Mean	512	1 *U*	0.5 *U*	3
Shrimp				
Sample 1	1490	2 *J*	0.5 *U*	29
Sample 2	2790	2	0.5 *U*	57
Sample 3	473	1 *J*	0.5 *U*	21
Sample 4	2820	3	0.5 *U*	31
Mean	1890	1.9 *J*	0.5 *U*	34
Freshwater finfish				
Catfish—sample 1	25	2 *J*	0.5 *U*	1 *U*
Catfish—sample 2	31	1 *U*	0.5 *U*	1 *U*
Catfish—sample 3	29	0.2 *J*	0.5 *U*	1 *U*
Rainbow Trout	555	1 *U*	0.5 *U*	4
Mean	160	1 *J*	0.5 *U*	2 *J*
Raw rice				
Sample 1	335	55	0.5 *U*	1 *U*
Sample 2	218	62	0.5 *U*	61
Sample 3	462	81	3	202
Sample 4	196	97	3	99
Mean	303	73.7	2	91

Note: The fourth sample listed for all of the above foods is a mean of triplicate analyses for that sample.
J—estimates value observed above the blank concentration, but less than the method detection limit
U—not detected at method detection limit; one-half the detection limit shown.

in a subsequent article. However, typical inorganic arsenic intakes are not expected to exceed those reported previously (i.e. 8–14 μg/day for adults) (Yost *et al.*, 1998).

Although this study relies on one sampling event in one state, the commodities sampled originated from diverse geographic locations (Table 1). This diversity reflects the homogeneous nature of contemporary US food supplies. Most of the foods with the highest inorganic arsenic concentrations were processed foods that would not be expected to have a local origin (i.e. rice, grape juice, cooked spinach, peanut butter, peas, cane sugar, corn meal and beet sugar). Seasonal influences are also likely to be minimal in foods such as these that may be stored for long periods without loss of quality. Consequently, the inorganic arsenic concentrations from this market basket survey are likely to be generally representative of typical concentrations in foods throughout the US.

Arsenic may serve an essential role in growth and nutrition (Uthus, 1994a,b; Uthus and Seaborn, 1996). Based on studies of arsenic deprivation in laboratory animals, an arsenic requirement for humans eating 2000 kcal/day has been estimated to be in the range of 12 to 25 μg/day (Uthus, 1994b). Deficiencies related to low arsenic intakes would be most likely to appear in individuals with altered arsenic homeostasis or metabolic stress (Uthus, 1994a). These doses should be compared to toxic

Table 5. Comparison of arsenic concentrations in rice (uncooked) (ng/g wet weight)

Source	Total arsenic	Inorganic arsenic	DMA	MMA
United States[a] (N = 4)	303	74	91	2
Taiwan[b] (N = 5)	120	83	21	21
Taiwan[c] (N = 5)	150	110	13	13
Canada[d] (N = 1)	240	100	–	–

[a]Present study (HCl digestion, hydride AA).
[b]Schoof *et al.* (1998) (HCl digestion, hydride AA).
[c]Schoof *et al.* (1998) (Split samples, ground, extracted with water and analysed by ICP-MS).
[d]Yost *et al.* (1998) (HCl/HBr digestion, hydride AA), "organic" arsenic reported to be 160 ng/g.

doses of arsenic. While chronic daily inorganic arsenic intakes of 600 μg or more have been associated with adverse effects, the nature of the dose–response at lower doses is a subject of great debate (Chappell *et al.*, 1997). Thus, accurate estimates of the range of arsenic dietary intakes and background exposures from other sources will be needed to balance nutritional needs with the possibility that sufficiently elevated concentrations in drinking water or in the environment might pose a threat to public health.

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Assessment of
Petition to Ban Chromated Copper Arsenate (CCA) - Treated Wood in Playground Equipment (Petition HP 01-3)
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United States Consumer Product Safety Commission

prepared for

Wood Preservative Science Council
Washington, D.C.

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Introduction

The Consumer Product Safety Commission (CPSC) concludes that children playing on chromated copper arsenate (CCA)-treated wood playground equipment have an increased risk for cancers of the lung or urinary bladder. In formulating this position, CPSC considers arsenic to be the most potent constituent of CCA and cancer to be the most sensitive toxicity endpoint. CPSC assumes that arsenic which can be dislodged from playground equipment to children's hands is subsequently transferred to their mouths resulting in ingestion and exposure. CPSC calculated an estimated mean handload of 7.6 μg arsenic for 2 hands and projected a 43% transfer to mouths thereby yielding a calculated daily exposure of about 3.5 μg. CPSC further assumed a frequency of contact of 156 days per year for 5 years from age 2-6 for their risk calculation. Based upon ecological epidemiological studies conducted in Taiwan, CPSC calculates a unit risk of 0.023 $(\mu g/kg/day)^{-1}$ for lung or bladder cancer leading to a predicted lifetime excess of 2 to 100 cases per million for the calculates exposures.

Based upon my experience in reviewing arsenic toxicity data as a member of the Upper Reference Levels Subcommittee of the National Research Council Committee on Dietary Reference Intake (National Research Council, 2002), I provide comments on the CPSC assessment.

Comments

1. A principal deficiency of the CPSC assessment is that it presents no actual internal exposure data. CPSC has provided some evidence for dislogable arsenic from CCA-treated wood, but no data on ingestion or bioavailability are provided. Such data

could be obtained from blood, urine or hair testing (Hinwood *et al.* 2003; Shraim *et al.*, 2003). In fact, hair testing of children playing on CCA-treated wood playground equipment compared that of children using other types of equipment would provide a measure of chronic exposure.

2. The calculated daily exposure from playground equipment of about 3.5 μg is below that of exposures resulting from consumption of drinking water from municipal supplies, which currently range from 10 μg/L to 50 μg/L.

3. The CPSC calculation of the unit risk for lung and bladder cancers relies entirely on dose response data on intake of arsenic-contaminated artesian well water and mortality from these cancers in a rural region of Taiwan (Chen *et al.*, 1988; Wu *et al.*, 1989; Chen *et al.*, 1992; Morales *et al.*, 2000). In none of the studies used for this calculation was arsenic exposure measured. Thus, calculations were not based on measured exposures.

4. The reported study population used for the risk calculation came from a rural area of Taiwan where the living standard was below the average (Wu *et al.*, 1989). The residents of this area were known to have "insufficient intake of fresh vegetables" which is a risk factor for lung (Alberg and Samet, 2003) and bladder (Negri and LaVecchia, 2001) cancers. Moreover, undernourishment is known to increase the risk of arsenic-related skin cancer (Hsueh *et al.*, 1995) and vascular diseases (Hsueh *et al.*, 1998). Hence, the calculations of the carcinogenic potency of arsenic in this population are not relevant to well nourished US children with access to playground structures.

5. Lung and bladder cancer are both related to cigarette smoking (International Agency for Research on Cancer, in press). The background incidences of these cancers

were high in the Taiwan studies, which is consistent with cigarette smoking or other exposures to combustion products such as occurs with indoor cooking over coal (Kleinerman *et al.*, 2002). A multiplicative effect on lung cancer has been reported for smoking and occupational (Pershagen *et al.*, 1981; Hertz-Picciotto *et al.*, 1992) and drinking water exposures (Ferreccio *et al.*, 2000) to arsenic and was noted in the CPSC toxicity review of Danello (2003). Such interactions, as may occur in the Taiwanese population, do not provide appropriate data for calculating potential effects in nonsmoking children.

6. CPSC provides no evaluation of the biological plausibility of the risk assessment for the potential low level exposures projected from contact with playground equipment.

7. The lack of concordance with epidemiologic studies in the U.S., which have revealed no cancer excess with drinking water exposures of up to 200 ppb (Morton *et al.*, 1976; Valentine *et al.*, 1992; Lewis *et al.*, 1999), is not addressed, although the toxicity report of Danello (2003) asserts that the "small populations did not have sufficient statistical power to detect the small increases in cancer incidence that would be expected at the relatively low doses experienced by the US populations." Nevertheless, a study of adequate sized populations in Belgium with moderately increased intake of arsenic (3 to 4-fold higher than nonexposed) revealed no association with bladder or lung cancer (Buchet and Lison, 1998).

8. The toxicity report of Danello (2003) notes effects of arsenic that "could act to prevent cancer." This raises the possibility that low exposures to arsenic might actually

have a hormetic effect (Calabrese and Baldwin, 1998), which would be compatible with its beneficial role in some physiological process (National Research Council, 2002).

Conclusions

The calculated exposures to children from playing on CCA-treated wood playground equipment are tenuous and, in any event, below other current exposures. The epidemiologic data used to calculate cancer risks from these exposures are not suitable for extrapolation. In my opinion, there has been no demonstration of any evident cancer hazard from use of CCA-treated wood products.

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Valentine, J.L., He, S.Y., Reisbord, L.S. and Lachenbruch, P.A. (1992) Health response by questionnaire in arsenic-exposed populations. *J. Clin. Epidemiol.*, 45:487-494.

Wu, M.-M., Kuo, T.-L., Hwang, Y.-H. and Chen, C.-J. (1989) Dose-response relation between arsenic concentration in well water and mortality from cancers and vascular diseases. *Amer. J. Epidem.*, 130:1123-1132.

CURRICULUM VITAE
GARY MURRAY WILLIAMS, M.D.

EDUCATION: Washington and Jefferson College,
Washington, Pa. B.A. 1963; Magna Cum Laude

University of Pittsburgh School of Medicine,
Pittsburgh, Pa. M.D., 1967

SUBSEQUENT TRAINING AND POSITIONS;

1967-1969	Intern and Resident in Pathology, Department of Pathology, Massachusetts General Hospital and Instructor in Pathology, Harvard University Medical School, Boston, Massachusetts.
1969-1971	Staff Associate, National Cancer Institute, Experimental Pathology Branch, Chemical Carcinogen Screening Unit, Bethesda, Maryland.
1971-1972	Visiting Scientist, Wenner-Gren Institute, Department of Cell Physiology, Stockholm, Sweden.
1971-1975	Assistant Professor, Department of Pathology, and Member, Fels Research Institute, Temple University School of Medicine, Philadelphia, Pennsylvania.
1975-1979	Chief, Division of Experimental Pathology, American Health Foundation; and Research Associate Professor, Department of Pathology, New York Medical College, Valhalla, New York.
1979-1980	Chief, Division of Pathology and Toxicology, American Health Foundation; and Research Professor, Department of Pathology, New York Medical College, Valhalla, New York.
1980-1987	Associate Director and Chief, Division of Pathology and Toxicology, American Health Foundation; Research Professor, Department of Pathology, New York Medical College, Valhalla, New York.
1987-1997	Director of Medical Sciences and Chief, Division of Pathology and Toxicology, American Health Foundation; Research Professor, Department of Pathology, New York Medical College, Valhalla, New York.

1997-1998	Director, Naylor Dana Institute and Chief, Division of Pathology and Toxicology, American Health Foundation; Research Professor, Department of Pathology, New York Medical College, Valhalla, New York; Visiting Lecturer, Graduate School of Health Sciences, New York Medical College, Valhalla, New York.
1999 - present	Professor of Pathology, Department of Pathology, Director of Environmental Pathology and Toxicology, Head, Program on Medicine, Food and Chemical Safety, New York Medical College, Valhalla, New York; Affiliated Faculty, Graduate School of Health Sciences, New York Medical College, Valhalla, New York.

CERTIFICATIONS:

1974	American Board of Pathology
1975	Physician, State Education Department, State of New York
1981	American Board of Toxicology, Recertified, 2002.
1984	Expert in Toxicology, Ministere des Affaires Sociales et de la Solidarite Nationale, Direction de la pharmacie et du medicament, Republic Francais
2000	Fellow in Toxicologic Pathology, International Academy of Toxicologic Pathology
2002	Fellow Royal College of Pathologists

AWARDS AND HONORS:

1963	Phi Beta Kappa, Washington and Jefferson College
1967	Sheard-Sandford Award, American Society of Clinical Pathologists
1967	Alpha Omega Alpha, University of Pittsburgh School of Medicine
1971	Research Training Fellowship, International Agency for Research on Cancer
1980	Association of University Pathologists

1981	Invited Contributor, Special Issue Food and Cosmetics Toxicology, 9:557, 1981, dedicated to Leon Golberg
1982	Arnold J. Lehman Award, Society of Toxicology
1984	Invited Contributor, Hommage au Professeur Rene Truhaut
1987	Citation Classics: Cancer Lett. 1:231, 1976 and Cancer Res. 37:1845, 1977. Institute for Scientific Information, Current Contents, Vol. 30, No.36, September 7, 1987
1988	Citation Classics: In Vitro 12:521, 1976; 12:821, 1976; 13:809, 1977, 14:824, 1978. Institute for Scientific Information. Current Contents, Vol. 32, No. 9, February 27, 1989
1989	Featured on cover of Cancer Research, Volume 49, November 1
1995	Featured on cover of Cancer Research, Volume 55, April 15
1996	Awards Lecture, Society of Toxicology
1997	Invited Contributor, Special Issue Cancer Letters, 118:1, 1997, dedicated to Phillipe Shubik
1998	Top 10 Most Frequently Cited Articles in 25 years of Toxicologic Pathology Toxicologic Pathology 10:3-10, 1982; Toxicologic Pathology 26:452, 1998
2001	Ambassador in Toxicology Award, Mid-Atlantic Chapter of the Society of Toxicology.
2002	Enhancement of Animal Welfare Award, Society of Toxicology.

