both children and adults were exposed to extremely high levels of arsenic but no increases in leukemia were noted (Chen *et al.*, 1985; Chen *et al.*, 1992). Although the number of studies that explicitly compare the toxicity of arsenic in adults and children is limited, existing data and analyses of lifetime cancer risk do not indicate a need for additional toxicity uncertainly factors to address child-specific sensitivity.

4 Comments on Risk Characterization Issues

This section includes comments on issues discussed in Tab I.

4.1 Validity of Sensitivity Analysis

In the risk assessment conducted by CPSC staff a deterministic approach was used, in which a single value was selected for each input parameter and was used to generate risk assessment results. To assess the potential influence of various sources of uncertainty and variability in input parameters on the risk assessment results, CPSC staff conducted a focused sensitivity analysis, applying alternative low-end and high-end parameter estimates in the risk algorithms and examining the impacts of the alternative values on the risk assessment results.

CPSC staff correctly determined that currently available data are insufficient to support a meaningful probabilistic risk assessment approach. Instead, the approach selected by CPSC staff for evaluating the influence of variability and uncertainty on the risk assessment results (*i.e.*, a deterministic risk assessment coupled with a focused sensitivity analysis) makes better use of available data. In addition, such an approach provides clearer and more readily interpreted analyses exploring the influence of various sources of uncertainty on the risk assessment results.

Although CPSC staff selected an appropriate framework for evaluating the range of plausible risk assessment results, several deficiencies exist in the way in which their evaluations were documented, implemented, and interpreted. For example, the documentation of the basis for selecting the input parameters applied in the sensitivity analysis is limited in many cases. This documentation should be expanded to provide more detail regarding the basis for the selected range of parameter values and, where available, should provide quantitative information presenting the segment of the underlying complete range of possible values that the selected range is intended to represent (*e.g.*, which percentiles of the complete range that the range applied in the sensitivity analysis corresponds to).

Some of the specific ranges applied in the sensitivity analysis also are implausible or inappropriate. As discussed above, the RBA value applied in the risk assessment conducted by CPSC staff to estimate the relative bioavailability of ingested dislodgeable arsenic (1.0) is overly conservative and fails to reflect substantial available data indicating that absorption of dislodgeable arsenic is likely to

be significantly less than absorption of arsenic dissolved in water. Similarly, the range of potential RBA values applied in the sensitivity analysis (0.2 to 1) is inappropriate. Based on available data, a more reasonable range of values is 0.1 to 0.7 (Gradient, 2001b). As discussed above, the high-end estimate of the hand transfer efficiency factor used in the sensitivity analyses (7) is also implausible and should be replaced by a more reasonable high-end value of 1. Finally, the high-end value for the concentration of dislodgeable arsenic on hands (300 μg/handload) is not supported by the available data. Instead, a high-end value for this parameter of approximately 3-fold less is more plausible and better supported by available data.

By using parameter estimates in the sensitivity analyses that overstate the plausible range of values for the input parameters, the sensitivity analysis approach applied by CPSC staff provides misleading perspectives on the results of the risk assessment. Specifically, when input parameter ranges that are unrealistically high are applied in the sensitivity analysis, the resulting risk estimates are skewed towards unrealistically high values. When compared to the results of the baseline risk assessment, these skewed high-end estimates then suggest that risk estimates could be substantially higher than is likely in light of more careful consideration of available scientific data. This bias is compounded if the relative degree of uncertainty reflected in the ranges selected for the various input parameters is not adequately accounted for when presenting the results of the sensitivity analyses. For example, the CPSC staff analysis notes that behavior corresponding to the high-end HTE (7) is "less likely" and that "CPSC staff has less confidence in the estimate based on the high value of soil ingestion." This lower degree of confidence needs to be retained in discussions of the sensitivity analysis and risk assessment results. By contrast, the presentation of the sensitivity analysis results (e.g., on p. A-4) presents all the results as if they have equal validity. The text and accompanying table should reflect the relative plausibility and likelihood of the various alternative risk estimates that were derived.

4.2 Modifications to Risk Assessment Results

As reflected in these comments, use of more technically sound exposure assumptions and consideration of additional context for carcinogenic risk estimates (including controversies surrounding procedures for quantifying carcinogenic risks associated with ingested arsenic and typical risk levels associated with natural or regulated exposures to arsenic) would substantially alter the perspective on potential adverse health risks presented in the risk analyses prepared by CPSC staff. The risk analyses conducted by CPSC staff suggest that potential risks associated with children's exposures to arsenic

through contact with playground equipment built with CCA-treated wood range from 2×10^{-6} to 1×10^{-4}. This risk assessment presents a misleading perception of likely actual risks for a number of reasons.

First, the high end of this range is largely driven by the unreasonable high-end CSF of 23 $(mg/kg\text{-}day)^{-1}$, which, as demonstrated in detail in these comments, is implausible and inconsistent with available epidemiological evidence in U.S. populations. Simply by eliminating this technically unsupported value from the CPSC staff risk estimates, the high end of the range of risk estimates presented by CPSC staff would be reduced by at least a factor of 6, to 2×10^{-5}. As noted, correction of an apparent error in the CSF calculations conducted by CPSC staff would reduce this estimate by an additional factor of 2, to 1×10^{-5}. Thus, it is clear that this single highly uncertain toxicity value is a primary factor contributing to the misimpression of elevated risks associated with this arsenic exposure source.

Second, these comments have identified numerous highly conservative assumptions that were applied in the CPSC staff risk analyses and have, in many cases, recommended more scientifically-supported modifications to the risk assessment approaches, many of which would alter the quantitative results of the risk analyses. As discussed in more detail in the following section, additional contextual issues also exist which should be considered in conducting the CPSC staff risk analyses and which would influence interpretation of the results. Consideration of these factors would substantially alter the perspective on potential health risks posed by the exposure scenarios addressed in these comments.

Specific modifications to the risk calculations recommended in these comments include adjusting the assumption regarding relative bioavailability of arsenic from ingested dislodgeable residue and by incorporating consideration of the influence of exposure time on exposure estimates. Specifically, the RBA assumption used in the CPSC staff risk analyses (100%) ignores the substantial body of evidence indicating that absorption of ingested arsenic in a variety of solid matrices, including dislodgeable residue from treated wood, is likely to be significantly less than absorption of dissolved arsenic in water. As reviewed in these comments, a more scientifically sound estimate of the relative bioavailability of arsenic from dislodgeable residue is unlikely to exceed 50% and may be as low as 10%. Similarly, the failure of the CPSC staff risk analyses to consider the influence of exposure time on exposures associated with a localized source such as a structure built of treated wood also leads to erroneously elevated exposure and risk estimates. As described in these comments, use of a fractional intake estimate to reflect this factor would reduce exposure estimates by a factor of 4-12 as a conservative estimate. Specifically, a fractional intake estimate of 0.25 reflects the assumption that children spend 2.9 hours/day playing outdoors (the

90th percentile value from a national survey) and that all of this time includes contact with a structure built of treated wood. Using mean data, a fractional intake estimate of 0.08 would reflect the assumption that children spend 1 hour/day playing outdoors in contact with a structure built of treated wood. Modified risk estimates reflecting these three specific quantitative recommendations (*i.e.*, eliminating the unsustainable high-end CSF and modifying the assumptions for the RBA and fractional intake) are summarized in Table 4-1.

Table 4-1
Summary of Modified Risk Estimates

	Unmodified CPSC Staff Risk Estimates	Modified Risk Estimates
Low End[a]	2×10^{-6}	2×10^{-8} to 3×10^{-7}
High End[b]	1×10^{-4}	2×10^{-7} to 2×10^{-6}

Notes:

(a) Low-end CPSC staff estimates assume a CSF of 0.41 (mg/kg-day)$^{-1}$, an RBA of 100%, and no fractional intake factor. Low-end modified risk estimates assume a CSF of 0.41 (mg/kg-day)$^{-1}$, an RBA of 10% or 50%, and a fractional intake factor of 0.08 or 0.25

(b) High-end CPSC staff estimates use a CSF of 23 (mg/kg-day)$^{-1}$, an RBA of 100%, and no fractional intake factor. High-end modified risk estimates assume a CSF of 3.7 (mg/kg-day)$^{-1}$, an RBA of 10% or 50%, and a fractional intake factor of 0.08 or 0.25

As shown in Table 4-1, incorporating only these three recommendations substantially changes the perspective on the range of risks associated with the exposure scenario examined in the risk analyses conducted by CPSC staff. Specifically, instead of suggesting that a risk estimate of 2×10^{-6} is likely to represent the low-end of the calculated risk range, the modified risk estimates indicate that this value more plausibly represents the high end of the risk range. If the apparent CSF calculation error noted above were corrected (*i.e.*, if a CSF value of 1.9 [mg/kg-day]$^{-1}$ were used), this value would be reduced by an additional factor of 2, to 1×10^{-6}. Moreover, the plausible low end of the risk range is reduced by two orders of magnitude to 2×10^{-8}. Even with these modifications, numerous conservative elements remain in this calculation. For example, as discussed above, all of the CSF values for ingested arsenic are likely to overestimate risks for U.S. populations exposed to low levels of arsenic. Similarly, the exposure times used to estimate the fractional intake factor are likely to represent a conservative estimate of the typical amount of time that children spend playing on playground equipment built of treated wood. As a result, risk estimates for this scenario are likely to be less than those suggested by the modified calculations. Thus, instead of suggesting that the risk estimates associated with this exposure scenario

almost certainly exceed a risk level of 1×10^{-6}, more scientifically-sound risk calculations indicate that the risk estimates for this exposure scenario are highly unlikely to exceed 1×10^{-6}.