RECOGNITION:

1996-01	Who's Who in American/50th-56th Editions
1996-00	Who's Who in the East/26-30th Editions
1996-03	Who's Who in Science and Engineering/3rd-7th (2003) Editions
2003	Who's Who in American Education - 6th Edition (2003)
1997/1998	American Men and Women of Science Directory of American Research & Technology

1998-00	Official American Board of Medical Specialties Directory of Board Certified Medical Specialists 30th-33rd Editions

SOCIETIES:

1974	American Association for Cancer Research
1978	Society of Toxicology
1981	Society of Toxicologic Pathologists
1991	International Society of Regulatory Toxicology and Pharmacology

EDITORIAL RESPONSIBILITIES:

1980	Co-Editor, Differentiation and Carcinogenesis in Liver Cell Cultures. Vol. 349. New York Academy of Sciences.
1980-1981	Consulting Reviewer, Oncology Overviews, International Cancer Research Data Bank.
1980-1986	Reviewing Editor, In Vitro.
1980	Co-editor, The Predictive Value of In Vitro Short-term Screening Tests in Carcinogenicity Evaluation. Elsevier/North Holland Biomedical Press.
1981-1983	Editorial Board, Fundamental and Applied Toxicology.
1981-1989	Editorial Board, Toxicology and Applied Pharmacology.
1981-1999	Editorial Board, Nutrition and Cancer.
1981	Meeting Report: Carcinogenesis and Gene Expression in Liver Cultures. Cancer Research 42:2462-2464, 1982.
1982	Consulting Reviewer, Oncology Overview, International Cancer Research Data Bank Program, National Cancer Institute.
1982-1993	Editorial Board, Mutation Research, Genetic Toxicology Testing Section.
1983	Co-Editor, Colon Carcinogenesis. CRC Press.
1983	Co-Editor, Cellular Systems for Toxicity Testing. Vol. 407. New York

Academy of Sciences.

1983 Co-Editor, Tests Courts de Cancerogenese/Short-term Tests for Carcinogenesis, Elsevier Science Publishers BV, Amsterdam.

1983-1992 Editorial Board, Chemico-Biological Interactions.

1983-1996 Editorial Board, Toxicologic Pathology.

1984-present Founding Editor, Cell Biology and Toxicology.

1987 Meeting Report: Causative and Modifying Factors in Digestive Tract Cancer. Cancer Research 47:922-923, 1987

1988-present Editorial Board, Archives of Toxicology

1988 Editor, Sweeteners: Health Effects, Princeton Scientific Publishing Company.

1989 Editorial Board, Complex Mixtures and Cancer Risk, IARC Scientific Publications, International Agency for Research on Cancer

1990 Meeting Report: American Health Foundation 20th Anniversary International Symposium on Causes and Prevention of Cancer. Preventive Medicine, in 20:534-547, 1991

1991-present International Advisory Board, European Journal of Cancer Prevention

1992 Proceedings of the Second International Conference on Longevity and Aging: Environmental and Nutritional Influences on Aging and Cancer Experimental Gerontology, Volume 27, Special Issue, 1992

1993 Editor-in-Chief, Antioxidants Chemical, Physiological, Nutritional and Toxicological Aspects, Princeton Scientific Publish. Co.

1994-present Area Editor for Carcinogenesis, Drug and Chemical Toxicology.

1997 Co-Editor, Reducing Dietary Fat: Putting Theory into Practice, Journal of The American Dietetic Association, Volume 97, Supplement 1, 1997

2001 Co-Editor, Toxicology, Special Issue, Volume 166, Number 3, Festschrift J.H. Weisburger.

2002 Guest Editor, International Symposium on Antimutagenesis and Anticarcinogenesis, European Journal of Cancer Prevention, Volume 11,

Supplement 2.

2003 Editorial Board, Toxicologic Pathology.

MEETINGS ORGANIZED:

1980 Conference on Differentiation and Carcinogenesis in Liver Cell Cultures. New York Academy of Sciences. New York, NY.

1980 Workshop on the Predictive Value of in vitro Short Term Screening Tests in the Evaluation of Carcinogenicity. Scientific Council of the Netherlands Cancer Society. Dalen, The Netherlands.

1982 Quo Vadis Symposium on Short Term Tests in Carcinogenesis and Mutagenesis. Research Center Clin-Midy. Montpellier, France.

1983 Conference on Carcinogenesis and Gene Expression in Liver Cultures United States-Japan Cooperative Cancer Research Program. Honolulu, Hawaii.

1984 Conference on Cellular Systems for Toxicity Testing, New York Academy of Sciences, New York, NY.

1986 Conference on Causative and Modulating Factors for Digestive Tract Cancer United States-Japan Cooperative Cancer Research Program. Tokyo, Japan.

1986 International Conference on Cancer Research. Theories of Carcinogenesis. The Norwegian Cancer Society, Oslo, Norway.

1986 Conference on Non-Mutagenic Carcinogens: How Much Risk to Man? The Robens Institute, University of Surrey, Guildford, England.

1987 Conference on Sweeteners: Health Effects. American Health Foundation, New York.

1987 International Symposium in Genetic Toxicology, National Science Foundation (U.S.) and Council of Scientific and Industrial Research (India), University of Calcutta, Calcutta, India.

1988 International Symposium on Causes and Prevention of Cancer, American Health Foundation in cooperation with American Cancer Society and National Cancer Institute, New York, NY.

1989 International Conference on Environmental and Nutritional Influences on

Aging and Cancer, American Health Foundation in cooperation with National Institute on Aging, New York, NY.

1990 Conference on Cancer Prevention for Black Americans, Metropolitan Life Insurance, Company, New York, NY.

1991 International Conference on Antioxidants: Chemical, Physiological, Nutritional and Toxicological Aspects, American Health Foundation, Tarrytown, NY.

1991 Second International Conference on Theories of Carcinogenesis. Norwegian Cancer Society, Oslo, Norway.

1992 1st International Short Course on Preclinical Drug and Chemical Safety, Tarrytown, NY.

1993 2nd International Short Course on Preclinical Drug and Chemical Safety, Tarrytown, NY.

1993 American Health Foundation, 25th Anniversary Conference and Celebration, Toward Optimal Health: Examining Goals for Nutrition and the Environment, Tarrytown, NY.

1994 3rd International Course on the Safety Assessment of Pharmaceuticals, Tarrytown, NY.

1995 International Congress on Hepatocytes-Applications in Cell Biology, Toxicology and Medicine, Tubingen, Germany.

1996 Conference, Reducing Dietary Fat: Putting Theory Into Practice, American Health Foundation, New York, NY.

1996 4th International Course on the Safety Assessment of Pharmaceuticals, Part I, White Plains, NY.

1996 4th International Course on the Safety Assessment of Pharmaceuticals, Part II, San Francisco, CA.

1997 5th International Course on the Safety Assessment of Medicines, Part I, White Plains, NY.

1998 6th International Course on the Safety Assessment of Medicine. Basic and Regulatory Aspects, White Plains, NY.

2000 7th International Course on the Safety Assessment of Medicine.

Basic and Regulatory Aspects, White Plains, NY.

2001 — 8th International Course on the Safety Assessment of Medicine. Basic and Regulatory Aspects, White Plains, NY.

2002 — International Symposium on Antimutagenesis and Anticarcinogenesis, New York Medical College, Valhalla, NY

2002 — 10th International Course on the Safety Assessment of Medicines, Advanced Course, Hyéres, Var, France.

2002 — International Symposium on Agricultural Exposures and Cancer, Oxford, England.

NATIONAL AND INTERNATIONAL RESPONSIBILITIES

1975 — Consultant, Pesticides, Toxic Substance and Solid Waste Management, United States Environmental Protection Agency.

1975-1978 — Member, Epidemiology Committee, Breast Cancer Task Force, NationalCancer Institute.

1976-1977 — Member, Program Committee, American Association for Cancer Research.

1976 — Member, Working Group on Evaluation of Carcinogenic Risk of Chemicals to Man: Some Miscellaneous Pharmaceutical Substances, International Agency for Research on Cancer.

1976-1978 — Co-Chairperson, Subcommittee on Rat Liver Tumors, Committee on Histologic Classification of Laboratory Animal Tumors, Institute of Laboratory Animal Resources, National Research Council.

1977-1978 — Member, Panel on Kepone/Mirex, Scientific and Technical Assessments of Environmental Pollutants, Environmental Studies Board, Commission on Natural Resources, National Research Council.

1979-1980 — Member, Panel on Unscheduled DNA Synthesis, Gene-Tox Program, U.S. Environmental Protection Agency.

1980-1981 — Member, Panel of Experts Associated with Technical Report Review Subcommittee, National Toxicology Program, Department of Health and Human Services.

1980 — Member, Working Group on Evaluation of Carcinogenic Risk of

	Chemicals to Man-Antineoplastic and Immunosuppressive Drugs, International Agency for Research on Cancer.
1980-1986	Panel of Reviewers, Netherlands Cancer Foundation.
1981	Advisor, Technical Committee, Society of Toxicology.
1981-1982	Member, Task Group on the Differentiation Between Genotoxic and Epigenetic Carcinogens, International Commission on Protection Against Environmental Mutagens and Carcinogens.
1982	Member, Working Group on the Evaluation of the Carcinogenic Risk of Chemicals to Humans: Chemicals and Industrial Processes Associated with Cancer in Humans, IARC Monographs Volumes 1 to 29, International Agency for Research on Cancer.
1982-1983	Consultant, Office of Health and Environmental Assessment, Reproductive Effects Assessment Group, U.S. Environmental Protection Agency.
1982-1983	Member, International Expert Committee to the Nutrition Foundation on the Relevance of Mouse Liver as a Model for Assessing Carcinogenic Risk, Nutrition Foundation, Incorporated.
1982-1983	Coordinator, Assays of DNA Damage, Collaborative Study on Short-Term Tests for Genotoxicity and Carcinogenicity. International Programme on Chemical Safety, World Health Organization.
1983	Member, Working Group on the Mechanisms of Chemical Carcinogenesis, International Agency for Research on Cancer.
1983-1984	Member, Expert Committee on Pathology/Toxicology and Expert Committee on Short-Term Testing, International Life Sciences Institute.
1984-1987	Assessor, National Health and Medical Research Council Panel of Independent Assessors, National Health and Medical Research Council, Commonwealth of Australia.
1984-1985	Member, Committee on the Carcinogenicity of Cyclamates, Food and Nutrition Board, Commission on Life Sciences, National Research Council.
1984-1985	Member, Task Group of DNA Repair, Subcommittee on Genetic Toxicology, American Society for Testing and Materials.

1985-1987	Member, Toxicology Study Section, National Institutes of Health.
1985	Vice-Chairman, Working Group on the Evaluation of the Carcinogenic Risk of Chemicals to Humans: Some Naturally Occurring Substances, Food Additives and Amino Acid Pyrolysates in Food, International Agency for Research on Cancer.
1985-1986	Member, Awards Committee, Society of Toxicology.
1986	Member, Working Group on the Evaluation of the Carcinogenic Risk of Chemicals to Humans: Genetic and Related Effects: An Updating of Selected IARC Monographs from Volumes 1 to 42, International Agency for Research on Cancer.
1987	Member, Working Group on the Evaluation of the Carcinogenic Risk of Chemicals to Humans: Overall Evaluations of Carcinogenicity: An Updating of IARC Monographs Volumes 1 to 42, International Agency for Research on Cancer.
1988	Participant, Tox-90s Conference, Society of Toxicology.
1989	Organizing Committee, Workshop on the Effects of pesticides on Human Health, Task Force on Environmental Cancer and Heart and Lung Disease.
1989	Chairman, Working Group and Chairman, Subgroup on Animal Carcinogenicity, Working Group on Evaluation of Carcinogenic Risk of Chemicals to Humans: Some Pharmaceutical Drugs, International Agency for Research on Cancer.
1989	Participant and Member of Editorial Board, Workshop on Complex Mixtures and Cancer Risk, International Agency for Research and Cancer.
1989	Participant, Working Group on Short-Term In Vitro and In Vivo Tests, Workshop on Research to Improve Predictions of Long-Term Chemical Toxicity, National Research Council.
1990-present	Member, Committee of Education on Toxicologic Pathology, International Federation of Societies of Toxicologic Pathologists.
1991	Member, Working Group on Approaches to Classifying Carcinogens According to Mechanisms of Action, International Agency for Research on Cancer.
1992-1993	Member, Expert Panel on Interpretive Review of the Potential Adverse

	Effects of Chlorinated Organic Chemicals on Human Health and the Environment, CanTox, Inc.
1993-1999	Member, Committee on Evaluation of the Research Program "Cancer Risk Factors and Prevention," German Cancer Center.
1993-present	Member, Board of Trustees, International Life Sciences Institute, Health and Environmental Sciences Institute. Chair, Membership Development Committee, 2002-2003.
1993-1999	Member, Cellular Telephone Advisory Committee, Harvard Center for Risk Analysis, Harvard School of Public Health.
1993-1999	Wireless Technology Research Peer Review Board.
1993-present	Member, Subcommittee on Carcinogenicity, International Federation of Societies of Toxicologic Pathologists.
1995-1998	Member, International Committee on Wireless Communication Health Research (ICWCHR).
1995-1997	Member, Committee on Research Opportunities and Priorities for EPA, Commission on Geosciences, Environment, and Resources, National Research Council.
1996	Reviewer, U.S. Environmental Protection Agency (EPA), PCBs: Cancer Dose-Response Assessment and Application to Environmental Mixtures.
1996	Participant, Developmental Planning for Office of Dietary Supplements (ODS), National Institutes of Health.
1996-1997	Member, Advisory Board to the Calcium Channel Blockers/Cancer Study, Boston University School of Medicine, Slone Epidemiology Unit.
1997	Member, Working Group on Short/Medium Term Carcinogenicity Tests and Genetic and Related Effects. International Agency for Research on Cancer.
1998	Member, Working Group - Re-evaluation of Some Industrial Chemicals. International Agency for Research on Cancer.
1999-present	Member, Subcommittee on Upper Reference Levels of Nutrients, Committee on Reference Levels of Nutrients, National Academy of Sciences, Institute of Medicine.

1999	Member, Working Group on Predictive Value of Gastric Neuroendocrine Tumours and Forestomach Tumours in Rodents for Carcinogenic Hazard Identification. Co-Chairperson, Forestomach Tumors. International Agency for Research on Cancer.
2000	Member and Report Coordinator, Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) Scientific Advisory Panel. U.S. Environmental Protection Agency.
2000-2002	Reviewer, Office of Dietary Supplements, National Institutes of Health. Annual Bibliography of Significant Advances in Dietary Supplement Research - 2000.
2001-present	Member, Accreditation Committee, International Academy of Toxicologic Pathology.
2002	Peer Review Member, U.S. Environmental Protection Agency "Perchlorate Environmental Contamination: Toxicological Review and Risk Assessment."
2002	World Health Organization Temporary Adviser, 59th Meeting of the Joint Expert Committee on Food Additives (JECFA).
2002	Participant, Joint FAO/WHO Project to Update the Principles and Methods for the Risk Assessment of Chemicals in Food. Workshop I: Introduction, Toxicological Tests & Evaluation, Human Data, Margins of Safety.
2003	Panelist, Dietary Supplement Use in the Elderly Conference. Office of Dietary Supplements. National Institutes of Health.
2003	Temporary Member, Metabolic Pathology Study Section, National Institutes of Health.