4.3 Context for Risk Assessment Results

Because arsenic is ubiquitous in the environment from a variety of natural sources, an important part of any risk assessment for arsenic exposures is consideration of the studied exposures in the context of exposures resulting from natural sources (*e.g.*, dietary sources) as well as other regulated sources (*e.g.*, drinking water). As discussed below, consideration of these factors indicates that, even if the arsenic intake estimates generated by CPSC staff are not adjusted to reflect more scientifically-sound assumptions, intake of arsenic associated with children's contact with play sets built of CCA-treated wood is relatively small compared with other exposure sources. As a result, reductions in this exposure source will not significantly influence the magnitude of children's potential overall exposures to arsenic or any associated health risks.

Several studies have estimated the dietary intake of inorganic arsenic by children and adults. In one study, Yost *et al.* (1998) quantified the adult dietary intake of inorganic arsenic using data from the U.S. Food and Drug Administration's (FDA) Total Diet Study (conducted in 1982 to 1990), which surveyed more than 5,000 food types from 100 locations across the U.S. to estimate the typical U.S. diet and total arsenic concentrations in food. These data were combined with data from a 1986 study by the Ontario Ministry of the Environment that measured the percentage of total arsenic consisting of inorganic arsenic in 14 types of food. Based on these data, the typical dietary intake of inorganic arsenic intake was estimated to be 8.3 μg/day for infants, 9.4 μg/day for toddlers, and 14.0 μg/day for adults, respectively.

A later study by Schoof *et al.* (1999a) quantified the adult dietary intake of inorganic arsenic using two other datasets. Data from the U.S. Department of Agriculture's (USDA) Continuing Survey of Food Intake by Individuals (CSFII) for 1989-1992 were used to estimate the type and quantities of foods consumed in the U.S. Arsenic concentration data were obtained from a market basket survey by Schoof *et al.* (1999b), in which 40 food commodities purchased in 4 locations were analyzed for their inorganic and total arsenic content. The food types included in this survey were selected to represent those food sources thought to contribute more than 90% of total dietary arsenic intake. As a result, this survey provided a more extensive characterization of arsenic concentrations in potential dietary sources than the OME survey. Based on these data, the mean dietary inorganic arsenic exposure for an adult was

estimated as 3.2 μg/day, with a median of 2.4 and a 90th percentile of exposure of 6.7 μg/day (Schoof *et al.*, 1999a).

The arsenic data generated in the Schoof *et al.* (1999b) market basket study were subsequently applied to estimate children's dietary intake of inorganic arsenic (Yost *et al.*, 2002). Combining the market basket data with the FDA estimates of total arsenic intake, the dietary intake of inorganic arsenic was estimated to range from 3.4 to 8.5 μg/day for children and 3.9 to 7.2 μg/day for toddlers. Using a dietary analysis software package, the USDA CSFII data regarding food consumption patterns, and arsenic data from the Schoof market basket survey, dietary inorganic arsenic intake for young children was estimated to have a mean value of 3.2 μg/day and a high-end (99th percentile) value of 9.4 μg/day.

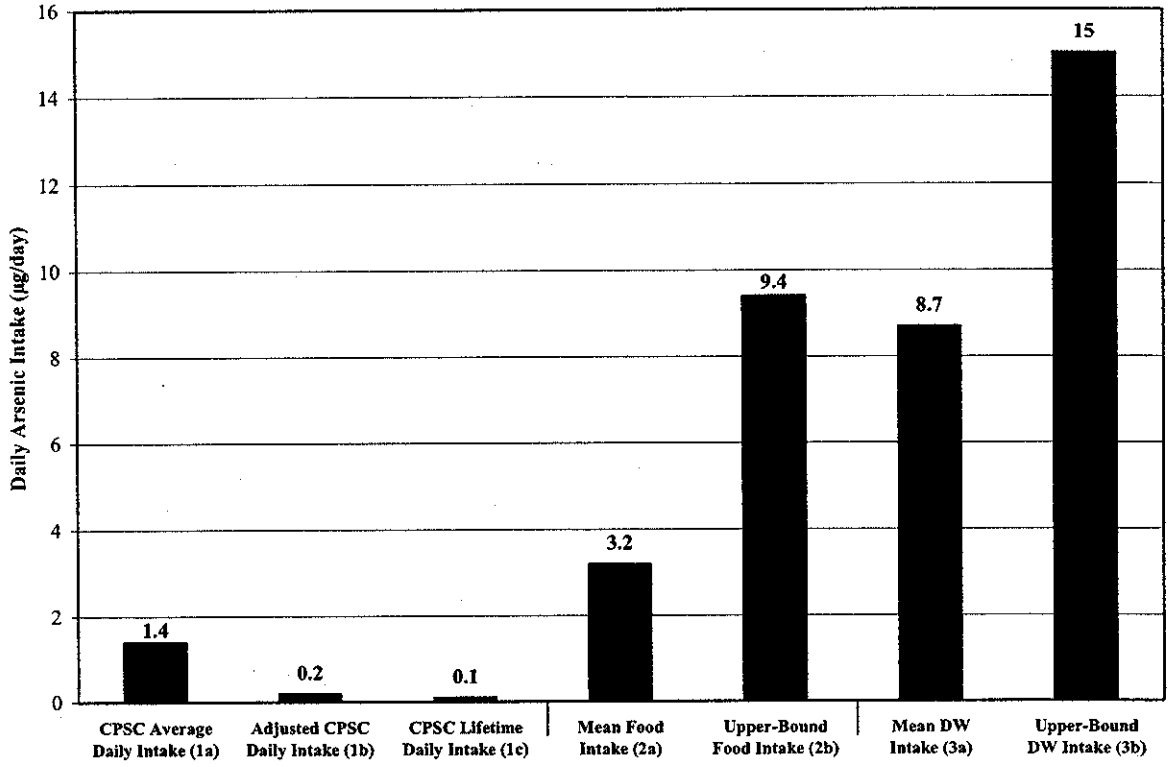
As noted above, another important natural source of exposure to inorganic arsenic is through drinking water. The current MCL for arsenic in drinking water is 10 μg/L, a value established by EPA as protective of public health. Assuming a mean drinking water consumption rate for young children of 0.87 L/day, the arsenic intake for a child consuming water containing arsenic concentrations equal to the allowable MCL concentration would be 8.7 μg/day. Using an RME estimate of drinking water consumption for a young child, the arsenic intake from this source would be 15 μg/day. Although a child's actual arsenic intake will vary depending on the arsenic concentrations present in his water supply, these estimates reflect the arsenic intakes that correspond to the health protective drinking water standard set by EPA.

Figure 4-1 compares the inorganic arsenic intake estimated by CPSC staff for children's exposures to play sets built of treated wood with a modified intake estimate (reflecting conservative application of several recommended changes described in these comment), intake estimates from dietary sources, and intake estimates corresponding to EPA's drinking water standard. As can be seen, inorganic arsenic intake associated with food and water is greater than that estimated by CPSC staff for children's exposures to treated wood. This difference is even more striking if average lifetime exposures are considered, the typical exposure estimate of primary concern when assessing potential carcinogenic health risks. For arsenic intake from dietary sources or drinking water, such intakes will likely continue throughout an individual's lifetime and intake is likely to increase. By contrast, the types of exposures estimated by CPSC staff for small children on treated wood play sets are likely to persist at that level for only a short period of time (approximately 5 years out of a 70-year lifetime). Thus, the lifetime-averaged intake of inorganic arsenic from this source (0.1 μg/day) will be an order of magnitude less than the

annual-average daily intake (1.4 μg/day) and will be approximately a factor of 30 to 100 less than corresponding estimates of intake from food or drinking water. As noted above, the intake estimates calculated by CPSC staff are likely to overestimate children's potential exposures to arsenic from play sets built of treated wood. As a result, these considerations further support the conclusion that arsenic exposures associated with children's contacts with play sets built of treated wood are likely to contribute negligibly to children's overall arsenic exposures. Moreover, these considerations indicate that reductions in children's arsenic exposures from this source are unlikely to substantially influence their overall inorganic arsenic exposures or consequent health risks.

Figure 4-1

Comparison of Daily Intakes of Inorganic Arsenic



Notes:

(1a) *CPSC staff average daily intake is calculated by averaging the daily intake (3.3 µg/day) over a one-year period (i.e., daily intake times 156 days/year of exposure divided by 365 days/year).*

(1b) *Adjusted CPSC staff daily intake reflects application of several of the modifications recommended in these comments (i.e., application of an RBA of 50% and a fractional intake factor of 0.25).*

(1c) *CPSC staff lifetime daily intake is calculated by averaging the CPSC staff daily intake (3.3 µg/day) over a 70-year lifetime.*

(2a) *Mean food intake is based on mean dietary intake for a child ages 2-5 years (Yost et al., 2002).*

(2b) *Upper-bound food intake is based on 99th percentile intake for a child ages 2-5 years (Yost et al., 2002).*

(3a) *Mean drinking water (DW) intake is based on mean intake estimated for a child ages 3-5 years old (USEPA, 1997b) consuming drinking water containing arsenic concentrations equal to the arsenic MCL of 10µg/L.*

(3b) *Upper-bound DW intake is based on 90th percentile intake estimated for a child 3-5 years old (USEPA, 1997b) consuming drinking water containing arsenic concentrations equal to the arsenic MCL of 10µg/L.*

5 References

Abernathy, C.O., Y.P Liu, D. Longfellow, H.V. Aposhian, B.D. Beck, B. Fowler, R. Goyer, R. Menzer, T. Rossman, C. Thompson, and M. Waalkes. 1999. Arsenic: Health effects, mechanisms of actions, and research issues. *Environ. Health Perspect.* 107:593-597.

Aposhian, H.V. 2001. "Bioavailability of Dislodgeable CCA." Unpublished report to FDA.

Axelson, O., M. Fredrikson, G. Akerblom, and L. Hardell. 2002. Leukemia in childhood and adolescence and exposure to ionizing radiation in homes built from uranium-containing alum shale concrete (Abstract). *Epidemiology* 13(2):146-150. Downloaded from http://www.ncbi.nlm.nih.gov/entrez on March 19, 2003.

Bates, M.N., A.H. Smith, and K.P. Cantor. 1995. Case-control study of bladder cancer and arsenic in drinking water. *Am. J. Epidemiol* 141:523-530.

Brown, K.G., H.R. Guo, T.L. Kuo, and H.L. Greene. 1997. Skin cancer and inorganic arsenic: Uncertainty-status of risk. *Risk Anal.* 17 (1):37-42.

Buchet, J.P.,H. Roels, R. Lauwerys, F. Bruax, F. Claeys-Thoreau, A. Lafantaine, and G. Verduyn. 1980. Repeated surveillance of exposure to cadmium, manganese, and arsenic in school-age children living in rural, urban, and nonferrous smelter areas in Belgium. *Environmental Research* 22:95-108.

Budy, A.M. and M.N. Rashad. 1976. Cancer mortality among carpenters in Hawaii. In *Prevention and Detection of Cancer: Proceedings of the Third International Symposium on Detection and Prevention of Cancer: Volume I - Etiology, April 26 to May 1, 1976, New York* (Ed: H.E. Nieburgs), Marcel Dekker, Inc., New York. pp. 901-907.

Camann, D.E., T.K. Majumadar, and P. Geno. 1995. "Determination of Pesticide Removal Efficiency from Human Hands Wiped with Gauze Moistened with Three Salivary Fluids." Final report to EPA by Man Tech under Contract 68-D5-0049. (As cited in USEPA, 1999.)

Carratelli, M., L. Porcaro, M. Ruscica, E. De Simone, A.A. Bertelli, and M.M. Corsi. 2001. Reactive oxygen metabolites and prooxidant status in children with Down's syndrome. *Int. J. Clin. Pharmacol. Res.* 21(2):79-84.

Chappell, W.R., B.D. Beck, K.G. Brown, R. Chaney, C.R. Cothern, K.J. Irgolic, D.W. North, I. Thornton, and T.A. Tsongas. 1997. Inorganic arsenic: A need and an opportunity to improve risk assessment. *Environ. Health Perspect.* 105(10):1060-1067.

Chen, C.J., Y.C. Chuang, T.M. Lin, and H.Y. Wu. 1985. Malignant neoplasms among residents of a blackfoot disease-endemic area in Taiwan: high-arsenic artesian well water and cancers. *Cancer Res.* 45:5895-5899.

Chen, C.J. and C.J. Wang. 1990. Ecological correlation between arsenic level in well water and age-adjusted mortality from malignant neoplasms. *Cancer Res.* 50:5470-5475.

Chen, C-J., C.W. Chen, M-M. Wu, and T-L. Kuo. 1992. Cancer potential in liver, lung, bladder and kidney due to ingested inorganic arsenic in drinking water. *Br. J. Cancer* 66:888-892.

Chiou, H.Y., S.T. Chiou, Y.H. Hsu, Y.L. Chou, C.H. Tseng, M.L. Wei, and C.J. Chen. 2001. Incidence of transitional cell carcinoma and arsenic in drinking water: A follow-up study of 8102 residents in an arseniasis-endemic area in Northeastern Taiwan. *Am. J. Epidemiol.* 153(5):411-418.

Clewell, H., P.R. Gentry, H.A. Barton, A.M. Shipp, J.W. Yager, and M.E. Andersen. 1999. Requirements for a biologically realistic cancer risk assessment for inorganic arsenic. *Int. J. Toxicol.* 18(2):131-147.

Concha, G., B. Nermell, and M. Vahter. 1998. Metabolism of inorganic arsenic in children with chronic high arsenic exposure in northern Argentina. *Environ. Health Perspect.* 106(6):355-359.

Consumer Product Safety Commission (CPSC). 2003. "Briefing Package: Petition to Ban Chromated Copper Arsenate (CCA)-Treated Wood in Playground Equipment (Petition HP 01-3)." February.

Cui, W. 2001. "Surface Arsenic Analysis of Commercial CCA Treated Southern Pine." Department of Forestry, Michigan State University.

Cuzick, J., P. Saisieni, and S. Evans. 1992. Ingested arsenic, keratoses, and bladder cancer. *Am J Epidemiol.* 136(4):417-421.

Decker, P., B. Cohen, J.H. Butala, and T. Gordon. 2002. Exposure to wood dust and heavy metals in workers using CCA pressure-treated wood. *Am. Ind. Hyg. Assoc. J.* 63(2):166-171.

Eaton, D.L. and C.D. Klaassen. 1996. Principles of toxicology. In *Casarett and Doull's Toxicology: The Basic Science of Poisons. Fifth Edition* (Ed: C.D. Klaassen), McGraw-Hill, New York, pp. 13-33.

Engel, R.R. and A.H. Smith. 1994. Arsenic in drinking water and mortality from vascular disease: an ecologic analysis in 30 counties in the United States. *Arch. Environ. Health* 49:418-427.

Fenske, R.A., K.G. Black, K.P. Elkner, C. Lee, M.N. Methner, and R. Soto. 1990. Potential exposure and health risks of infants following indoor residential pesticide applications. *Amer. Jour. Publ. Health* 80:689-693. (As cited in USEPA, 1999.)

Ferreccio, C., C. Gonzalez, V. Milosavjlevic, G. Marshall, A.M. Sancha, and A.H. Smith. 2000. Lung cancer and arsenic concentrations in drinking water in Chile. *Epidemiology* 11(6):673-679.

Florida Physicians Arsenic Workgroup (FPAW). 2002. http://www.preservedwood.com/safety/0730cca-docs1.html. Site visited February 27, 2003.

Freeman, N.C.G, M. Jimenez, K.J. Reed, S. Gurunathan, R.D. Edwards, A. Roy, J.L. Adgate, E.D. Pellizzari, J. Quackenboss, K. Sexton, and P.J. Lioy. 2001. Quantitative analysis of children's microactivity patterns: The Minnesota Children's Pesticide Exposure Study. *J. Expos. Anal. Environ. Epid.* 11:501-509.

Frost, F., G. Craun, and K.G. Brown. 2002. Detection of excess arsenic-related cancer risks. *Environ. Health Perspect.* 110(1):A12-A13.

Gradient Corporation (Gradient). 2001a. "Comments on EPA Background Documents for October 23-25, 2001 Science Advisory Panel Meeting Regarding CCA-Treated Wood". Prepared for Arch Wood Protection, Inc. and Osmose, Inc. October 17.

Gradient Corporation (Gradient). 2001b. "Evaluation of Human Health Risks from Exposure to Arsenic Associated with CCA-Treated Wood". Prepared for Arch Wood Protection, Inc. and Osmose, Inc. October 5.

Guo, H.R., S.R. Lipsitz, H. Hu, and R.R. Monson. 1998. Using ecological data to estimate a regression model for individual data: The association between arsenic in drinking water and incidence of skin cancer. *Environ. Res.* 79:82-93.

Harrington, J.M., J.P. Middaugh, D.L. Morse, and J. Housworth. 1978. A survey of a population exposed to high concentrations of arsenic in well water in Fairbanks, Alaska. *Am. J. of Epidemiology* 108:377-385. (As cited in Valberg *et al.*, 1998).

Houlihan, J. 2003. Testimony Before the Consumer Product Safety Commission, CCA Ban Petition HP01-3. Environmental Working Group. March 17.

Hsueh, Y.M., H.Y. Chiou, Y.L. Huang, W.L. Wu, C.C. Huang, M.H. Yang, L.C. Lue, G.S. Chen, and C.J. Chen. 1997. Serum B-carotene level, arsenic methylation capability, and incidence of skin cancer. *Cancer Epidemiol. Biomarkers Prev.* 6(8):589-596.

Infante-Rivard, C., E. Olson, L. Jacques, and P. Ayotte. 2001. Drinking water contaminants and childhood leukemia. *Epidemiol.* 12:13-19.

Jovanovic, S.V., D. Clements, and K. MacLeod. 1998. Biomarkers of oxidative stress are significantly elevated in Down syndrome. *Free Radic. Biol. Med.* 25(9):1044-1048. December.

Kalman, D.A., J. Hughes, G. van Belle, T. Burbacher, D. Bolgiano, K. Coble, N.K. Mottet, and L. Krajinovic, M., D. Labuda, and D. Sinnett. 2001. Childhood acute lymphoblastic leukemia: Genetic determinants of susceptibility and disease outcome. *Rev. Environ. Health* 16(4):263-279.

Lewis, D.R., J.W. Southwick, R. Ouellet-Hellstrom, J. Rench, and R.L. Calderon. 1999. Drinking water arsenic in Utah: A cohort mortality study. *Environ. Health Perspect.* 107(5):359-365.

Lu, C., and R.A. Fenske. 1999. Dermal transfer of chlorpyrifos residues from residential surfaces: comparison of hand press, hand drag, wipe, and polyurethane foam roller measurements after broadcast and aerosol pesticide applications. *Environ. Health Perspect.* 107(6):463-467. (As cited in USEPA, 1999.)

Maine Department of Human Services (MEDHS). 1998. Evaluation of children's health hazards from arsenic exposure associated with the use of CCA-treated wood in residential structures and municipal playgrounds (Draft). August.

Mazumder, D.N.G., J.D. Gupta, A. Santra, A. Pal, A. Ghose, and S. Sarkar. 1997a. Chronic arsenic toxicity in West Bengal -- the worst calamity in the world. *Journal of the Indian Medical Association* 96(1):4-7, 18.