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President – Steven H. Lamm, MD

March 28, 2003

To: CCA Docket
Consumer Product Safety Commission
Washington, DC

Dear Commissioners:

Having reviewed the Commission staff report of February 2003 on CCA pressure-treated wood in playground equipment and having attended the Commission hearings on March 17th and 18th, 2003, we have prepared comments for you to address certain issues that were raised but not answered. The primary question repeatedly raised but not answered which we wish to address is: What are the arsenic exposure levels at which the cancer risk is *de minimis* for various human cancers, as far as the data will permit answering? We approach this question using data from published studies and from datasets and analyses in the public domain. Those analyses that have not yet been published in the peer-reviewed or in agency-reviewed literature have been presented at appropriate professional meetings and are being prepared for publication in the peer-reviewed literature.

The following comments are intended to present the up-to-date epidemiological findings on ingested arsenic and internal cancer. This includes research work that CEOH has conducted on its own (or with some US government funds). We hope you find these useful and would be glad to assist you in any further inquiries.

Attached to these comments are published, presented, and pending papers that we have developed on human cancer risks from arsenic exposure over the past nearly thirty years. We have also attached a copy of a report we prepared about fifteen years ago for an industrial group on the specific risks to children from arsenic in playground equipment that you might consider. At that time the issue was skin cancer and arsenic in CCA-treated playground equipment rather than bladder and lung cancer.

Today, we wish first to address the more generic issue of the assessment of human carcinogenic risk from the ingestion of arsenic, whether from water, soil, or wood fibers and then second to apply this understanding to the special case of CCA-treated lumber for playground use.

Cordially,

Steven H. Lamm, MD
Michael Kruse, PhD

Background of Steven H. Lamm, MD

I am a physician and epidemiologist who has been in the practice of assessing the risk to human health for chemical and biological exposures for over thirty years. Since 1980, I have been president of Consultants in Epidemiology and Occupational Health, Inc. providing such services for governments, industries, and citizens. I am board-certified in pediatrics, preventive medicine, and occupational medicine and am a charter fellow of the American College of Epidemiology. I am on faculty at the Johns Hopkins Bloomberg School of Public Health (Health Policy and Management), the Georgetown University School of Medicine (Pediatrics), and the Uniformed Services University of the Health Sciences School of Medicine (Preventive Medicine and Biometrics). I hold fellowships in a number of professional societies (FAAP, FACOEM, FACE, etc.)

I have been active in the study of the health effects to humans from arsenic exposure for at least twenty-five years. Arsenic and benzene are the only two known human carcinogens for which no animal model has been developed. Therefore, the use of epidemiological health studies and mortality studies for people exposed to either of these substances have been high in my active career life.

In the late 1970s, I was part of the team that conducted the medical examinations of the arsenic-exposed smelter workers at the Anaconda copper smelter in Montana. I published with Dr. William Lederer our analysis of the lung cancer mortality that demonstrated that the arsenic-associated lung cancer risk was proportional to the cumulative arsenic exposure of those workers who had been in jobs where the exposures exceeded the old arsenic standard of 500 ug/M^3 and that the lung cancer mortality risk was independent of the cumulative arsenic exposure for those workers whose jobs did not include those high exposures. I have been involved in issues relating to the permitted airborne arsenic levels both in the workplace (OSHA) and in the environment (EPA).

I have dealt with issues of the levels of arsenic in soil both with respect to a clean-up from an industrial site in California and the comparative risk for alternative clean-up methods and as a consultant to advise the community of Spring Valley, Washington, DC on the risks associated with their arsenic contamination problem. In the mid 1980s, I dealt with the issue of the comparative risks of skin cancer in children playing on CCA-treated playground equipment in a risk assessment document that is still in circulation.

For many years we have analyzed the data from the Globe, Colorado cadmium smelter study and identified arsenic exposure as the source of increase lung cancer risk among the employees of that plant.

A list of our publications relating to arsenic is attached.

For many years, I held that the arsenic and cancer issue in the Blackfoot-Endemic area of Southwest Taiwan was too complex, had too many confounding factors, and had too much lost data to serve as the foundation for an arsenic cancer risk assessment. I argued that if it were the only place to show such findings that the rule should not be developed from analysis of an exception and that if it occurred elsewhere then that area should be studied with the current technology and approaches of today. In 1994, Dr. Chen from Taiwan informed us that a similar occurrence had been published in the Chinese public health literature from Inner Mongolia.

Through the assistance of Professor He of the Chinese Academy of Preventive Medicine, we received an invitation to meet with the investigators in Huhhot, Inner Mongolia in 1994. Out of this meeting came the Inner Mongolia Cooperative Arsenic Project (IMCAP) that is a collaboration between my organization and US scientists and the scientists from the Anti-epidemic and Sanitation station in Huhhot. This cooperation has lead to the analysis of their data and its presentation to scientific meetings. One analysis of these data was funded by the Agency for Toxic Substances and Disease Registry (ATSDR) and is there as a report. This study found skin cancers only among those with exposures above 150 ug/L. The dose-relationship of dermatological findings of chronic arsenicism and skin cancer were explored.

We have since continued our investigation of the relationship of human cancers and arsenic exposure, focused now on bladder cancer. We have developed a re-analysis of the SW Taiwan data that demonstrates that the arsenic-related bladder cancer mortality was related only to those villages totally dependent on the artesian wells, and we have developed an analysis of US data that finds no increased risk of bladder cancer mortality for the arsenic exposure levels experienced in the United States (3-59 ug/L). Information on these studies is included within our report to CPSC. These were presented at the International Conference on Arsenic and Health in San Diego, California in June 2002 and will be presented at the US Geological Survey's April 2003 meeting on geochemistry and health in Reston, Virginia. These studies are being prepared for publication in peer-reviewed journals.

CEOH Publications related to Arsenic

1. **Lamm SH**, WH Lederer. Inorganic Arsenic: The Importance of Accurate Exposure Characterization in Risk Assessment. In: Risk Analysis in the Private Sector. C Whipple, VT Covello, editors. New York: Plenum Press, 1985: 149-163.

2. **Lamm, SH**. Separating out sources of lung cancer risk at cadmium plant. 4th International Symposium-Epidemiology in Occupational Health Como, Italy September 10-12, 1985; 120.

3. **Lamm SH**. Cadmium and prostate cancer: Pooling the data from updated studies. La Medicina del La Voro 1986; 77(1):111.

4. **Lamm SH**. Analysis of mortality studies of Globe, Colorado cadmium workers. In: Cadmium 86, Edited Proceedings, Fifth International Cadmium Conference San Francisco, 1986:120-123.

5. **Lamm SH**, S Tirey. Comparative risk and benefit analysis of alternative remedial plans for an arsenic-contaminated industrial site. In: Managing Environmental Risks Air Pollution Control Association, 1988, 38-60.

6. **Lamm SH**, M Parkinson, M Anderson, W Taylor. Determinants of lung cancer risk among cadmium-exposed workers. Annals of Epidem 1992; 2:195-211.

7. **Lamm SH**, TA Hall, JS Kutcher. Particulate exposure among cadmium workers-Is the risk due to cigarette, cadmium, or arsenic particulates? In: Inhaled Particles VII, edited by J Dodgson and R.I. McCallum, 1994, pp 873-878.

8. Byrd DM, ML Roegner, JC Griffiths, **SH Lamm**, KS Grumski, R Wilson, S Lai. Carcinogenic risks of inorganic arsenic in perspective. Int Arch Occup Hyg 1996 68(6):484-494.

9. Luo ZD, YM Zhang, L Ma, GY Zhang, X He, R Wilson, D Byrd, J Griffiths, S Lai, L He, K Grumski, **SH Lamm**. Chronic Arsenicism and Cancer in Inner Mongolia - Consequences of Well Water Arsenic Levels Greater than 50 ug/l. Proceedings of the Second International Conference on Arsenic and Health, San Diego, California, June 1995 in Arsenic: Exposure and Health Effects. Edited by C.O. Abernathy, R.L. Calderon, and W.R. Chappell. Chapman & Hall, 1997, pages 55-68.

Revised: 5/29/00

The Risk of Human Cancer from Arsenic Exposure

(CEOH to CPSC March 28, 2003)

The critical question before regulatory agencies with respect to arsenic has been:

> *What are the risks to humans of developing various adverse health effects from exposure to arsenic at environmental exposure levels?*

While there are a host of various adverse health effects from arsenic exposure that are of medical and public concern, the US regulatory focus has been on human cancers. The focus has been on human cancers rather than on laboratory rodent cancers since humans have appeared to be unique in their susceptibility to cancer from arsenic exposure. Epidemiological studies, i.e., studies of human populations and their variation in cancer risk with changes in arsenic exposures, have served as the basis for assessing human risk of specific cancers. Similarly, there have been a wide range of exposure scenarios that describe the environmental exposure and route of exposure. Agencies concerned with inhalation exposure have focused on epidemiological studies of smelter workers with arsenic exposure measurements (air or urine) and their cancer occurrences. Agencies concerned with oral or ingested exposure have focused on epidemiological studies of communities with arsenic exposure measurements in their drinking water and their cancer occurrences. Since arsenic is essentially not absorbed through dermal exposure, agencies concerned with dermal exposures have converted the exposure scenario to one of oral or ingested exposure and performed their analyses of the drinking water studies. The drinking water studies have historically served as the basis for CPSC consideration – first for skin cancer, and more recently for internal cancers of the bladder and lung.

The standard format for calculating a human cancer risk from a specific exposure is a matter of integrating or accumulating the calculated marginal risks from specific exposures expressed in a specific form (dose-metric) and related to the magnitude and duration of exposure, the time relationship with respect to either age or time since exposure, and a unit risk value or cancer slope factor (CSF) that represents the amount of increased risk of that cancer for every unit of increase in exposure. Depending upon the circumstances, the unit of exposure may be ug/L, ug/M^3, or ug/day.

The CPSC risk assessment has used a special case of the above format in which it has assumed that the appropriate measure of increased dosage is an increased daily arsenic ingestion in units of mg/kg/day averaged over a lifetime, a risk independent of time or age at exposure, and a cancer unit risk value independent of both age and dose-rate or magnitude of exposure.

The fundamental model that CPSC has developed is:

$$\text{Risk Estimate} = \text{Exposure} \times \text{Unit Risk Value}.$$

They have raised multiple issues respecting the exposure measure and have used for the arsenic unit risk value for cancer the ranges derived by EPA (2001) and NRC (2001).

Evaluating the accuracy of these risk assessments, then, involves two different questions.

1. What is the best estimate of the exposure of people to arsenic?

2. What is the best estimate of the unit risk values (also referred to as the cancer slope factor, or CSF) for arsenic in that exposure range? In particular, how much does an increase of one unit of arsenic increase one's risk of developing cancer, and is this unit risk constant over every level of exposure?

The CPSC 2003 risk assessment concerns exposure to arsenic through contact with wood in playground equipment and decks. The CPSC staff has done an impressive job of estimating the amount of exposure due to contact with these structures. Some issues relating to exposure – specifically, those regarding the bioavailability of arsenic under these particular circumstances and the significance of this exposure level relative to background exposure through the diet – still merit further investigation. Time-related issues – e.g., latency of cancers associated with arsenic, the effects of relatively short-duration (approximately five years) exposure from playground equipment, and young age at time of exposure – also warrant further scrutiny.

While the focus of CPSC has been on exposure, the focus of this document is on the unit risk value or the CSF value and its utility and veracity. The unit risk value or CSF used in the CPSC risk assessment is taken from values for the CSF estimated by the EPA and NRC. The CPSC lower value of 0.00041 is the lower bound of the EPA estimate, and the CPSC higher value of 0.023 is the upper bound of the NRC estimate.

In this document, we will not take issue with the exposure assessment developed by CPSC, but we will take issue with the translation of the exposure assessment into a risk assessment. Specifically, we will discuss two particular issues that raise questions about these CSF estimates: (1) the model used to estimate the CSF, and (2) the data used to make these estimates.

A dose-response model is built on the premise that (1) each person in a study has an intrinsic and individual dose-response relationship with respect to a particular exposure agent and circumstance and a particular cancer, and that (2) aggregation of these individuals and their risks will develop a model that yields generalizable and valid risk predictions for people in other populations and to identify the personal characteristics and exposure characteristics that modify that risk.

We shall focus on examining the relationship between the *dosage* as reflected by the amount of exposure in a unit of time and *unit risk value* (CSF) as reflected by amount of cancer developed from a unit of exposure.

The model that the CPSC staff chose to use is the most restricted of the possible models. It assumes that the unit risk value (CSF) is constant over all dosages and all sources, i.e., it is independent of both the dosage and the characteristics of exposure. This model demands that the increase in risk associated with a 100 ug/L increase in exposure be the same whether one goes from 0 ug/L to 100 ug/L or from 500 ug/L to 600 ug/L. The CPSC staff used the unit risk values (CSF) developed by NRC (2001) and EPA (2001) in their application of the model.

The most general (least restricted) model for this relationship allows each possible exposure level and source to have its own CSF value. Such a presentation presents much data, but little information. The goal is to find a useful, generalizable model that compresses the data and maximizes the information. Unlike the restricted model, the general model permits the increase in risk associated with a 100 ug/L increase in exposure to be different when one goes from undetectable to 100 ug/L or from 500 ug/L to 600 ug/L. The general model allows for the possibility that the increase in risk associated with a specific increase in exposure can differ depending on the actual exposure level and the source of the exposure. The question in using more restricted or less restricted models is whether important and meaningful information is being lost in the aggregation of the data under particular restricted conditions.

We present below our analyses of the data underlying the studies used that are generally used in developing unit risk factors for arsenic exposure and human cancers. Our analyses challenge the presumption of a fixed unit risk and demonstrate that across studies the data fit better to a model that allows the unit risk value to be different at high dosages than at low dosages and from one source to another.