Mazumder, D.N.G., R. Haque, N. Ghosh, B.K. De, A. Santra, D. Chakraborty, and A.H. Smith. 1998. Arsenic levels in drinking water and the prevalence of skin lesions in West Bengal, India. *International Journal of Epidemiology* 27(5): 871-877.

Midgett, J.D. 2003a. Memo to P. Bittner re: Children's Contact with Playground Structures. January 13.

Midgett, J.D. 2003b. Memo to P. Bittner re: Playground Usage Estimate for CCA-Wood Risk Assessment. January 13.

Moore, L.E., M. Lu, and A.H. Smith. 2002. Childhood cancer incidence and arsenic exposure in drinking water in Nevada. *Archives of Environ. Health* 57(3):201-206.

Morales, K.H., L. Ryan, T-L. Kuo, M-M. Wu, and C-J. Chen. 2000. Risk of internal cancers from arsenic in drinking water. *Environ. Health Perspectives* 108(7):655-661.

Morton, W., G. Starr, D. Pohl, J. Stoner, S. Wagner, and P. Weswig. 1976. Skin cancer and water arsenic in Lane County, Oregon. *Cancer* 37:2523-2352.

National Cancer Institute (NCI). 2002. "SEER Cancer Statistics Review, 1973-1999" (Eds: L.A.G. Ries, M.P. Eisner, C.L. Kosary, B.F. Hankey, B.A. Miller, L. Clegg, B.K. Edwards). National Cancer Institute, SEER Program. Downloaded from http://seer.cancer.gov/csr/1973_1999/.

National Institute of Health (NIH). 2002. Facts about Down's syndrome. Downloaded from http://www.nichd.nih.gov/publications/pubs/downsyndrome/down.htm on March 21, 2003. Last updated on September 3, 2002.

National Research Council (NRC). 2001. *Arsenic in Drinking Water: 2001 Update,* National Academy Press, Washington, DC.

National Research Council (NRC). 1999. *Arsenic in Drinking Water*, National Academy Press, Washington, DC. Subcommittee on Arsenic in Drinking Water. 310 pp.

Ng, J.C. and M.R. Moore. 1996. Bioavailability of arsenic in soils form contaminated sites using a 96 hour rat blood model. In *The Health Risk Assessment and Management of Contaminated Sites: Proceedings of the Third National Workshop on the Health Risk Assessment and Management of Contaminated Sites, South Australian Health Commission, Adelaide* (A. Langley, B. Markey, and H. Hill, Eds.).

Osmose. 2001. "Surface Chemical Analysis of CCA Treated Southern Pine Lumber." Research Document 33-258. June 4.

Peoples, S.A. 1976. "The Amount and Valence of Arsenic Excreted in the Urine of Dogs Fed CCA-C in Their Diet." University of California, Davis, CA.

Peoples, S.A and H.R. Parker. 1979. "The Absorption and Excretion of Arsenic from the Ingestion of Sawdust of Arsenical Treated Wood by Dogs." University of California, School of Veterinary Medicine, Davis, CA. July.

Pott, W.A., S.A. Benjamin, and R.S.H. Yang. 2001. Pharmacokinetics, metabolism, and carcinogenicity of arsenic. *Rev. Environ. Contam. Toxicol.* 169:165-214.

Rahman, M.M., U.K. Chowdhury, S.C. Mukherjee, B.K. Mondal, K. Paul, D. Lodh, B.K. Biswas, C.R. Chanda, G.K. Basu, K.C: Saha, S. Roy, R. Das, S.K. Palit, Q. Quamruzzaman, and D. Chakraborti. 2001. Chronic arsenic toxicity in Bangladesh and West Bengal, India: A review and commentary. *Clin. Toxicol.* 39(7):683-700.

Roberts, S.M., W.R. Weimar, J.R. Vinson, J.W. Munson, and R.J. Bergeron. 2001. Measurement of arsenic bioavailability from soils using a primate model. Abstract presented at the Annual Society of Toxicology Meeting. March.

Romach, E.H., C.Q. Zhao, L.M. Del Razo, M.E. Cebrian, and M.P. Waalkes. 2000. Studies on the mechanisms of arsenic-induced self tolerance developed in liver epithelial cells through continuous low-level arsenite exposure. *Toxicol. Sci.* 54:500-508.

Ruby, M.V., R. Schoof, W. Brattin, M. Goldade, G. Post, M. Harnois, D.E. Mosby, S.W. Casteel, W. Berti, M. Carpenter, D. Edwards, D. Cragin, and W. Chappell. 1999. Advances in evaluating the oral bioavailability of inorganics in soil for use in human health risk assessment. *Environmental Science & Technology* 33(21):3697-3705.

Schoof, R.A., J. Eickhoff, L.J. Yost, E.A. Crecelius, D.W. Cragin, D.M. Meacher, and D.B. Menzel. 1999a. Dietary exposure to inorganic arsenic. In *Arsenic Exposure and Health Effects* (Eds: W.R. Chappell, C.O. Abernathy and R.L. Calderon), Elsevier Science B.V. pp. 81-88.

Schoof, R.A., L.J. Yost, J. Eickhoff, E.A. Crecelius, D.W. Cragin, D.M. Meacher, and D.B. Menzel. 1999b. A market basket survey of inorganic arsenic in food. *Food Chem. Toxicol.* 37 839-846.

Scientific Certification Systems (SCS). 1998. "Metal Removal from CCA-Treated Lumber Under Simulated Normal Use Conditions." Report to Osmose. November 23.

Scientific Certification Systems (SCS). 2001. "Metal Removal from CCA-Treated Lumber Under Simulated Normal Use Conditions." Report to Arch Wood Protection, Inc.

Smith, A.H., A.P. Arroyo, D.N.G. Mazumder, M.J. Kosnett, A.L. Hernandez, M. Beeris, M.M. Smith, and L.E. Moore. 2000. Arsenic-induced skin lesions among Atacameno people in northern Chile despite good nutrition and centuries of exposure. *Environ. Health Perspect.* 108(7):617-620.

Snow, E.T., Y. Hu, S. Chouchane, and C.C. Yan. 1999. Changes in the DNA repair and redox capacity of human keratinocytes exposed to very low doses of arsenic. *Environ. Mol. Mutagen.* 33(Suppl. 33):59.

Solomon, K.R. and J.E. Warner. 1989. "Persistence, Leaching, and Bioavailability of CCA and Pentachlorophenol Wood Preservatives." Interim Report 4 to the Ontario Ministry of the Environment. December 13.

Southwick, J.W., A.E. Western, M.M. Beck, T. Whitley, R. Isaacs, J. Petajan, and C.D. Hansen. 1983. An epidemiological study of arsenic in drinking water in Millard County, Utah. In *Arsenic: Industrial, Biomedical, Environmental Perspectives. Proceedings of the Arsenic Symposium* (Eds: W.H. Lederer and R.J. Fensterheim), Van Nostrand Reinhold, New York. (As cited in Valberg *et al.*, 1998).

Stilwell, D.E. 1998. Environmental Issues on the Use of CCA Treated Wood. Downloaded from http://www.caes.state.ct.us/FactSheetFiles/AnalyticalChemistry/fsAC001f.htm on May 21, 2001.

Tollestrup, K., F.J. Frost, L.C. Harter, and G. McMillan. 2002. Mortality in children residing near the ASARCO copper smelter in Ruston, Washington. *Am. J. Epidemiol.* 155(11):SER Abstract #154.

Tsai, S.M., T.N Wang, and Y.C. Ko. 1999. Mortality for certain diseases in areas with high levels of arsenic in drinking water. *Arch Environ Health.* 54(3):186-193.

Tucker, S.B., S.H. Lamm, F.X. Li, R. Wilson, *et al.* 2001. "Relationship Between Consumption of Arsenic-Contaminated Well-Water and Skin Disorder in Huhhot, Inner Mongolia." Inner Mongolia Cooperative Arsenic Project (IMCAP) Study. Final Report. Department of Dermatology, University of Texas, Houston, and Department of Environmental Epidemiology, Institute of Environmental Engineering and , Chinese Academy of Preventative Medicine, Beijing, China.

U.S. Environmental Protection Agency (USEPA). 1989. "Risk Assessment Guidance for Superfund (RAGS), Vol. I, Human Health Evaluation Manual (Part A)." Office of Emergency and Remedial Response, Washington, D.C. OSWER Directive 9285.7-01A. EPA-540/1-89-002. December.

U.S. Environmental Protection Agency (USEPA). 1997a. "Report on the Expert Panel on Arsenic Carcinogenicity: Review and Workshop." Prepared by the Eastern Research Group, Inc. (ERG). National Center for Environmental Assessment. August.

U.S. Environmental Protection Agency (USEPA). 1997b. "Exposure Factors Handbook. Volume I: General Factors and Volume III: Activity Factors." Office of Research and Development, Washington, D.C. EPA/600/P-95/002Fa, EPA/600/P-95/002Fc. August.

U.S. Environmental Protection Agency (USEPA). 2001. Arsenic in drinking water. Final Rule. *Federal Register* 66(14)7000-7010. January 22.

U.S. Environmental Protection Agency (USEPA). 2003. "Draft Final Guidelines for Carcinogen Risk Assessment." EPA/630/P-03/001A. February.

Vacarro. 1990. (As cited in USEPA, 1999; complete reference not provided in source document.)

Valberg, P.A., B.D. Beck, P.D. Boardman, and J.T. Cohen. 1998. Likelihood ratio analysis of skin cancer prevalence associated with arsenic in drinking water in the USA. *Environ. Geochem. and Health* 20:61-66.

Vig, B.K., M.L. Figueroa, M.N. Cornforth, and S.H. Jenkins. 1984. Chromosome studies in human subjects chronically exposed to arsenic in drinking water. *Am. J. of Industrial Medicine* 6:325-338. (As cited in Valberg *et al.*, 1998).

Washington State Department of Ecology (WA Ecology). 1991. Memo from Lon Kissinger to Marian Abbett re: Gastrointestinal Absorption of Arsenic from Arsenic Contaminated Soil. Washington State Department of Ecology, Olympia, WA. September 12.

Washington State Department of Ecology (WA Ecology). 1996. "Model Toxics Control Act Cleanup Levels and Risk Calculations (CLARC II) Update." Pub. #94-145. Washington State Department of Ecology. February.

Waalkes, M.P., J.M. Ward, J. Liu, and B.A. Diwan. 2003. Transplacental carcinogenicity of inorganic arsenic in the drinking water: Induction of hepatic, ovarian, pulmonary, and adrenal tumors in mice. *Toxicology and Applied Pharmacology* 186:7-17.

West Virginia Department of Environmental Protection (WVDEP). 1998. "West Virginia Voluntary Remediation and Redevelopment Act Guidance Manual." Charleston, WV.

Wu, M.M, T.L. Kuo, Y.H. Hwang, and C.J. Chen. 1989. Dose-response relation between arsenic concentration in well water and mortality from cancers and vascular diseases. *Am J Epidemiol.* 130(6):1123-1132.

Yost, L.J., R.A. Schoof, and R. Aucoin. 1998. Intake of inorganic arsenic in the North American diet. *Hum. Ecol. Risk Assess.* 4(1):137-152.

Yost, L.J., R.A. Schoof, and M. Garry. 2002. Estimation of Dietary Intake of Inorganic Arsenic in Children. In *The Society for Environmental Geochemistry and Health (SEGH) Fifth International Conference on Arsenic Exposure and Health Effects, Book of Abstracts*, San Diego, CA, July 14-18, 2002. pp. 98.

Attachment A

Relative Bioavailability of Inorganic Arsenic

This attachment provides more detailed information regarding the basis for assuming reduced relative bioavailability for arsenic derived from dislodgeable materials as recommended in these comments. Both the regulatory and technical bases for developing relative bioavailability adjustment (RBA) factors are discussed. Information is provided on studies of the relative bioavailability of dislodgeable arsenic, as well as other relevant media such as arsenic in soil originating from CCA-treated wood. Arsenic leaching studies that provide additional information regarding the likely bioavailability of arsenic from sources associated with wood treated with chromated copper arsenate (CCA) are also reviewed.

Overview

A critical factor determining the magnitude of potential exposures and risks associated with a chemical is its bioavailability, *i.e.*, the amount of the chemical that is actually absorbed into the body. A chemical's bioavailability is influenced by such factors as the species of the chemical, the matrix in which it is present, the amount of time that a chemical is in a matrix, and the route by which exposure occurs. When chemicals are ingested, bioavailability is determined by the amount of a chemical that is dissolved in gastrointestinal fluids and absorbed across the gastrointestinal tract into the bloodstream. An ingested chemical that is adsorbed to soil or some other solid medium like wood dust may be absorbed less completely than the same ingested dose of the chemical when dissolved in water (NEPI, 2000).

Another important factor to consider is the relative bioavailability of the chemical under the exposure conditions of interest when compared to the bioavailability of the chemical under the exposure conditions present in the study that forms the basis for the quantitative toxicity factor for the chemical (USEPA, 1989). Frequently, quantitative toxicity factors are calculated based on studies where the chemical was administered in food or water. By contrast, risk assessments for chemicals in the environment often require assessments of the exposures and risks associated with chemicals in soil or other solid media. Where the bioavailability of the chemical observed in the toxicity study is likely to differ from that under the exposure conditions of interest, a relative bioavailability adjustment (RBA) factor is derived. The RBA factor for a specific chemical reflects the absorption fraction from the exposure medium of interest in the risk analyses (*e.g.*, soil or wood dust) relative to the absorption fraction from the exposure medium used in the relevant toxicity study (*e.g.*, food or water).

It is widely recognized that the bioavailability of many metals and organic chemicals in soil or other solid media tends to be considerably lower than bioavailability from food or water (see, *e.g.*, Ruby *et al.*, 1999; Alexander, 2000). Bioavailability from soil and other solid media can be affected by a number of factors, including the form of the chemical, its solubility, the size distribution of the ingested particles, the type of soil or other medium, the degree of encapsulation of the chemical within an insoluble matrix, and the nutritional status of the exposed individual.

Guidance from the U.S. Environmental Protection Agency (EPA) recognizes the need to make adjustments for the reduced bioavailability of compounds in soil and other media. For example, EPA's *Risk Assessment Guidance for Superfund* (USEPA, 1989) notes:

> "If the medium of exposure in the site exposure assessment differs from the medium of exposure assumed by the toxicity value (*e.g.*, RfD values usually are based on or have been adjusted to reflect exposure *via* drinking water, while the site medium of concern may be soil), an absorption adjustment may, on occasion, be appropriate. For example, a substance might be more completely absorbed following exposure to contaminated drinking water than following exposure to contaminated food or soil (*e.g.*, if the substance does not desorb from soil in the gastrointestinal tract)."

EPA guidance also recommends the use of RBA factors "to adjust a food or soil ingestion exposure estimate to match an RfD or slope factor based on the assumption of drinking water ingestion " (USEPA, 1989).

The risk analyses conducted by the staff of the Consumer Product Safety Commission (CPSC) focus on potential exposures and risks associated with arsenic from dislodgeable materials on the surface of CCA-treated wood. To assess the potential bioavailability of arsenic from this source, data from bioavailability studies using wood dust and dislodgeable residue itself are of interest. For arsenic present in material directly contacted and dislodged from CCA-treated wood, data from two studies of dogs fed sawdust from CCA-treated wood suggest a relative bioavailability estimate of 47% (Peoples, 1976; Peoples and Parker, 1979). Initial results from a recent study in which hamsters were fed dislodgeable arsenic support reduced RBA estimates for dislodgeable arsenic and suggest that the RBA value may be in the range of 10-20% (Aposhian, 2001). Additional animal studies of the bioavailability of dislodgeable arsenic have been designed with input from EPA and other regulatory agencies and are currently underway. The results of these studies, as well as other factors indicating the reduced bioavailability of dislodgeable arsenic, should be incorporated into CPSC's risk analyses. Other factors supporting a reduced bioavailability of dislodgeable arsenic from CCA-treated wood include the chemistry of the

wood treatment process, which is designed to fix arsenic and the other metals within the wood matrix; the form of arsenic found on the wood surface; studies indicating that only a small proportion of dislodgeable arsenic is soluble; and toxicology and epidemiology studies indicating few adverse effects that are attributable to arsenic exposure from CCA-treated wood.

In addition to the animal studies available for deriving an estimate of oral bioavailability, other factors support an assumption of reduced bioavailability for dislodgeable arsenic. First, the chemical process that occurs during wood treatment is designed to bind the CCA in the wood so that the fixative will persist and prevent deterioration of the wood over a long period of time (Bull, 2001). Second, a study of the composition of dislodgeable materials suggests that a substantial proportion of the arsenic observed on the surface of CCA-treated wood is insoluble. Specifically, an analysis of dislodgeable surface materials collected from samples of CCA-treated wood found that arsenic comprised a maximum average value of 0.2% of the surface material on the treated wood and that approximately 94-100% of the surface arsenic was insoluble in water (Cui, 2001; Osmose, 2001). X-ray diffraction techniques have shown the form of arsenic on the surface of CCA-treated wood to be non-crystalline amorphous oxide complexes (Kamdem, 2001; Kamdem and Cui, 2001), which is consistent with the foregoing observations. Overall, these findings support the assumption that the bioavailability of arsenic present in dislodged materials is less than would be expected based on consideration of the total measured arsenic concentration.

Additional evidence of the reduced bioavailability of dislodgeable arsenic comes from the results of leaching studies. Data from leaching studies indicate that arsenic is not released from treated wood to any appreciable extent under normal outdoor conditions (*e.g.*, when exposed to rainwater) and is primarily mobilized from the wood through physical transport of dislodgeable particles (*e.g.*, wood particles). Based on a review of the leaching studies, two key observations support reduced RBA factors for dislodgeable arsenic. First, the duration of the leaching studies in acidic solutions ranged from 4 to 40 days. This duration is significantly longer than the period of time that food (or ingested dislodgeable arsenic) remains in the human stomach, *i.e.*, approximately 4 hours (Vander *et al.*, 1994). Thus, the leaching studies are likely to overestimate arsenic leaching that would occur in the human gastrointestinal tract. Second, the reported amount of arsenic leached in these studies ranged from 17 to 44%. Together, these observations suggest that the RBA estimate of 47% for dislodgeable arsenic that is derived from the dog studies is likely to represent a conservative value. The lower RBA values suggested by the

preliminary results from the hamster studies (*i.e.*, 10-20%) are also consistent with the results of the leaching studies.

The reduced bioavailability of arsenic associated with dislodgeable materials is also consistent with extensive information in the scientific literature indicating the generally reduced relative bioavailability of arsenic from soil and other solid matrices, including soil from a CCA treatment site. Overall, based on rabbit, monkey, dog, and swine studies published in the peer-reviewed literature, relative bioavailability estimates for arsenic in soil range from near zero to approximately 50%. The corresponding oral bioavailability for soluble forms of arsenic (*i.e.,* the type of arsenic present in the epidemiological and animal studies upon which the standard toxicity factors are based) reported in published *in vivo* studies is as high as approximately 95%. Results from two studies of soil from CCA wood treatment sites revealed a similarly reduced relative bioavailability of arsenic. In particular, results from a study in which primates were fed soil collected at a CCA treatment site indicate an RBA value of 16.3% (Roberts *et al.*, 2001).