Recent data analyses indicate that the more useful models lie between the two extremes of the model with different unit risks for each sub-population described by exposure and the model with the same unit risk for each sub-population described by exposure. In particular, analysis of a broad range of studies conducted in Taiwan, the United States, and Latin America indicates that there is an inflection point in the unit risk value when the arsenic exposure exceeds a dosage in the low hundreds of ug arsenic per day. At exposures above this point, there indeed is a significant association between arsenic exposure and risk of cancer. At exposures below this point, however, our best estimates of the CSF value are statistically indistinguishable from zero, indicating that within this exposure interval there is no discernable association between arsenic exposure and risk of cancer. In this lower range, the evidence does not demonstrate an increased human cancer risk with an increased arsenic exposure.

Although this model is consistent with our best scientific understanding of how arsenic acts on the human body, and although the studies supporting this model have been presented to various regulatory agencies (including EPA), these agencies have not incorporated these facts in their recommendations. Since CPSC has relied on these other agencies' estimates of CSF values, their own risk assessment also fails to take these scientific developments into consideration, and this has a decisive impact on their results.

The second area for questioning these risk assessments relates to the data that were used in estimating risk and deriving safe levels of exposure. The purpose of these assessments is to gauge the risk that the U.S. population faces from exposure to arsenic. In the Morales (2000), EPA (2001), and NRC (2001) reports, the water arsenic levels from Taiwan are transformed to equivalent US water arsenic levels in a process that includes undemonstrated assumptions of differences in body weight, in water consumption rates, and in arsenic ingestion from food and cooking processes. There is nothing transparent about the way the Taiwan water arsenic concentrations have been transformed to US equivalents.

It is striking, then, to see that the data used to make these assessments come from regions of the world that are dramatically different from the United States with respect to arsenic exposure. While it is very uncommon to find arsenic in drinking water above concentrations of 50 ug/L in the U.S., the most important sources of data for assessing risk in the U.S. come from SW Taiwan, where arsenic levels are typically in the range of hundreds of ug/L.

The basic issue here concerns which data are most relevant for assessing the risks of arsenic exposure to U.S. populations. Data on cancer risk at the exposure levels most approximating the US experience is clearly preferable as long as it is sensitive enough to address the question at issue. With respect to the CPSC 2003 risk assessment in particular, the relevant exposure levels from CCA-treated wood playground equipment are very small compared to the arsenic exposures from drinking water in other parts of the world. However, although both published and unpublished data sufficient to answer that question are available, neither the EPA nor the NRC has sought them or given them consideration. We suggest that these data are in fact both sensitive enough and of adequate quality to warrant their use in any quantitative assessment of cancer risk due to arsenic exposure in the U.S. population.

I. Model Assumptions and The Dose-Response Relationship

The basic assumption of the EPA (2001) and NRC (2001) risk assessments for arsenic is that the CSF – the increase in risk that comes with an increase of 1 ug/L in exposure – is the same at every level of exposure. The cornerstone of these two assessments is Morales et al. (2000), which presents a careful and sophisticated statistical analysis of internal (bladder, lung, and liver) cancer data and arsenic levels in SW Taiwan. Given the relationship between this study and the EPA and NRC risk assessments, one would expect that the data presented in Morales et al. would conform to the assumption that the CSF value in fact is constant across the entire range of exposure levels considered. As revealed in Figure 1 below, however, this is not the case.

Figure 1

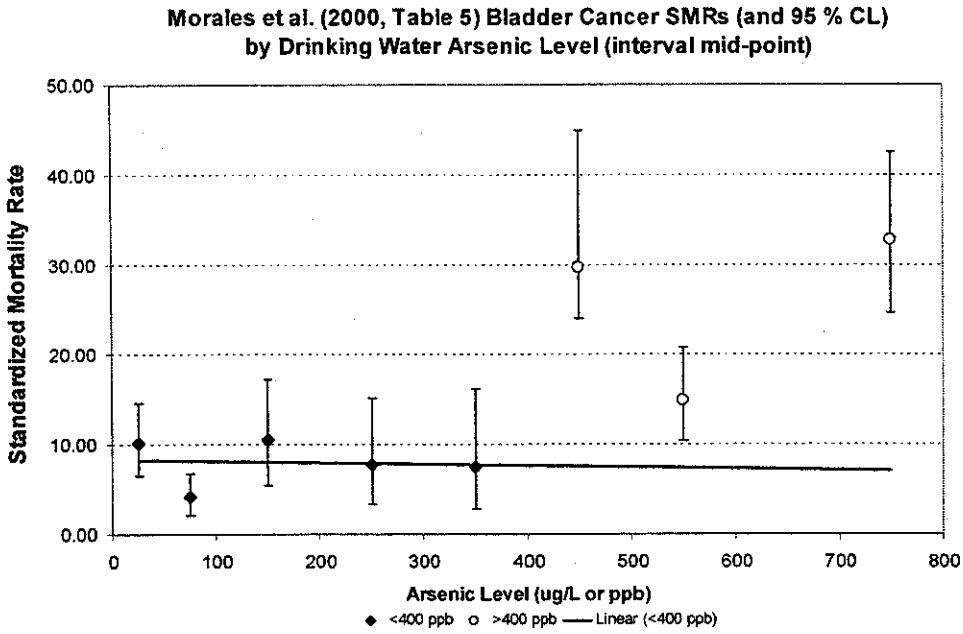


Figure 1 is simply a graphic representation of the standardized mortality rates (SMRs) for male and female bladder cancers (using the general population of Taiwan as a reference population) and median arsenic exposure levels that are reported in Table 5 of Morales et al. (2000). Figure 1 is a direct graphic presentation of numbers presented tabularly in Morales et al. (2000). The exposure strata come directly out of Morales et al. (2000) and are in the untransformed Taiwan arsenic concentrations of ug/L. In light of EPA's and NRC's assumption about the constant value of the CSF, we would have expected to see a monotonically increasing linear trend in these data, with SMR values steadily increasing as the exposure level increases.

Contrary to this expectation, however, the bladder cancer mortality rates shown in Figure 1 indicate that the bladder cancer mortality rates in the first group (<400 ug/L) show no association with arsenic exposure level. The linear regression demonstrates that the arsenic level has no effect on the bladder cancer SMR and that the slope is indistinguishable from zero (β=-0.0015, 95% CI –0.036 - +0.034). The figure shows that all the exposure-stratified risks calculated for arsenic levels > 400 ug/L are significantly separated from the linear trend line derived form the rates in the < 400 ug/L strata. Further, it is noteworthy that for the second group, the SMR variability within the group overwhelms any SMR-arsenic relationship.

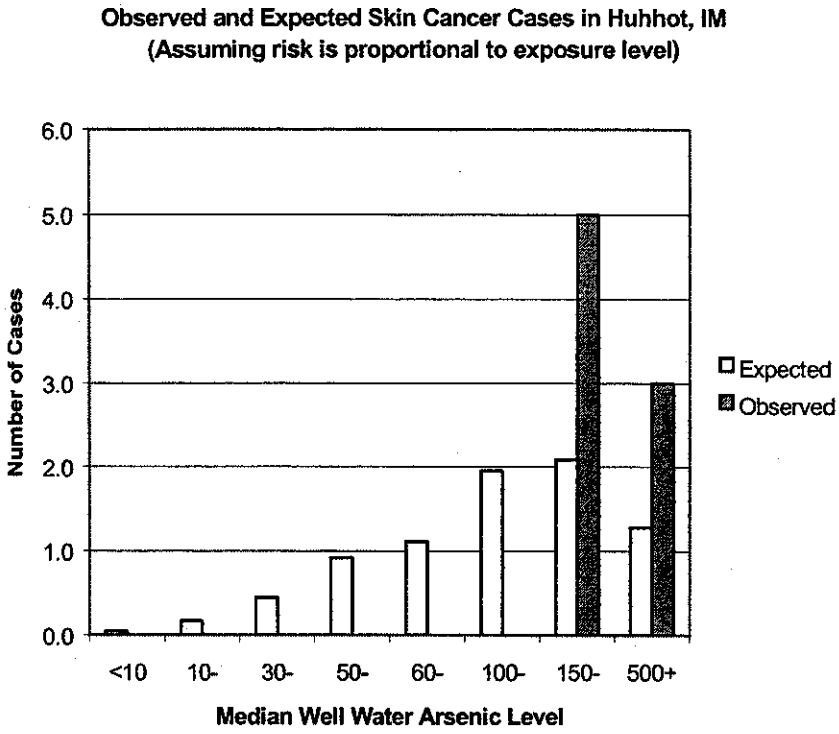
This result suggests that there is a significant difference in the relationship between arsenic exposure and the risk of bladder cancer around the level of 400 ug/L. This results is consistent with the analysis of bladder cancer risk and drinking water arsenic levels in Taiwan was independently conducted by H-R Guo and Y-C Tseng (2000) using data across Taiwan rather than restricting itself to the BFD-endemic area in SW Taiwan. Their arsenic levels in drinking water data came from the nationwide

survey conducted by the Taiwan Provincial Institute of Environmental Sanitation (Lo et al., 1977) and was verified when a proportion of wells were retested later (Chen et al., 1988). Their bladder cancer mortality data came from the township household registry offices and the bladder cancer incidence data came from the National Cancer Registration Program. Their analysis demonstrated for both males and females and for both incidence and mortality rates that a significant increase in bladder cancer rates occurred only for those areas with arsenic levels in the drinking water greater than 640 ug/L (ppb). Thus, two independent analyses of Taiwan data for bladder cancer suggest that dose-relationships at high dose rates are different than those at low dose rates.

This same discontinuity has been seen in other studies of arsenic exposure and human cancers. Lamm and Lederer (1985) demonstrated this for lung cancers and arsenic inhalation (plus ingestion) among the Anaconda copper smelter workers. Byrd et al. (1996) demonstrated this in their systematic review of skin cancer risk and drinking water arsenic levels. Most recently, the Inner Mongolia Cooperative Arsenic Project (IMCAP) reported a discontinuity in the skin cancer risk among villagers in Huhhot, Inner Mngolia with exposure up to 2,000 ug/L, similar to the SW Taiwan arsenic exposures.

IMCAP, in its 2001 report to the Agency for Toxic substances and Disease Registry (ATSDR) entitled "Relationship between Consumption of Arsenic-contaminated Well Water and Skin Disorders in Huhhot, Inner Mongolia" (July 5, 2001) analyzed rates of skin cancer and arsenic dermatoses (hyperkeratoses and dyspigmentation) across well water arsenic level exposure strata. Figure 2 presents their findings for skin cancer in their population of 3,228 residents based on individual peak arsenic exposure levels.

Figure 2



There were no cases of skin cancer reported among those whose peak arsenic well water level did not reach 150 ug/L. The expecteds in Figure 2 are based on the assumption that skin cancers were not related to arsenic exposure levels but were dependent upon the number of people in each strata. The observations indicate a statistically significant deficit of skin cancers among those with exposures below 150 ug/L only, thus rejecting the linear no-threshold model. Figure 2 indicates the non-observance of skin cancers among those with < 150 ug/L exposure.

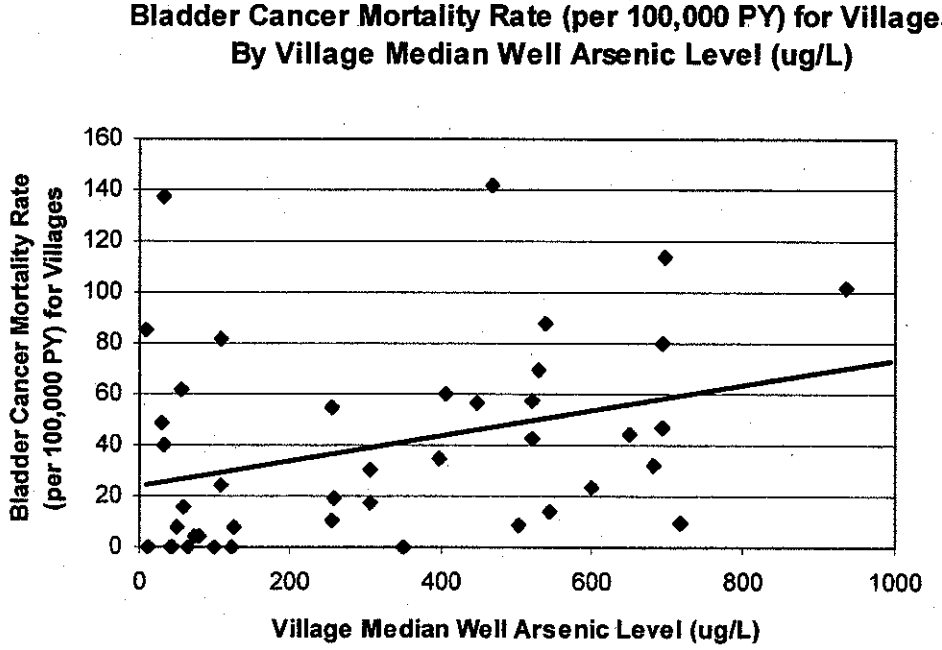
The similarity in pattern between Figure 1 and Figure 2 is particularly intriguing, as Figure 1 comes from the very study that serves as the basis of EPA (2001) and NRC (2001). The difference in both studies of a low cancer risk population at low arsenic exposures and a much higher risk at high arsenic exposure levels prompted us to look at the Taiwan study population more closely in order to understand why there might be such a discontinuity.

The SW Taiwan study population was drawn from 42 villages located in the coastal region of SW Taiwan. One of the virtues of this dataset is that it is one of the largest study populations ever published, covering approximately 500,000 person-years of observation, of which 300,000 were for people with less than 400 ug/L exposure. This region has been investigated for water-associated health conditions for over fifty years, and the water sources in this region have long been known to contain high levels of arsenic.

Prior to 1988, the area had been referred to as the "Blackfoot Disease-endemic area" because of the peripheral vascular disease that occurred there and had not been reported in any other arsenic area. In 1992, however, the nomenclature changed, and since that time the area has been referred to as a "chronic arseniasis-endemic area." This shift in terminology has had a discernable effect on the analyses conducted on data from this region. In the period prior to 1988, the factor assumed to be most relevant to the risk of human cancers was exposure to water from artesian wells. After 1992, however, the distinction between artesian wells and other ("shallow") wells was dropped; instead, exposure was conceived of only in terms of arsenic concentrations.