The chemistry of arsenic in soil also suggests a reduced bioavailability. Arsenic is generally tightly bound to soils (Cooper, 1990; USDA, 1980). Arsenates, including chromium arsenate, are the form of arsenic in found in treated wood, released from treated wood as dislodgeable arsenic, and observed in soil in the vicinity of structures built of CCA-treated wood. Arsenates strongly bind to ferric hydroxides, which are abundant in soils. Arsenates can also form insoluble complexes with ferric iron, aluminum, or calcium, all of which are abundant in soil (Cooper, 1990). Unless there are unusual circumstances, arsenic will remain in the arsenate form. Reducing conditions can yield changes in the form of arsenic found in the environment; however, such conditions are rare in surface soils. In the arsenate form, arsenic is in its +5 oxidation state, which is a less soluble and less mobile form than arsenite (As^{+3}) (ATSDR, 2000; Masscheleyn *et al.*, 1991 as cited in Townsend, *et al.*, 2001). In fact, arsenite (As^{+3}) was looked for and not found in properly treated wood (Nygren and Nilsson, 1993). These observations, regarding the chemical species of arsenic in soil near treated wood structures, its strong binding to soil, and its reduced solubility and mobility, all support a reduced bioavailability of CCA-derived arsenic in soil.

Additional support for the recommended assumptions regarding the reduced bioavailability of arsenic associated with CCA-treated wood is provided below.

Bioavailability of Dislodgeable Arsenic

Several studies have assessed the bioavailability of arsenic associated with CCA-treated wood. These studies have examined the bioavailability and toxicity of arsenic in sawdust from CCA-treated wood and provide a useful basis for estimating the relative bioavailability of dislodgeable arsenic. They are also the most relevant studies currently available. In these studies, dogs were fed sawdust from CCA-treated wood (Peoples, 1976; Peoples and Parker, 1979). In the first of these studies, two dogs were fed sawdust from CCA-treated wood (equal to an arsenic dose of 39 mg/day) for a period of 5 days (Peoples, 1976). Urine and feces samples were collected from these animals on the days when the sawdust was administered as well as for several days before and after this treatment period. Arsenic absorption was then assessed by comparing the amounts of arsenic excreted in urine with the total ingested arsenic dose. This comparison yielded an estimate of absolute arsenic absorption of 26% based on data from one animal and 29% based on data from the other.

A test group using ingested soluble arsenic was not included in the study; therefore, relative bioavailability cannot be calculated from the study results. Data presented in Hollins *et al.* (1979), however, indicate that absorption of soluble arsenic is similar in dogs and monkeys. As a result, RBA estimates were derived by comparing the absolute arsenic bioavailability measured in this study with the soluble arsenic bioavailability estimate for monkeys (68%) observed in a study by Freeman *et al.* (1995). This calculation yields RBAs of 38% and 43% for the two animals in this study.

In a second study, a dog was fed sawdust from CCA-treated wood (equal to an arsenic dose of 6 mg/day) for a period of 8 days (Peoples and Parker, 1979). Chemical analyses indicated that the dog received an additional 0.135 mg/day of arsenic through dietary sources. Comparison of the total arsenic intake during the feeding period with the amount of arsenic excreted in the urine indicated that approximately 40% of the ingested arsenic was absorbed. Using the same approach as noted above, an RBA estimate of 59% was derived. The absorption estimates derived in these two studies are relatively similar to each other and are consistent with the range of bioavailability estimates observed for arsenic in soil, as described below. Thus, these data support use of an RBA value of 47% for estimating the relative bioavailability of dislodgeable arsenic from CCA-treated wood.

Another recently conducted bioavailability study has administered dislodgeable arsenic to hamsters *via* oral gavage (Aposhian, 2001). Initial results from this study support reduced bioavailability

estimates for dislodgeable arsenic and suggest that the RBA value for dislodgeable arsenic may be in the range of 10-20%. Moreover, additional animal studies of the bioavailability of dislodgeable arsenic have been designed with input from EPA and other regulatory agencies. These data should be used to derive a refined estimate of the bioavailability of dislodgeable arsenic.

A single study of dermal absorption of arsenic from CCA-treated sawdust also observed reduced bioavailability of this material. Specifically, no significant change in urinary arsenic excretion was observed in a single dog exposed to a test patch of the sawdust for 2 days (Peoples, 1979).

Finally, while only a few studies have been undertaken to directly evaluate the toxicity of arsenic in sawdust from CCA-treated wood, the available data do not indicate substantial uptake and adverse health effects associated with this material. For example, the researchers who conducted the two bioavailability studies of CCA-treated sawdust reported that no signs of toxicity were observed in the dogs used in the studies (Peoples, 1976; Peoples and Parker, 1979). Similarly, a teratogenicity study saw no significant adverse maternal or fetal toxicity (Hood, 1979). In this study, mice were exposed to CCA-treated sawdust *via* dermal contact or ingestion in the diet. In a study of mice exposed to treated sawdust administered in the diet or *via* oral gavage, no chromosomal damage or apparent adverse hematological effects were observed (Graham, 1979). In a retrospective epidemiology study of carpenters in Hawaii, the patterns of cancer mortality in this group were compared with cancer mortality in the general population (Budy and Rashad, 1976). In particular, the mortality rates were examined before and after the use of arsenic-treated wood in Hawaii, including CCA-treated wood. This study observed no adverse health effects related to the use of arsenic-treated wood. Thus, although these studies do not conclusively demonstrate an absence of effects from these materials, they also have not observed any significant adverse health impacts associated with exposure to these materials.

Evaluation of Physical and Chemical Characteristics Influencing the Bioavailability of Dislodgeable Arsenic

Other factors also support an assumption of reduced bioavailability for dislodgeable arsenic. First, the chemical process that occurs during wood treatment is designed to bind the CCA in the wood so that the fixative will persist and prevent deterioration of the wood over a long period of time (Bull, 2001). As discussed below, data from leaching studies indicate that arsenic is not released from treated wood to any appreciable extent under normal outdoor conditions (*e.g.*, when exposed to rainwater) (Ziobro, 2000)

and is primarily mobilized from the wood through physical transport of dislodged particles. Moreover, a study of the composition of dislodgeable materials suggests that a substantial proportion of the arsenic observed on the surface of CCA-treated wood is insoluble. Specifically, an analysis of dislodgeable surface materials from CCA-treated wood found that arsenic comprised a maximum average value of 0.2% of the surface material on the treated wood and that approximately 94-100% of the surface arsenic was insoluble in water (Cui, 2001; Osmose, 2001). This finding supports the assumption that the bioavailability of arsenic present in dislodged materials is less than would be expected based on consideration of the total measured arsenic concentration.

Studies evaluating the leachability of arsenic from small sized wood particles (*e.g.*, sawdust and chipped wood) used in some of the leaching studies can provide insights regarding the leachability and potential bioavailability of dislodgeable arsenic from a CCA-treated structure. To assess the bioavailability of ingested dislodgeable arsenic, the leaching studies conducted at or near the pH of the human stomach (pH 1.0-3.5) are more relevant than those conducted at a neutral pH range (pH 5.0-7.5). These studies are described briefly here.

Murphy and Dickinson (1990) found no change in the arsenic content of CCA type C wood subjected to simulated rain at pH 3.0 and pH 5.6. Similarly, Ziobro (2000) found no change in the amount of fixed arsenic in CCA-treated lumber in a deck exposed for 7 years in Florida. Cooper (1991) observed that only 2.9 to 6.9% of the arsenic was leached from small CCA-treated wood specimens (with dimensions of 1 cm × 1 cm × 4 cm) exposed to acidic solutions (at pH values of 3.5, 4.5, and 5.5) for 13 days. In another study, Warner and Solomon (1990) subjected small blocks of treated wood for 40 days to a citric acid buffered solution at pH 3.5, and to a sulfuric acid solution at pH 2.5. The citric acid buffer reportedly leached 68% of the arsenic from the blocks. Following up on these results, Cooper (1991) conducted a similar experiment and determined that the citric acid buffer, not the pH of the solution, caused the release of arsenic. Warner and Solomon (1990) also reported that sulfuric acid at pH 2.5 released 39.7% of the arsenic after 40 days of digestion. Sulfuric acid is an oxidizing acid and may have deteriorated the wood itself, enhancing the leaching power of the acidic solution. By contrast, stomach acid consists of hydrochloric acid, which is not an oxidizing acid. CPSC (1990) performed a number of experiments to evaluate the leaching of arsenic from treated wood under acidic conditions. In one set of experiments, 4 days of leaching in HCl at pH 1.0 released 44% of the arsenic from a small piece (32 mg) of treated wood. Similarly, a nitric acid solution at pH 1.0 leached 43% of the arsenic from a 34 mg piece of wood in 4 days. In another series of experiments, 17-19% of the arsenic was leached by HCl at pH 1.0

in 18 days, and 18-31% of the arsenic was released in a nitric acid solution at pH 1.0 after 17 days (CPSC, 1990).

Based on the results of the preceding leaching studies, two key observations support reduced bioavailability estimates for dislodgeable arsenic. First, the duration of the leaching studies in acidic solutions ranged from 4 to 40 days. This duration is significantly longer than the period of time that food or ingested dislodgeable arsenic would be in the human stomach (*i.e.*, approximately 4 hours; Vander *et al.*, 1994). Therefore, the results of the leaching studies would be expected to overestimate the amount of leaching that would occur during passage through the stomach. Second, the reported amount of leached arsenic in all of these studies ranged from 17 to 44% (with the exception of the experiment performed in citric acid solution). These observations support the 47% bioavailability estimate for dislodgeable arsenic recommended in these comments.