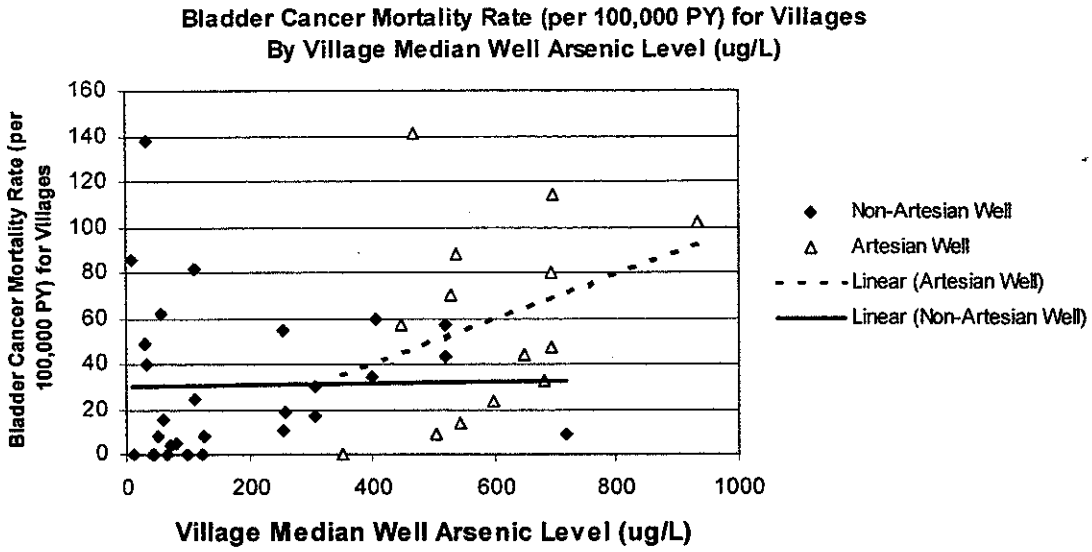
This shift in perspective has had a remarkable impact on the conclusions drawn from the very same data. This impact is demonstrated below in the various analyses of the database underlying the Morales et al. (2000) analysis. Figure 3 below plots the bladder cancer mortality rates for each of the 42 villages studied against the median arsenic level of its wells. These data were obtained from Table A-10 (pages 308-309) in the appendix of the 1999 report of the National Research Councils report "Arsenic in Drinking Water." Under the assumption that the only aspect of exposure that is relevant to the bladder cancer risk assessment is the median arsenic level for the village, the linear dose-response trend plotted there seems appropriate (β=0.0496, 95% CI 0.0051 – 0.0941; p=0.0300).

Figure 3



If we look at these same data points from the pre-1988 perspective, however, we find very different results. Figure 4 plots the very same data points from Figure 3. This time, however, the villages are distinguished not only by the median level of arsenic in their wells, but also by the type of wells used – artesian or non-artesian.

Figure 4



Just as seen before in Figure 1, Figure 4 indicates that the study population is made up of two distinct sub-populations – those subjects whose water sources were not restricted to artesian wells and whose arsenic exposure levels were generally below 400 ug/L and those subjects whose water sources were restricted to artesian wells and whose arsenic exposure levels were generally above 400 ug/L. Figure 4 suggests that this distinction corresponds primarily to the kind of well (artesian vs non-artesian) used and then to the arsenic level. For those villages with non-artesian wells, the bladder cancer mortality rate is apparently independent of the arsenic levels in those wells (β=0.0036, 95% CI -0.0689 – +0.0762; p=0.92). In contrast, the estimated slope of the regression line for villages with only artesian wells is much steeper (β=0.0975, 95% CI -0.0766 – 0.2716; p=0.25). While these slopes are not statistically significantly different from each other, their patterns are most striking. These, however, are based on crude risk estimates, and whether the slopes would be statistically significant after the data were adjusted for age and other demographic variables is not known.

The precise reason for the two groups is not yet ascertained, because little specific information has been publicly released about the villages in the study. The issue probably relates (as it should) to the exposure assessment and not to the outcome (cancer) assessment. The original SW Taiwan citation for the internal cancers (C-J Chen et al., 1985) cites the association as being between high-arsenic artesian well water and cancer – an association that appears to be supported by the results presented above in Figure 4. Their Chart 4 demonstrates that the markedly high rates are related to artesian well villages and not to shallow well villages. Lu (1990) has previously published articles about organic or organometallic substances (including, but not limited to, humic acids, fluorescent substances, and fungal toxins) that are also in the village water and have vascular and mutagenic effects. The study population was specifically limited to the Blackfoot-Disease endemic area by design, however; whether the factors related to that

disease act as confounders or effect-modifiers on the relationship between bladder cancer mortality and arsenic exposure is unknown.

These are, we stress, hypotheses that may explain the differences that we have found in the two subpopulations. The precise mechanism responsible for the difference illustrated in Figure 1 and Figure 4 is, at present, unknown; there may in fact be several different factors at work here. The lack of an explanation for the difference does not, however, show that this difference does not exist or is not important, and the reasons for the differences should be sought before these data are used as the basis of a quantitative risk analysis for arsenic. The risk estimate for arsenic ingestion exposure would certainly be different if it were based on the data from the 60 % of the SW Taiwan population base with exposures in the 0 – 400 ug/L exposure range rather than including the high exposure group in the estimation procedure. There is nothing in US environmental arsenic exposures (except possibly some old industrial sites) to which the high exposure data can be directly related.

II. Availability and Appropriateness of U.S. Data

Ideally, an assessment of the risk posed to residents of a particular region by exposure to a given substance would be based on data obtained from that specific region. In the case of assessing the risks associated with exposure to arsenic in drinking water within the U.S., this has not been done. Instead, EPA (2001) and NRC (2001) have largely relied on data from other regions – SW Taiwan and Latin America in particular – when estimating the risks for U.S. populations exposed to arsenic.

These studies do provide valuable information about the relationship between environmental exposure to various levels of arsenic in drinking water for a variety of health effects, including several types of cancers. However, using these data to estimate the risk in the U.S. population may be the source of considerable uncertainty or bias. The most obvious difference between SW Taiwan and the U.S. is in arsenic exposure: while levels in the U.S. rarely exceed 50 ug/L, the Taiwan data come from a region in which concentrations are far higher. This means that inferences based on these data will be strongly influenced by outcomes that are largely irrelevant to the exposures for U.S. populations. For instance, EPA has discussed the importance of the dermal signs of chronic arsenicism – yet numerous studies carried out in the US in the 1980s have looked for dermal signs of chronic arsenicism among people with arsenic exposure from drinking water in the US and have found none. Both the absence of evidence of dermal arsenicism and the absence of Blackfoot-disease with drinking water consumption in the US are strong evidence that the SW Taiwan experience at high exposures is not relevant to US experience at US exposures.

These statements can be made independent of issues concerning differences in body weight, water consumption, additional arsenic exposures, dietary adequacy, and ethnic variations. Geographic, ethnic, and social differences between places as diverse as the U.S., Taiwan, and Latin America constitute additional sources of variability that must otherwise be considered. Water intact, body weight, and arsenic exposure from food are

important factors in estimating risk, and all these are all liable to vary considerably within these regions.

Further, the relative paucity of data from Taiwan for exposures in the range relevant to U.S. populations (from undetectable concentrations up to 50 ug/L) requires that the risk assessment for low-level exposure be extrapolated from the higher range, rather than being based directly on data in that interval. This, in turn, means that this assessment will be particularly sensitive to the model used and the criteria used to select such a model.

Recognition of the dangers involved in basing risk assessments for one region on data from another led the NRC (2001) to stress the importance of comparing the assessments derived from non-U.S. sources to one based on a "real-world situation" – i.e., one dealing with U.S. populations exposed to levels found in the U.S. Despite this recognition, neither EPA (2001) nor NRC (2001) have made use of US government data for examining in the U.S. the bladder cancer mortality-arsenic exposure relationship as an ecological replicate of the SW Taiwan study at the exposure levels of concern.

There are, indeed, studies of U.S. populations whose results are relevant to any quantitative assessment of risk associated with U.S. populations exposed to arsenic. These include three published studies that found no increased risk of bladder cancer at U.S. exposure levels:

1. Engel and Smith (1994) have published results concerning the risk of various cancers in U.S. counties with population-weighted mean arsenic levels of 5 ug/L or greater. The mean arsenic concentrations in the public drinking water supplies in those counties ranged between 5.4 and 91.5 ug/L – levels that are dwarfed by Taiwan exposures, but are high when compared to typical U.S. levels. They identified 30 such counties and examined their causes of mortality over a 17-year period (1968-1984). Their data show that the SMR for both all cancers and lung cancers was 1.0 for those with drinking water levels of 5-10 ug/L and significantly less than 1.0 for those with higher drinking water arsenic levels (10-91.5 ug/L).

2. Bates et al. (1995) conducted a case-control study involving 117 bladder cancer cases and 266 controls in Utah. Of the 88 towns involved in the study, 81 had drinking water levels of arsenic below 10 ug/L, six had levels between 10 and 50 ug/L, and only one had levels above 50 ug/L. While exposure to arsenic appeared to increase the risk of bladder cancer among smokers, the relationship found among smokers did not appear to be dose-dependent. A markedly increased bladder cancer risk was shown only for ever-smokers observed for 30-39 years. For smokers, the odds ratios for cumulative doses of 19-33 mg and doses >53 mg, were 3.33 and 3.32, respectively; the odds ratio for a cumulative dose of 33-53 mg, however, was only 1.93. For non-smokers, there was no evidence of an increased risk of bladder cancer with any measure of arsenic exposure

3. Lewis et al. (1999) compared the bladder cancer rates of Millard County, Utah with those of the state of Utah as a whole. Drinking water sources in Millard County are

contaminated with arsenic at median levels of 14-166 ug/L, yet the rates of bladder cancer and cancer of other urinary organs for Millard County were found to be statistically indistinguishable from those of the state of Utah as a whole, even among those exposed to the highest levels of arsenic. The median arsenic level for the county was 100 ug/L as was the weighted mean level. Lewis et al. (1999) found no significant increased risk of cancer of the bladder and other urinary organs among either males or females (SMR 0.42 with 90% CI 0.08-1.22 for males; SMR 0.81with 90% CI 0.10-2.93 for females).

None of the data used in these studies entered the EPA (2001) and NRC (2001) risk assessments for arsenic. NRC (2001) presented some of the reasons for excluding the most recent of these studies, Lewis et al. (1999), from their assessment. According to that report, one important reason for excluding Lewis et al. was that Millard County (Utah), a rural county with a very high prevalence of Mormons, probably differed from the state as a whole in ways that would significantly affect the study's results. Specifically, NRC highlighted the problems posed by the likely difference in smoking rates between the study and reference populations, since the rate in Utah is 12-13% while the predominantly Mormon population in Millard County had strict religious prohibitions against the use of tobacco.

These presumptions are not demonstrable from the Utah state cancer data. When the bladder cancer rates from Millard County are compared to those from other Utah counties, Millard County appears to be quite representative of the state as a whole. Figure 5 below plots publicly available data on the age-adjusted bladder cancer rates (male and female combined) for each county in Utah and for the state as a whole. These data are plotted on the X-axis (log-scale) by the number of cases (which reflects the population size) and on the Y-axis by the bladder cancer rate.

Figure 5

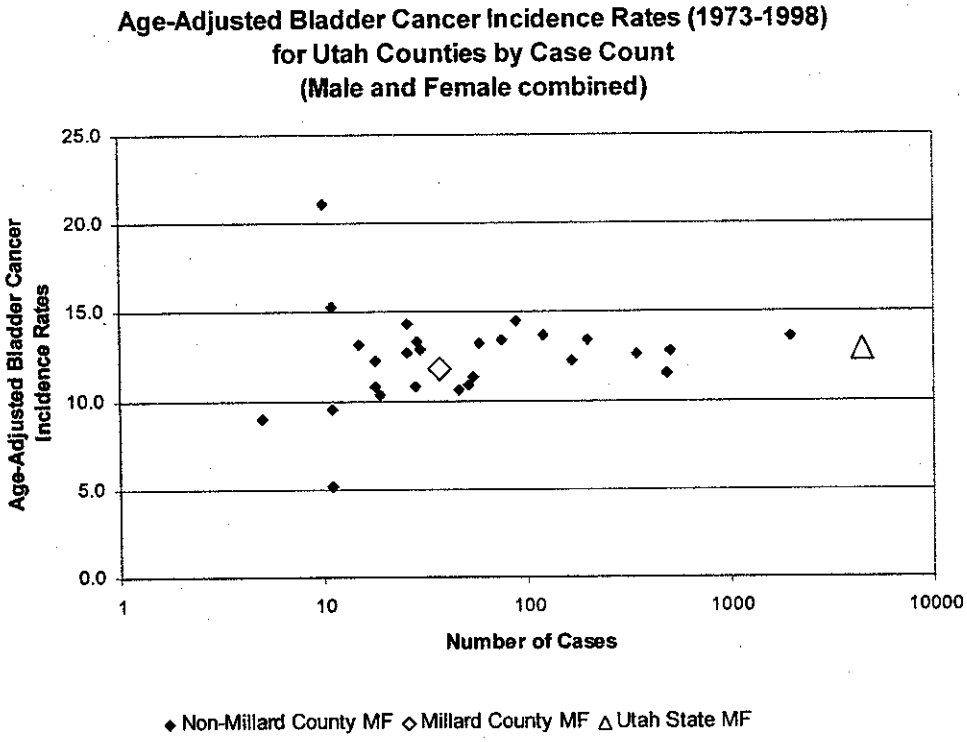


Figure 5 does indicate that the state rate of bladder cancer is somewhat greater than Millard County's rate. However, it also makes evident that the rate in Millard County is not greater than that of other rural (and probably heavily Mormon) counties. This, in turn, means that the lack of a significant increase in the risk of bladder cancer in the study population was not simply an artifact generated by the choice of a particular comparison population. Rather, this result appears to be precisely what it should be – a consequence of the data.

The most significant limitation of the three U.S. studies described above may be the size of their study populations. Given the small number of cases of bladder cancer – three male and two female – found in the Lewis et al. study, it was suggested in NRC (2001) that the failure of these studies to replicate results from the larger Taiwan studies may simply have been a result of their relative insensitivity. Indeed, it was pointed out in NRC (2001) that when the data used in the Lewis et al. (1999) study were reanalyzed without a comparison population, the resulting risk estimate was equivocal. While this estimate was statistically indistinguishable from zero, it was also indistinguishable from the risk predicted by Morales et al. (2000) that was used in the EPA (2001) assessment.

This particular criticism appears to reflect a general assumption by many researchers and agencies that while the theoretical risks predicted by their models at typical US levels of exposure are significant enough to direct public policy, they are not large enough to be detected by any study that actually looks at the population said to be at risk. That is, not only are existing US studies considered insufficiently powerful to discriminate reliably between no risk and the elevated risk predicted by the theoretical

models, but it is assumed that no such study is ever likely to be able to serve as an independent check on the predictions of these risk models.

This pessimism is unfounded. Frost, Craun and Brown (2002) calculated the sample sizes needed to discriminate reliably between the elevated risks of bladder cancer predicted by the NRC and EPA risk analyses and the background rate indicated by Lewis et al. (1999) and showed them to be quite feasible for exposure levels greater than 50 ug/L. This is borne out in comparing the five male and female bladder cancer deaths reported by Lewis et al. to the number that would have been expected if the risk estimates presented in Morales et al. were correct. A Morales et al. risk estimates predicts a 1 % bladder cancer mortality risk in the population from an exposure at 400 ug/L arsenic for males and 250 ug/L arsenic for females. These risk estimates and the assumption of both a linear dose-response curve and a mean exposure level of 100 ug/L for members of the Lewis et al. cohort would yield a prediction of 22 bladder cancer deaths in the Lewis study. Based on a Poisson-distribution, an observation of fewer than 14 cases of bladder cancer deaths in the Lewis study would have demonstrated that the Morales estimates significantly over-predicted the bladder cancer mortality risk in Millard County. Rather than even 13 bladder cancer deaths having been found, only five such cases were observed in this data set assembled by the National Cancer Institute. The data in the Lewis study are sufficient to demonstrate that the risk estimate based on the Taiwan data and the Morales analyses vastly over-predicts the arsenic associated bladder cancer mortality rate in the United States, or at least in Millard County, Utah.

The arsenic levels considered in the Lewis et al. study exceed what is typically considered a high level of exposure in the United States (30 – 50 ug/L), and it is possible that the studies in the published literature discussed above are insufficiently sensitive to detect the predicted increased risk in this low range and below. However, publicly available data on both cancer mortality rates and U.S. arsenic levels in drinking water are sufficient to overcome this particular limitation. The US Geological Survey has developed a publicly available database that provides arsenic level distributions on a county-aggregated basis for both public water supplies and for ground waters. By using county-specific cancer-specific mortality rates and numbers from the National Cancer Institute and the US Environmental Protection Agency and information from state departments of health and/or the environment regarding each county's source drinking water sources, specifically groundwater, we have produced an ecological study of drinking water arsenic and bladder cancer mortality with 75 million person-years of observation and nearly 5,000 bladder cancer deaths of white males in the U.S. Our analysis of these data has been summarized below. We point out, however, that since the data sources are publicly available government data, any interested agency – including the CPSC – should be able to make their own independent evaluation of these results.

Using groundwater arsenic data provided by the USGS, we identified 268 counties in the contiguous U.S. that had median groundwater source arsenic levels of 3 ug/L or greater. Of these, 187 counties were reported by state authorities to use only groundwater for their drinking water source. In order to get robust data, analysis was further limited to the 133 of these counties that were found to have had at least one white male bladder cancer death in each of the study decades: 1950-1959, 1960-1969, and

1970-1979. The risk of bladder county mortality for white males in the counties compared to that predicted from age-adjusted state rates is shown in Figure 6.

Figure 6

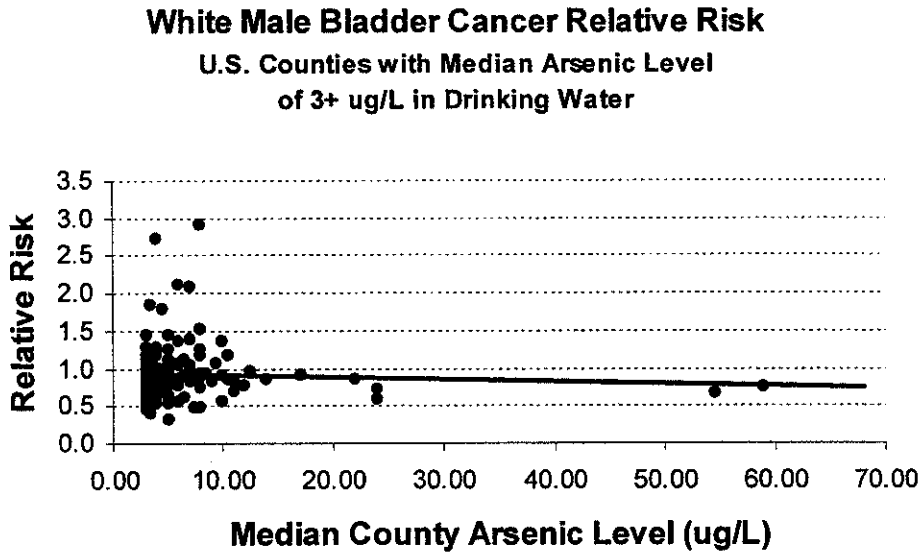


Figure 6 indicates that the exposure in these 133 counties ranges from 3 to 59 ug/L, with 60% of these counties clustered in the range of 3 – 5 ug/L. The relative risk for these counties cluster somewhat below 1.00, and linear regression indicates a slope that is indistinguishable from zero ($R^2 = 0.0035$, $\beta = -1.143$, 95 % CI -4.481 – +2.194). To account for the possibility that the few data points at exposure levels above 20 ug/L were unduly influential in the regression analysis, a second line (not shown) was fitted using data only from counties with exposure between 3 and 20 ug/L; this also yielded a slope indistinguishable from zero ($R^2 = 0.0097$, $\beta = +0.014$, 95 % CI -0.011 – +0.039).

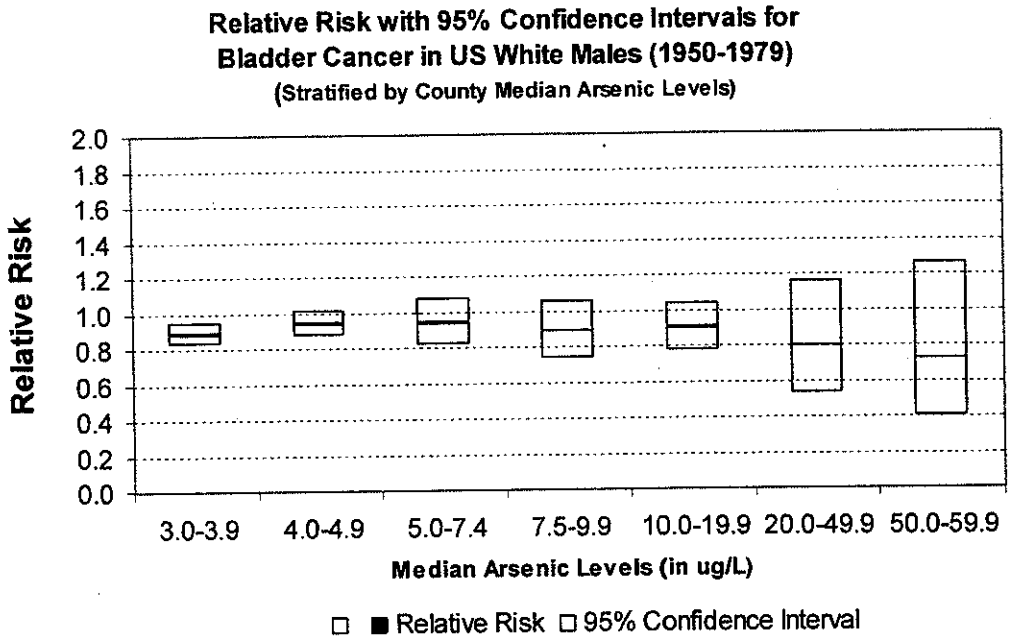
Table 1 presents a stratified analysis of the relative risk, and shows that that the overall relative risk is 0.91 and ranges between 0.89 and 0.95 over the exposure range of 3 to 19.9 ug/L. The only statistically significant result is at the lowest exposure level, and at higher levels of arsenic exposure, the relative risk appears to drop, rather than rise.

Table 1

ug/L	Counties	1960 White Male Population	Median Arsenic Exposure	Expected	Observed	Obs/Exp	95% CI
3.0-3.9	53	1,108,868	3.00	2,204	1,962	0.8902	0.8377-0.9460
4.0-4.9	22	833,587	4.00	1,604	1,519	0.9470	0.8829-1.0158
5.0-7.4	28	246,638	6.00	433	409	0.9456	0.8253-1.0811
7.5-9.9	14	114,459	8.00	259	231	0.8919	0.7471-1.0648
10.0-19.9	11	156,775	11.00	386	349	0.9042	0.7824-1.0448
20.0-49.9	3	24,124	24.00	58	46	0.7931	0.5388-1.1674
50.0-59.9	2	13,734	56.75	29	21	0.7241	0.4132-1.2691
Totals:	**133**	**2,498,185**		**4,973**	**4,537**	**0.9123**	**0.8767-0.9501**

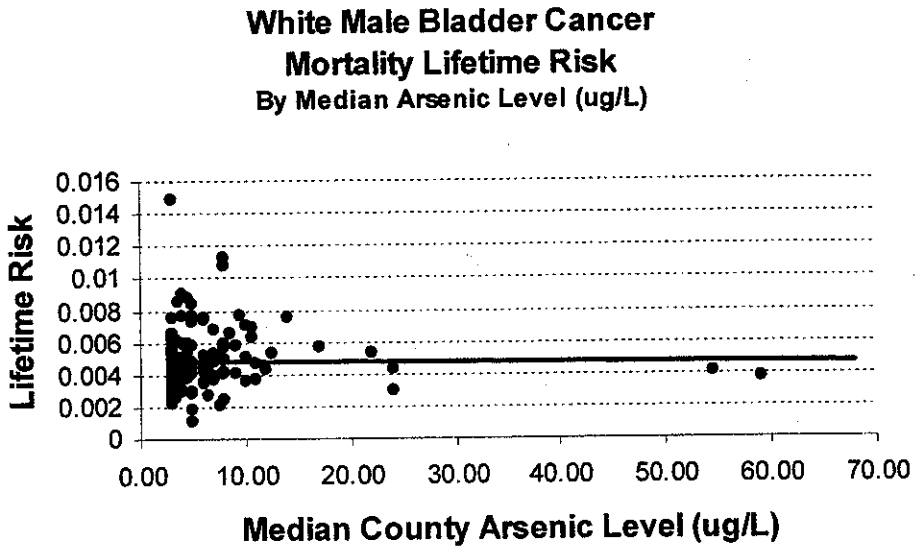
These same data are presented graphically in Figure 7.

Figure 7



The above analyses [Figures 6 and 7, Table 1] have presented the county-specific mortality rates relative to the rates for the state. The absolute values of the lifetime risks of bladder county mortality for white males in these 133 counties have been calculated and are plotted in Figure 8.

Figure 8



Within the exposure range of 3 – 60 ug/L, the lifetime risk is approximately 0.005 (1/200), and linear regression shows a slope indistinguishable from zero, revealing no evidence of an arsenic-dependent risk in this exposure range (R^2=0.0002). The slope of this regression line (which corresponds to the lifetime increased risk per 1 ug/L arsenic exposure) is -3.5×10^{-6} with 95 % confidence limits of -5.0×10^{-5} to $+4.2\times10^{-5}$. The NRC predicted risk of $+4.6\times10^{-5}$, based on extrapolation and adjustment from the SW Taiwan data, falls outside the range that is consistent with the US experience shown here in the 75 million person-year study. This is in disagreement with the prediction of the model in the draft NRC report and is able to reject the NRC prediction, but it is not sensitive enough to dismiss the lower risk estimate developed by EPA (2001).

This analysis has two important virtues. First, its size – based on publicly available data covering 75,000,000 person-years of observation, it is approximately 150 times as large as the SW Taiwan study that has served as the foundation of current risk assessments for arsenic exposure. Second, the data in this study are of U.S. residents exposed to levels of arsenic – 3 to 60 ug/L – that represent the top of the realistic range of arsenic exposures one finds in the U.S. Drawn from the most relevant population at the most relevant level of arsenic exposure, these publicly-available data obviate the need to extrapolate from a non-US population exposed to arsenic in levels that is orders of magnitude higher than those found in the U.S.

These analyses of US bladder cancer mortality rates for white males and US groundwater arsenic levels demonstrate no increased risk of bladder cancer mortality with increasing arsenic exposure in the range of 3 – 59 ug/L. This is the same conclusion that was reached from analysis of the SW Taiwan data for villages with well water arsenic levels < 400 ug/L.

III. Application to CPSC Concerns

This report began by showing that the underlying model for cancer risk assessment has both a unit risk or potency component and an exposure component. We have focused upon the unit risk component raising the issues that the data underlying the unit risk measure used by the CPSC staff were not the most relevant and reliable data available for assessing arsenic risk at the exposure levels with which the CPSC is concerned.

The CPSC has returned to the issue of the quantitative cancer risk for children playing on CCA-treated wooden playground equipment from the arsenic exposure. In its current study of this issue, the CPSC has relied heavily on the prior work on the risks associated with arsenic in drinking water conducted by the EPA and NRC. At the EPA, these analyses led to the establishment of a drinking water arsenic standard of 10 ug/L. This translates into the determination that a daily ingestion rate of 20 ug arsenic for an entire 75-year lifetime would be acceptable, assuming a consumption of two liters of water per day.

CPSC's exposure assessment has concluded that the absorbed arsenic exposure of children using CCA-treated playground equipment would be about 3 ug per day of use

for a period of five years. Even assuming that the playground equipment was used every day of those five years, the estimated increase in arsenic exposure due to contact with CCA-treated wood implies an additional average daily arsenic ingestion of 0.2 ug. This would indicate a marginal increase in exposure that is only about 1 % of what the USEPA drinking water standard finds to be "safe".