Bioavailability of Arsenic in Soil and Other Solid Matrices

As noted above, the reduced bioavailability of dislodgeable arsenic is also supported by data indicating reduced bioavailability of arsenic from soil and other solid matrices. Recognition of the importance of this factor in assessing potential exposures and risks associated with arsenic is reflected in generic regulatory guidance (*e.g.*, MIDEQ, 2000; WVDEP, 1998; WA Ecology, 1991, 1996; USEPA, 1989) as well as regulatory decisions reached at specific sites (*e.g.*, Gradient, 2000; USEPA, Region 3, 1998; USEPA, Region 8 and MDEQ, 1996; MIDEQ, 1995; ODEQ, 1994). Typically, the selected RBA values for arsenic in soil have been less than 50% at both the state and federal level.

These regulatory actions have been based on studies of the oral bioavailability of soil-bound arsenic. Several reviews of these studies have been prepared (*e.g.*, Valberg *et al.*, 1997; Ruby *et al.*, 1999; NEPI, 2000). The results from the available published arsenic bioavailability studies are summarized in Table A-1. In all of these studies, soil-bound arsenic has been found to be less bioavailable than soluble arsenic compounds. Specifically, all of the reported relative bioavailability estimates for soil-bound arsenic from the peer-reviewed literature are less than 50%.

Table A-1
Estimates of Oral Bioavailability of Arsenic in Solid Matrices

Site	Sample Type[a]	Test Species	As Conc. in mg/kg	Mean Relative Bioavailability (%)	Source
Anaconda, MT	Residential soil	Rabbit	3,900	47	1
Anaconda, MT	Residential soil (9)	Monkey	410	20[b]	2
	Residential house dust (4)		170	28[b]	2
Mining/Smelter Sites	Soil, sediment, smelter slag, and mill tailings (13)	Pig	233 to 17,500	3 to 43	3
Butte, MT	Soil[c]	Rat	626	37.8[d]	4
Villa de la Paz, Mexico	Mining waste	Rat	9,647	12	5
Gelderland, Netherlands	Bog ore soil	Dog	339	12[e]	6

Sources:
(1) Freeman et al., 1993
(2) Freeman et al., 1995
(3) Rodriguez et al., 1999
(4) Ellickson et al. 2001
(5) Rodriguez et al., 1998
(6) Groen et al., 1994

Notes:
a = Number in parentheses indicates number of samples.
b = Mean relative bioavailability based on urinanalysis.
c = National Institute of Standards and Technology (NIST) standard reference soil.
d = Absolute bioavailability estimate.
e = Relative bioavailability estimate derived based on absolute bioavailability estimate for soil from cited study (0.08) and bioavailability estimate for soluble arsenic (0.68) from Freeman et al., 1995.

As indicated by the studies reviewed above, most of the available data suggest that the bioavailability of ingested arsenic in soil is less than 50%, which is significantly less than that for ingested arsenic dissolved in water. In one study conducted by EPA that has not been published in the peer-reviewed literature, an RBA estimate of 78% was derived for ingested arsenic in soil (USEPA, Region 10, 1996). In this study, immature swine were fed soil, as well as other metals-containing materials, collected in the vicinity of a smelter site in Tacoma, Washington. Treated animals were given a single dose of arsenic, with doses from soil ranging from 0.04 to 0.24 mg of arsenic per kg of body weight. Arsenic bioavailability was assessed based on arsenic analyses of blood samples and regression analyses using these results. Although the results of this study suggest that the relative bioavailability of arsenic in soil can be greater than 50% under some conditions, several limitations in this study weaken confidence in the results. In particular, because the regression analyses were based on only three data points, uncertainty exists in the quantitative significance of these results. In addition, the first blood sample was not collected from the animals until 15 minutes after the arsenic doses were administered. Because arsenic is rapidly cleared from the blood, the blood arsenic concentration was likely underestimated for animals dosed with arsenic intravenously. As a result, the relative bioavailability

values calculated using the intravenous data from this study are likely to overestimate the actual bioavailability of the soil-bound arsenic.

The evidence for reduced bioavailability of soil arsenic from *in vivo* and *in vitro* laboratory studies is supported by a study of arsenic exposures in children living in the vicinity of a former copper smelter. Based on urinary arsenic measurements, actual arsenic exposures from soil were less than those predicted using standard risk assessment assumptions (Walker and Griffin, 1998; Cohen *et al.*, 1998). The relative bioavailability of arsenic in site soils was estimated to be about 20% based on Freeman *et al.* (1995). When site-specific relative bioavailability estimates were incorporated into the exposure calculations, predicted exposures more closely matched observed exposures (Walker and Griffin, 1998; Cohen *et al.* 1998).

A few studies are available that have specifically examined the bioavailability of soil arsenic associated with CCA-treated wood. The results observed in these studies are consistent with the general results observed in other studies of soil containing arsenic from various sources, *i.e.*, these results suggest that the bioavailability of CCA-related arsenic from soil or dislodgeable materials is reduced relative to the bioavailability of dissolved arsenic. Two animal studies have used soil obtained from CCA treatment sites. In the first study, soil from nine samples collected at a wood treatment site that used CCA was mixed with water and administered to rats *via* gavage (Ng and Moore, 1996). The researchers selected rats for use in these studies because they accumulate arsenic in their blood to a greater extent than other species, and thus, can serve as a sensitive indicator of arsenic uptake. Results from the test animals were compared with results from rats administered an equivalent dose of arsenic in an aqueous solution containing sodium arsenite or sodium arsenate, or in wheat flour spiked with calcium arsenite. Blood arsenic concentrations were measured 96 hours after the arsenic dosing (*i.e.*, the time at which the researchers state that maximum blood arsenic concentrations would be attained). Relative bioavailability was then estimated by comparing the blood arsenic concentrations observed in the soil group with the concentrations observed in the other three groups. These calculations yielded relative bioavailability estimates of 13.4% (relative to sodium arsenite), 32.2% (relative to calcium arsenite), and 38.0% (relative to sodium arsenate). These results are well within the range of RBA estimates observed in the soil studies discussed above.

In the second study, five *Cebus apella* monkeys received oral doses of arsenic in soil collected at four types of sites, including a CCA wood treatment site (Roberts *et al.*, 2001). Because primates are

more similar physiologically to humans than rats, and because the primate study design was stronger and more comprehensive than the rat study, the data from this study provide a stronger basis for assessing the relative bioavailability of soil arsenic associated with CCA-treated wood. To estimate the relative bioavailability of the soil arsenic, urinary excretion of arsenic following dosing with soil was compared to that observed following an oral dose of an aqueous solution of sodium arsenate. The researchers found that the pharmacokinetic behavior of the arsenic, including the proportions of arsenic excreted in urine and feces, was similar to observations made in humans. In this test system, the relative bioavailability of arsenic in the CCA treatment site soils was estimated to be 16.3%. Arsenic in soil from the other three types of sites evaluated in this experiment (*i.e.*, an electrical substation, a pesticide application site, and a cattle dip vat site) also showed reduced bioavailability. Specifically, the relative bioavailability of arsenic in the soil from the other sites ranged from 10.7 to 24.7%. Again, these results are well within the range of estimates observed for other studies of arsenic in soil and support the likelihood of reduced bioavailability of arsenic associated with CCA-treated wood.

References

Agency for Toxic Substances and Disease Registry (ATSDR). 2000. "Toxicological Profile for Arsenic." Prepared for the U.S. Department of Health and Human Services. September.

Alexander, M. 2000. Aging, bioavailability, and overestimation of risk from environmental pollutants. *Environmental Science and Technology* 34(20):4259-4265.

Aposhian, H.V. 2001. "Bioavailability of Dislodgeable CCA." Unpublished report to FDA.

Budy, A.M. and M.N. Rashad. 1976. Cancer mortality among carpenters in Hawaii. In *Prevention and Detection of Cancer: Proceedings of the Third International Symposium on Detection and Prevention of Cancer: Volume I - Etiology, April 26 to May 1, 1976, New York* (Ed: H.E. Nieburgs), Marcel Dekker, Inc., New York. pp. 901-907.

Bull, D.C. 2001. The chemistry of chromated copper arsenate. II. Preservative-wood interactions. *Wood Science and Technology* 34:459-466.

Cohen, J.T., B.D. Beck, T.S. Bowers, R.L. Bornschein, and E.J. Calabrese. 1998. An arsenic exposure model: Probabilistic validation using empirical data. *Human Ecol. Risk Assess.* 4(2):341-377.

Consumer Product Safety Commission (CPSC). 1990. "U.S. Consumer Product Safety Commission Project Report: Playground Equipment – Transmittal of Estimate of Risk of Skin Cancer from Dislodgeable Arsenic on Pressure Treated Wood Playground Equipment." Provided by Hickson Corporation, Atlanta, GA.

Cooper, P.A. 1990. Leaching of CCA from treated wood. In *Proceedings of the Canadian Wood Preservers Association, Volume II*, pp. 144-169.

Cooper, P.A. 1991. Leaching of CCA from treated wood: pH effects. *Forest Products Journal* 41(1): 30-32. January.

Cui, W. 2001. "Surface Arsenic Analysis of Commercial CCA Treated Southern Pine."

Ellickson, K.M., R.J. Meeker, M.A. Gallo, B.T. Buckley, and P.J. Lioy. 2001. Oral bioavailability of lead and arsenic from a NIST standard reference soil material. *Arch. Environ. Contam. Toxicol.* 40(1):128-135.