Furthermore, it must be understood that if the drinking water standard is set at 10 ug/L, very few water systems will be over about an average of 3-5 ug/L in order to assure that they are not found to be over the standard at a particular sampling time. Thus, it is likely that very few people would have daily arsenic ingestion rates greater than 6 – 10 ug arsenic from their drinking water, in which case a marginal lifetime average increase of 0.2 ug arsenic per day would still place them well in the range that EPA has determined to be "safe".

At a practical level, then, childhood contact with CCA-treated wood represents an exposure source that, given what EPA has already deemed to be safe, can represent only the most minimal theoretical increase in cancer risk. What has focused attention on this type of exposure, then, is not its small contribution to individuals's total arsenic exposure, but the predictions of theoretical risk models.

As we observed at the beginning of this document, the predictions generated from such models depend on two distinct components: (1) exposure and (2) the unit risk factor (or CSF). Our focus has been on the latter of these. Specifically, we have attempted to draw attention to some of the shortcomings of the processes used by EPA and the NRC to estimate the values of the CSF which CPSC has used in their own risk assessment for arsenic exposure from CCA-treated wood, and that have led to what we believe to be estimates of risk far higher than are warranted by the relevant and reliable scientific findings.

An underlying principle of risk assessment for a specific purpose is that it should use the most relevant and reliable data or information available for the question that is being asked. Since CPSC is asking what the quantitative cancer risk assessment is for children playing on CCA-treated wooden playground equipment from the arsenic exposure, the best possible risk data to use would be arsenic-related cancer mortality data for children playing on such equipment. Such data do not exist and, as a practical matter, are unlikely ever to be available, given the impossibility of distinguishing children by their individual historical playground equipment. Given that such data are not available, which of the available data ought we to use?

Although risk data on children playing on CCA-treated playground equipment is not feasible to obtain, direct measurement of exposure data on such children is feasible to obtain. Such a study could be done using urinary arsenic levels of the children as a measure of their arsenic exposure (assuming the marginal increase in arsenic exposure due to this contact can be discriminated from background levels), but such a study has not been done. Such studies have been done for children to assess their absorption of arsenic from environmental arsenic contamination from smelter sites and other arsenic-contaminated areas.

The next best exposure metric that has been developed is from modeling the exposure to children from arsenic transfer to their hands and from their hands to their mouths. A similar process was used over 15 years ago in California (see attached report). In its current report to the Commission, the CPSC staff has estimated that this exposure would be approximately 3 ug arsenic per day of CCA-treated playground equipment use. For the purposes of this report, we will work with that number and ask what sort of risk that exposure represents.

What assessment might be made to determine whether an increased exposure of 3 ug/day for a child is a *de minimis* risk? Here, CPSC has the option of approaching the question either from a scientific basis or from the standpoint of regulatory policy. If CPSC were to seek the most relevant and reliable data set for this examination, we would suggest the 133 US county study database. On the basis of those data (and using white male bladder cancer mortality rates), we would predict that the additional risk did not rise above the *de minimis* risk level, since no increased risk with increased exposure was found in the 3-59 ug/L range. This concentration level is equal to a daily dosage of 3 to 59 ug arsenic (inorganic) for a child drinking one liter of water per day, or a daily dosage of 6 to 118 ug arsenic (inorganic) for an adult drinking two litters of water per day. Thus, when the assessment of risk is based on the most relevant data available, the 3 ug/day dose that CPSC estimates to be due to contact with CCA-treated playground equipment would not be associated with an increased risk of bladder cancer mortality.

As we have explained above, this conclusion is a robust one, supported both by studies that have focused on US populations exposed to arsenic in drinking water and by results of non-US studies concerning low levels of arsenic exposure. Indeed, the conclusions drawn from the US data above coincide with those that would have been drawn if the CPSC had chosen to base its analysis on the data from the SW Taiwan villages with well water arsenic levels below 400 ug/L. These studies also provide data that are relevant to the critical issue of the effect of age at the time of exposure. One of the factors of particular concern to the CPSC is that the exposure they are concerned with is limited to a narrow window during childhood. These ecological studies (SW Taiwan, Latin America, and the US), however, are based on the expectation that the study population had been steady and that the families had been using the local water supply since the beginning of their lives. Thus, these exposures would certainly include the age at exposure interval that concerns the CPSC.

CPSC, of course, has the ability to continue to base their risk assessment on the existing analyses of the EPA and NRC – despite the fact that these analyses are based on data that are far less relevant to, or representative of, the exposure of interest than other available sources. It is understandable that, despite their acknowledging weaknesses in the data used in the EPA and NRC analyses, the CPSC staff would hesitate to revisit issues that have already been considered by other US governmental entities. But by choosing not to look behind these analyses and assess them in light of alternatives, the CPSC itself risks depending on data that are least likely to be either relevant or reliable for assessing cancer risk at the ug/day level that is their principal concern.

IV. Conclusion

Our discussion above outlines some of the reasons why we believe that the EPA and NRC assessment of the health risks from consuming arsenic-containing drinking waters are not based on the most relevant and reliable data available and why therefore they should not serve as the basis of the CPSC's assessment of cancer risk from arsenic ingestion from CCA-treated playground equipment. The preponderance of the evidence indicates that arsenic at US drinking water levels is not a carcinogenic risk or is at least a smaller arsenic risk than the these assessments claim. As we have explained above, risk assessments that suggest otherwise are subject to two distinct lines of criticism regarding the model used and the data.

1. Two published studies (Morales et al. 2000; Guo and Tseng 2000) from Taiwan have shown no change in bladder cancer risks at exposures below several hundreds of ug/L arsenic, exposures far greater than the range of concern (US equivalent exposure of 3 – 50 ug/L). These indicate that the appropriate approach to modeling the relationship between arsenic exposure and the risk of cancer is to use a model that reflects this significant difference instead of assuming that the CSF is constant over the range of possible exposure levels.

2. Published U.S. studies (Engel and Smith 1994; Bates et al. 1995; Lewis et al. 1999) and analyses based on publicly available data are of sufficient sensitivity to demonstrate that there is no effect on bladder cancer mortality rates at U.S. exposure levels. Since these are the most relevant data available for assessing risk to U.S. populations exposed to arsenic, they are a particularly valuable resource for any quantitative risk analysis and should be considered.

The risk assessments upon which the CPSC 2003 assessment is based violate a fundamental rule of scientific study: when a formula has been derived to address the risk at low doses, by whatever method, it is mandatory to compare the prediction with ALL available data whether used in deriving the formula or not. Indeed this was correctly included in the charge to the NRC committee responsible for updating the 1999 *Arsenic in Drinking Water Report*: "Determine whether the EPA risk estimates at 3,5,10 and 20 ug/l are consistent with available scientific information, including information from new studies." Yet this was done in only one page (page 187) out of a 189 page report. Moreover, as noted above, this alleged demonstration of consistency with the US data was inadequate. This essential task was not done well, and the document fails to explain how the available data agree or disagree with the predicted risk. If these had been provided, the major discrepancies that we discuss here would inevitably have been found.

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1969-1970	Montreal Children's Hospital Montreal, Quebec, Canada Residency-Pediatrics Special Project: Electronmicroscopy of Heart Muscle
1968-1969	University of Oregon Medical School Hospital and Associated Clinics Portland, Oregon Internship-Rotating
1964-1968	University of Southern California School of Medicine Los Angeles, California Medical Doctorate (M.D.)
1963-1964	University of Southern California Graduate School Los Angeles, California Master of Science in Biophysics (M.S.) Nerve Action Potential Conduction
1961-1963	University of California, Los Angeles Los Angeles, California Bachelor of Science in Chemistry (B.S.) Radiation Chemistry
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Professional

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1972-1975	Lecturer in International Health and Consultant in Family Planning Development Administrators Training Program

	University of Connecticut Hartford, CT
1971-1973	Medical Director Middletown Free Clinic Middletown, CT
1970-1972	Epidemic Intelligence Service Officer Centers for Disease Control Atlanta, GA Attached to the Connecticut State Department of Health, Department of Preventable Disease and the Connecticut State Tumor Registry
1968	WHO/USPHS Smallpox Eradication Program Kaduna, Nigeria

Public Agency Consultant Activities

1988, 2001	Lecturer, Committee for Advanced Scientific Education U.S. Food and Drug Administration
1998 –	Food Advisory Committee (Temporary Voting Member) U.S. Food and Drug Administration
1995 - Present	Consultant on Vaccine Complications Health Resources and Services Administration, USPHS
1994 - Present	Consultant to government of Hohhot, Inner Mongolia, Health Effects of Arsenic Contaminated Drinking Water
1993 - Present	Consultant to TERIS (Teratology Information Service-University of Washington)
1993	Consultant to the United States Department of Justice on Mustard Gas
1990	Occupational Health Program for Hazardous Waste Inspectors, State of Connecticut, Department of Health Services,
1990	U. S. Justice Department on Epidemiology and Toxic Tort Litigation
1986	Consultant, Halogenated Organics Subcommittee Environmental Health Committee, Science Advisory Board, Environmental Protection Agency
1986	Senate Commerce Hearing on Product Liability, Committee on Commerce, Science and Transportation
1985	Consultant in Epidemiology, Gynecomastia in Haitians, U.S. Department of Justice

1985-1986	Member, Epidemiology Study Section Small Business Incentive Grants Program, National Institutes of Health
1984	Consultant in Drug Effect Epidemiology (Teratology), U.S. Federal Court, Cincinnati, OH
1983	Consultant in Epidemiology, Office of Civil Rights, U.S. Department of Justice
1977	Consultant in Birth Defect Epidemiology, National Center for Health Statistics
1973	USAID Consultant in Family Planning Training for Korea, Thailand, Bangladesh, and Pakistan
1972	Vaccine Morbidity Studies in Amazonian Indians, Yale-PAHO
1971	Short-Term Consultant on Cholera in the Philippines, World Health Organization

Honors

International Council for the Control of Iodine Deficiency Diseases, 2002
American Thyroid Association, Member 2002
Vicennial Medal, Georgetown University, 1995
American College of Occupational and Environmental
Medicine, Fellow 1992
American College of Toxicology, Member 1989
American College of Occupational Medicine, Fellow 1988
American Academy of Occupational Medicine, Fellow 1987
American Occupational Medicine Association, Fellow 1985
American College of Preventive Medicine, Fellow 1983
American Board of Preventive Medicine,
Occupational Medicine 1983 (Board-Certified)
Preventive Medicine 1975 (Board-Certified)
American College of Epidemiology, Charter Fellow 1982
Certified "A" Reader, Coal Workers' Health Surveillance Program, NIOSH 1978
American Academy of Pediatrics, Fellow 1976
American Board of Pediatrics in Pediatrics, 1975 (Board-Certified)
Royal Society of Tropical Medicine, Fellow 1974
Annual Prize of the Society for Epidemiologic Research, May 1972

Academic Appointments

Annual Lectures and Student Proctorships

1988-Present	Graduate Program in Public Health F. Edward Hebert School of Medicine Uniformed Services University of the Health Sciences 4301 Jones Bridge Road Bethesda, MD 20814
1986-Present	Preventive Medicine Residency Program Department of Health Policy and Management School of Hygiene and Public Health Johns Hopkins University 624 N. Broadway Street, Room 482 Baltimore, MD 21205-1996

Committee Assignments

1998 – 2001	Section Council, Epidemiology Section American Public Health Association
1996	Member, Ergonomics Committee American Industrial Hygiene Association
1996	Member, Scientific Committee on Epidemiology International Commission on Occupational Health
1996	Member, Section on Epidemiology American Academy of Pediatrics
1990	Liaison to the American College of Occupational Medicine, American Industrial Hygiene Association
1988	Chairman, AIDS in the Workplace Symposium American Industrial Hygiene Conference
1985-1989	Chairman, Occupational Medicine Committee, American Industrial Hygiene Association
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1976-1978	Secretary-Treasurer, Society for Epidemiologic Research, Washington DC 20007
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Member of Journal Review Panels

Agency for Toxic Substances and Disease Registry Journal
American Industrial Hygiene Association Journal
American Journal of Epidemiology
American Journal of Preventive Medicine
American Journal of Public Health
American Journal of Obstetrics and Gynecology
Annals of Epidemiology
Applied Occupational and Environmental Hygiene
Critical Reviews in Toxicology
Health and Ecological Risk Assessment
Journal of Occupational and Environmental Medicine
Milbank Quarterly
Occupational and Environmental Medicine
Public Health Reports
Reproductive Teratology
Journal of the American College of Occupational and Environmental Medicine
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Memberships in Professional Societies

1990 +	International Society for Environmental Epidemiology
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1988 +	Society of Toxicology
1986 +	American Medical Association
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1984 +	International Commission on Occupational Health (formerly Permanent Commission on Occupational Health)
1984 +	Air Pollution & Hazardous Waste Control Association (formerly APCA)
1984 +	Asthma & Allergy Foundation of America
1984 +	Society for Risk Analysis
1983 +	American Conference of Governmental Industrial Hygienists, Inc.
1982 +	American Public Health Association
1980 +	American Industrial Hygiene Association
1975 +	American Academy of Pediatrics (intermittent)
1970 +	Society for Epidemiologic Research

Publications

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2. **Lamm SH**. Education problems in U.S.A. Lancet 1970 April 18; 1:839.

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INORGANIC ARSENIC: IMPORTANCE OF ACCURATE EXPOSURE CHARACTERIZATION FOR RISK ASSESSMENT

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ABSTRACT

Workers at the Anaconda Smelter in Montana were studied to investigate the patterns of association between exposure to airborne inorganic arsenic and respiratory cancer risk. This group has been previously studied using as exposure categories the qualitative exposure intensity groupings developed by the National Cancer Institute (NCI): "Heavy," "Medium," and "Light." Significant excess risk had been observed in each of these qualitative exposure categories. The exposure data upon which this classification was based have subsequently been lost. In recent years, several quantitative analyses have been attempted to relate the risks in these broad qualitative groupings to available summary exposure data. Analysis of all known exposure data indicates wide variation in the actual exposure levels of the workers within each group, particularly for the "Light" category, and gross overlap in exposure ranges between groups.

Recently, Higgins et al., of the University of Michigan, have developed a rather well defined quantitative exposure classification scheme for the Anaconda work force which represents a decided improvement over the earlier NCI groupings for purposes of quantitative risk assessment. Higgins established four distinct exposure intensity categories associated with non-overlapping quantitative exposure intervals. Analysis using Higgins' classifications demonstrated an excess lung cancer risk only among workers in the high and very high exposure groups (exposure levels 500 $\mu g/m^3$ or greater), but none in

the medium and low exposure groups. In summary, workers who were not exposed to airborne inorganic arsenic levels of 500 $\mu g/m^3$ or greater for at least 30 days evidenced no excess respiratory cancer risk.

Both the qualitative and the quantitative characterization of risk are dependent upon accurate definition of distinct and separate exposure classes. Previous analysis showing an excess risk in the NCI "Light" exposure group probably reflected the inappropriate inclusion of workers with relatively high exposures. However, this analysis, using Higgins' exposure classes, suggests that a threshold may exist for the association between arsenic exposure and respiratory cancer.

KEY WORDS: Arsenic, Respiratory Cancer, Exposure Data, Threshold, Risk Assessment

Several epidemiological studies demonstrating an increased incidence of respiratory cancer among workers with occupational exposure to inorganic arsenic have served as data sources for the carcinogenic risk assessments for arsenic. The Anaconda smelter studies presented by Lee and Fraumeni and subsequently updated by Lee-Feldstein represent the largest known data base. These analyses used a qualitative exposure classification developed in the mid 1960s by the National Cancer Institute (NCI) that was based on unpublished exposure data by Hendricks and Archer. This exposure data has subsequently been lost and thus cannot be validated.

Higgins et al. have recently refined the exposure classification based on all known exposure data and have reassessed the Anaconda mortality risk. Using this well-defined quantitative exposure classification, analysis leads to a new interpretation of the respiratory cancer risk associated with inorganic arsenic exposure at the Anaconda smelter.

The initial epidemiological study of the Anaconda work force using the NCI qualitative exposure classification scheme was published by Lee and Fraumeni in 1969.[1] The cohort contained 8,045 male employees of the Montana copper smelter with at least one year employment between 1938 and 1956, whose mortality was observed from 1938 through 1963. The exposure classification is described briefly in one paragraph which states that based upon unpublished *data of Hendricks* and Archer, workers in the arsenic refinery, the arsenic roaster, the stack cottrells, and the main flue were classified as having "Heavy" exposures; workers in the converters, reverberatory furnace, copper roaster, and acid plant were considered to have "Medium" exposures; and "persons in all other areas" were classified as having "Light" arsenic exposures.

Subsequent updates of the Anaconda cohort have continued to use the same qualitative classification scheme. Lubin et al. (1981) reported the 1964-1977 mortality experience of those workers known to be alive in 1964, but continued to classify workers according to the NCI classification using the pre-1957 work history.[2] Lee (now Lee-Feldstein) also followed up the study group and in 1983 reported the mortality experience of the total group from 1938 through September, 1978, but used the entire work history through 1977 to assign workers to the NCI exposure classification groups.[3,4]

In each of these studies, workers were assigned to the highest exposure category in which they had spent at least one year. Table I demonstrates that significant excess respiratory cancer mortality risk was observed by Lee-Feldstein[4] for all three NCI exposure groups in the total Anaconda cohort.

In 1975, the NCI exposure classifications were reviewed by H. F. Morris, an industrial hygienist at the Anaconda smelter, and an average quantitative value was associated with each category. He concluded that "Lee and Fraumeni divided their exposure categories in about (emphasis added) the correct manner."[5] Morris derived "average" exposure values of 290 $\mu g/m^3$, 580 $\mu g/m^3$, and 11,270 $\mu g/m^3$ for the "Light", "Medium", and "Heavy" categories, respectively (Table I).

These average values were subsequently assigned to the three NCI exposure groups by several researchers and adopted by them in the development of quantitative risk assessments.[6,7,8,9] These risk assessments were primarily performed to determine the risk associated with

TABLE I

NCI EXPOSURE CATEGORIES AND
RESULTS FOR ANACONDA SMELTERMEN
(1938-1977)

Category	Exposure Estimate - 8 hr TWA+		Respiratory Cancer Mortality Risk++	
	Average	Range of Measurements	O/E	SMR
Heavy	11,270 ug/m^3	(2,600-26,070)	33/6.4	514*
Medium	580 ug/m^3	(12-1,458)	93/20.9	446*
Light	290 ug/m^3	(30-2,590)	136/58.9	231*

+ Morris, 1975 (5)
++Lee-Feldstein, 1983 (4)
* p <.01

relatively low to medium exposure levels (0-500 $\mu g/m^3$), but were greatly dependent on the risks found at rather heavy exposures (up to 26,000 $\mu g/m^3$). The assessments applied the linear, no threshold model to the risk observed in the NCI exposure categories paired with the Morris "average" exposure values. This resulted in predictions of significant excess risk at even the lowest arsenic exposure levels. These risk assessments, however, assumed that Morris' data were applicable to the NCI exposure classifications and that these classifications adequately described the worker's exposure. Furthermore, they assumed that the data were used consistently, and grouped the workers into separate and distinct exposure categories. Review of Morris' data revealed that these assumptions did not hold.

There appear to have been some changes in the exposure classifications between the original Lee and Fraumeni 1969 report[1] and the updated Lee-Feldstein 1983 report.[3,4] Both studies reported analyses for the same 8,045 men. The earlier paper reported 3,257 men as having no greater than "Light" exposure levels in their work experience. The later paper reported 4,448 workers as having no greater than "Light" exposure levels in their work experience (Table II). This discrepancy has yet to be explained. The ascertainment that all workers in the "Light" exposure group only had "Light" exposure is, however, most important to the assessment of lung cancer risk at low

TABLE II

NUMBER OF WORKERS BY EXPOSURE CATEGORY FOR LEE AND FRAUMENI AND LEE-FELDSTEIN STUDIES

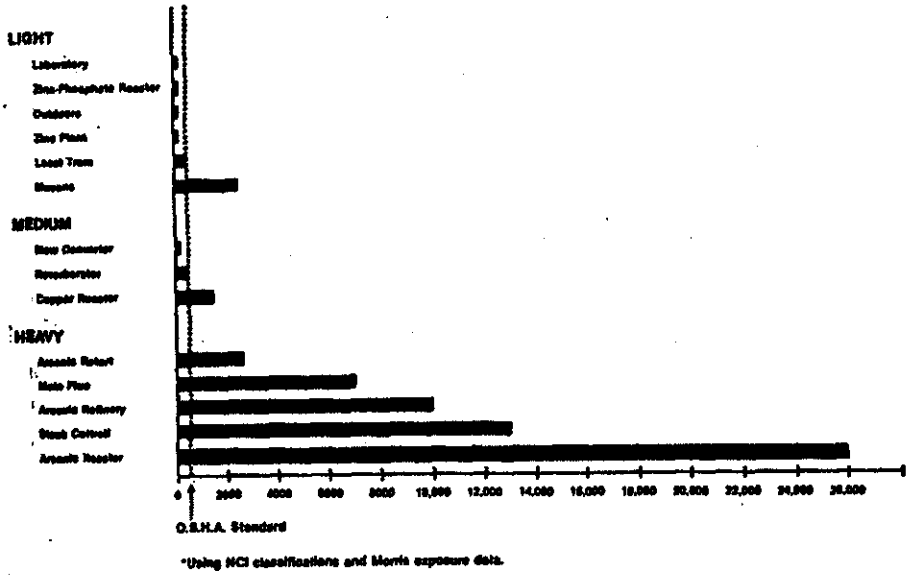
	Lee and Fraumeni[+] (1969)	Lee-Feldstein[++] (1983)	Percent Change
Heavy	402	451	+12%
Medium	1,526	1,585	+4%
Light	3,257	4,448	+37%
Excluded	2,862	1,561	-54%
TOTAL	8,047**	8,045	

+ Lee and Fraumeni, 1969 (1)
++Lee-Feldstein, 1983 (4)
* These workers are described as having worked less than 12 months in their category of maximum arsenic exposure in both studies. However, recent personal communications reveal that other unidentified workers were excluded from the study as well.
**Two female workers included in the Lee and Fraumeni study were excluded in the Lee-Feldstein study.

levels of arsenic exposure. It may be that some work areas have been reclassified as "Light," having possibly been previously classified as having unknown exposure levels.

The "Heavy" and "Medium" NCI exposure groups represent more homogeneous groups than the NCI Light group. This is because these groups were restricted to those with at least one year of "Heavy" or "Medium" exposure. Workers in the "Light" group had widely varied exposures. For example, the exposure measurements compiled by Morris, as shown in Figure 1, reveal that the exposures of the masons were far greater than any others in the "Light" category, with an average of 2,900 $\mu g/m^3$. The 2,900 $\mu g/m^3$ average for the masons was derived from work area measurements ranging from over 500 $\mu g/m^3$ to almost 13,000 $\mu g/m^3$. Clearly, the mortality experience of this group is ill-suited to assess the risk associated with exposures of 0-500 $\mu g/m^3$.

Similar classification problems are apparent for work areas where quantitative measurements were not available. For example, the NCI scheme assigned maintenance, surface, and shop employees to the Light



*Using NCI classifications and Morris exposure data.

Figure 1

Area Average Arsenic Concentrations
For Montana Smelter Departments

group, although they, similar to the masons, worked in many different areas of the plant, and would have been exposed to relatively high levels during the course of their work. The NCI classification scheme also included slag workers in the "Light" exposure group, although the reverberatory furnace area where these employees worked was characterized by higher exposures.

Due to the imprecision in the NCI "Light" exposure category, the conclusion that the risk observed in that group is due to workers with relatively low (0-500 $\mu g/m^3$) exposure is not well supported. In contrast, the quantitative classification system developed by Higgins is better suited to examine the risk associated with these low levels of exposure to airborne inorganic arsenic. Higgins divided jobs at the Anaconda smelter into four exposure groups with associated quantitative exposure values: low (0-99 $\mu g/m^3$); medium (100-499 $\mu g/m^3$); high (500-4,999 $\mu g/m^3$); and very high (above 5,000 $\mu g/m^3$).[10,11] In several pages of text and tables, Higgins explained the extensive exposure data he obtained from the Montana State Health Department, the Anaconda Company, and other sources. He also described the system used for deriving average exposures for job areas and the assignments made for each area in the study. The average exposure in each of Higgins' four groups and the range of averages within each is shown in Table III and Figure 2. Significantly, the ranges do not overlap and are much narrower than the NCI groups, indicating greater homogeneity of exposure experience within the groups. Table IV compares the Higgins and NCI classification schemes and reveals the differences in assignment of several groups of workers, including masons, maintenance, surface, shop, slag, unknown, converter, casting, and acid plant.

On the basis of this more precise exposure classification system, Higgins analyzed the mortality of a stratified, random sample of 1,800 workers out of the entire 8,045 man Anaconda cohort. This sample included all workers who worked more than two years in the NCI "Heavy" category, and a 20 percent random sample of the remainder. Higgins linked individual workers to their entire in-plant exposure histories. Workers were classified on the basis of the highest exposure area to which they were assigned for at least 30 days (30-day ceiling classification method). Workers were also separated into four cumulative exposure categories (less than 500 $\mu g/m^3$ - years; 500-2,000 $\mu g/m^3$ - years; 2,000-12,000 $\mu g/m^3$ - years; and 12,000 or more $\mu g/m^3$ - years).

Higgins' 30-day ceiling method of classifying individuals into exposure groups is analogous to the NCI one-year ceiling method, but greater care has been given to the separation of the exposure groups. Analysis of the Higgins data leads to a very different conclusion than that of the earlier NCI classification scheme. While the NCI classification scheme indicates a rough dose-response relationship among the three intensity exposure groups (Figure 3), the Higgins exposure category analysis (Figure 4) makes clear that workers whose 30-day ceiling exposures did not exceed 500 $\mu g/m^3$ have no excess lung cancer risk

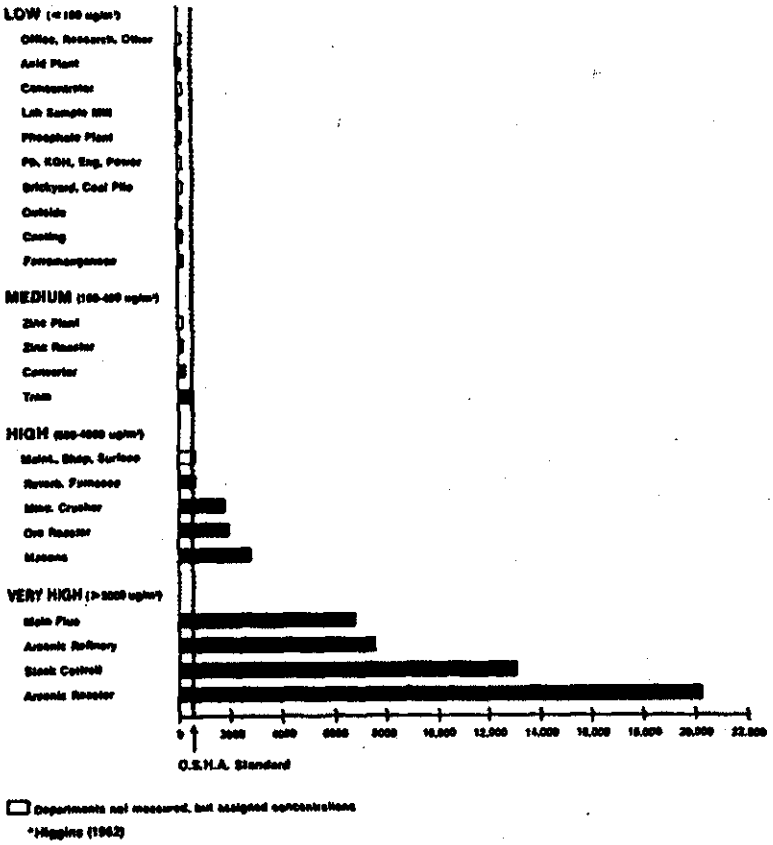


Figure 2

Average Arsenic Concentrations
For Montana Smelter Departments
By 30-Day Ceiling Arsenic Categories*

(i.e., SMR is not greater than 100). These data suggest that the excess risk observed in the NCI "Light" group is due to the inclusion of individuals who had high intensity exposures.

This result is confirmed when the Higgins data are analyzed in terms of the risk associated with various cumulative exposure levels.