Freeman, G.B., J.D. Johnson, J.M. Killinger, S.C. Liao, A.O. Davis, M.V. Ruby, R.L. Chaney, S.C. Lovre, and P.D. Bergstrom. 1993. Bioavailability of arsenic in soil impacted by smelter activities following oral administration in rabbits. *Fund. Appl. Toxicol.* 21:83-88.

Freeman, G.B., R.A. Schoof, M.V. Ruby, A.O. Davis, J.A. Dill, S.C. Liao, C.A. Lapin, and P.D. Bergstrom. 1995. Bioavailability of arsenic in soil and house dust impacted by smelter activities following oral administration in cynomolgus monkeys. *Fund. Appl. Toxicol.* 28:215-222.

Gradient Corporation (Gradient). 2000. "Human Health Risk Assessment (HHRA), Hurley Soils Investigation Unit, Volume I-III." Prepared for the State of New Mexico Environment Department (NMED). February 22.

Graham, B.Y. 1979. "*In Vivo* Cytogenetic Studies of Chromated Copper Arsenate Treated Sawdust in Mouse Bone Marrow." University of Alabama, Dept. of Chemistry. April 30.

Groen, K., H.A.M.G. Vaessen, J.J.G Kliest, J.L.M. de Boer, T. van Ooik, A. Timmerman, and R.F. Vlug. 1994. Bioavailability of inorganic arsenic from bog ore-containing soil in the dog. *Environ. Health Perspect.* 102(2):182-184.

Hollins, J.G., S.M. Charbonneau, F. Bryce, J.M. Ridgeway, G.K.H. Tam, and R.E. Willes. 1979. Whole body retention and excretion of [^{74}As] arsenic acid in the adult beagle dog. *Toxicol. Lett.* 4:7-13.

Hood, R.D. 1979. "Evaluation of Chromated Copper Arsenate (CCA) Impregnated in Sawdust for Teratogenicity and Maternal Toxicity in Mice and Rabbits." 14 p.

Kamdem, D.P. 2001. "ESEM of CCA Type C Treated Southern Pine." Michigan State University, Department of Forestry.

Kamdem, D.P. and W. Cui. 2001. "X-Ray Diffraction of CCA Treated Wood Surface." Michigan State University, Department of Forestry.

Masscheleyn, P.H., R.D. Delaune, and W.H. Patrick, Jr.. 1991. A hydride generation atomic absorption technique for arsenic speciation. *Journal of Environmental Quality* 20:96-100. (As cited in Townsend *et al.*, 2001)

Michigan Department of Environmental Quality (MIDEQ). 1995. Interoffice Communication from L.D. Larson (Toxicologist) to B. Crowles (Environmental Quality Analyst) re: the Ralph Crego Park Site in Lansing, MI. Michigan Department of Natural Resources, Lansing, MI. February 24.

Michigan Department of Environmental Quality (MIDEQ). 2000. Environmental Response Division Operational Memorandum #18. www.deq.state.mi.us/erd/opmemos/opmemo18/opmemo18.html.

Murphy, R.J. and D.J. Dickinson. 1990. The effect of acid rain on CCA treated timber. In *Proceedings of the Wood Presentation Symposium*, Cannes, France, Feb. 19-20. IRG/WF/3600.

National Environmental Policy Institute (NEPI). 2000. Assessing the Bioavailability of Metals in Soil for Use in Human Health Risk Assessments. Bioavailability Policy Project Phase II, Metals Task Force Report. Summer. Downloaded from http://www.nepi.org/pubs/metals-bio%20final.pdf on June 27, 2001.

Ng, J.C. and M.R. Moore. 1996. Bioavailability of arsenic in soils form contaminated sites using a 96 hour rat blood model. In *The Health Risk Assessment and Management of Contaminated Sites: Proceedings of the Third National Workshop on the Health Risk Assessment and Management of Contaminated Sites, South Australian Health Commission, Adelaide* (A. Langley, B. Markey, and H. Hill, Eds.).

Nygren, O. and C.A. Nilsson. 1993. Determination and speciation of chromium, copper and arsenic in wood and dust from CCA-impregnated timber. *Analysis* 21:83-89.

Oklahoma Department of Environmental Quality (ODEQ). 1994. "Record of Decision for Operable Unit One of the National Zinc Site, Bartlesville, Oklahoma." ODEQ, Tulsa, OK.

Osmose. 2001. "Surface Chemical Analysis of CCA Treated Southern Pine Lumber." Research Document 33-258. June 4.

Peoples, S.A. 1976. "The Amount and Valence of Arsenic Excreted in the Urine of Dogs Fed CCA-C in Their Diet." University of California, Davis, CA.

Peoples, S.A. 1979. "The Dermal Absorption of Arsenic in Dogs from Sawdust from Wood Treated with ACA and CCA-C." University of California, School of Veterinary Medicine, Department of Physiological Science, Davis, CA. July.

Peoples, S.A and H.R. Parker. 1979. "The Absorption and Excretion of Arsenic from the Ingestion of Sawdust of Arsenical Treated Wood by Dogs." University of California, School of Veterinary Medicine, Davis, CA. July.

Roberts, S.M., W.R. Weimar, J.R. Vinson, J.W. Munson, and R.J. Bergeron. 2001. Measurement of arsenic bioavailability from soils using a primate model. Abstract presented at the Annual Society of Toxicology Meeting. March.

Rodriguez, V.M., L. Dufour, L. Carrizales, F. Diaz-Barriga, and M.E. Jiménez-Capdeville. 1998. Effects of oral exposure to mining waste on *in vivo* dopamine release from rat striatum. *Environ. Health Perspect.* 106(8):487-491. August.

Rodriguez, R.R., N.T. Basta, S.W. Casteel, and L.W. Pace. 1999. An *in vitro* gastrointestinal method to estimate bioavailable arsenic in contaminated soils and solid media. *Environ. Sci. Technol.* 33(4):642-649.

Ruby, M.V., R. Schoof, W. Brattin, M. Goldade, G. Post, M. Harnois, D.E. Mosby, S.W. Casteel, W. Berti, M. Carpenter, D. Edwards, D. Cragin, and W. Chappell. 1999. Advances in evaluating the oral bioavailability of inorganics in soil for use in human health risk assessment. *Environmental Science & Technology* 33(21):3697-3705.

Townsend, T., K. Stook, T. Tolaymat, J.K. Song, H. Solo-Gabriele, N. Hosein, and B. Khan. 2001. "New Lines of CCA-Treated Wood Research: In-Service and Disposal Issues." Report #00-12. March 19.

U.S. Department of Agriculture (USDA). 1980. "The Biologic and Economic Assessment of Pentachlorophenol, Inorganic Arsenicals, Creosote. Volume I: Wood Preservatives." Cooperative Impact Assessment Report. Technical Bulletin Number 1658-1. November 4.

U.S. Environmental Protection Agency (USEPA). 1989. "Risk Assessment Guidance for Superfund (RAGS), Vol. I, Human Health Evaluation Manual (Part A)." Office of Emergency and Remedial Response, Washington, D.C. OSWER Directive 9285.7-01A. EPA-540/1-89-002. December.

U.S. Environmental Protection Agency, Region 3 (USEPA, Region 3). 1998. "Final Risk Assessment Report for the Palmerton Zinc Site." U.S. EPA, Region 3, Philadelphia, PA.

U.S. Environmental Protection Agency, Region 10 (USEPA, Region 10). 1996. "Bioavailability of Arsenic and Lead in Environmental Substrates. 1. Results of an Oral Dosing Study of Immature Swine." U.S. EPA, Region 10, Superfund/Office of Environmental Assessment, Seattle, WA. EPA 910/R-96-002. February.

U.S. Environmental Protection Agency, Region 8 and Montana Department of Environmental Quality (USEPA, Region 8 and MDEQ). 1996. "Record of Decision. Community Soils Operable Unit. Anaconda Smelter NPL Site, Anaconda, Montana." U.S. EPA, Region 8, Helena, MT and MDEQ, Helena, MT.

Valberg, P.A., B.D. Beck, T.S. Bowers, J.L. Keating, P.D. Bergstrom, and P.D. Boardman. 1997. Issues in setting health-based cleanup levels for arsenic in soil. *Regul. Toxicol. Pharmacol.* 26:219-229.

Vander, A.J., J.H. Sherman, and D.S. Luciano. 1994. Chapter 18: Regulation of organic metabolism, growth and energy balance. In *Human Physiology* (K.M. Prancan and J.W. Bradley, Eds.), Mc-Graw Hill, p. 602.

Walker, S. and S. Griffin. 1998. Site-specific data confirm arsenic exposure predicted by the U.S. Environmental Protection Agency. *Environ. Health Perspect.* 106(3):133-139.

Warner, J.E. and K.R. Solomon. 1990. Acidity as a factor in leaching of copper, chromium and arsenic from CCA-treated dimension lumber. *Environmental Toxicology and Chemistry* 9:1331-1337.

Washington State Department of Ecology (WA Ecology). 1991. Memo from Lon Kissinger to Marian Abbett re: Gastrointestinal Absorption of Arsenic from Arsenic Contaminated Soil. Washington State Department of Ecology, Olympia, WA. September 12.

Washington State Department of Ecology (WA Ecology). 1996. "Model Toxics Control Act Cleanup Levels and Risk Calculations (CLARC II) Update." Pub. #94-145. Washington State Department of Ecology. February.

West Virginia Department of Environmental Protection (WVDEP). 1998. "West Virginia Voluntary Remediation and Redevelopment Act Guidance Manual." Charleston, WV.

Ziobro, R.J. 2000. "CCA Retention Analysis of an Above Ground Depletion Deck Exposed at the Gainesville Test Plot." Research Document 33-184. April 12.

Attachment B

Validity of CSF Estimates for Arsenic Ingestion

The risk assessment prepared by CPSC staff uses a range of carcinogenic slope factors (CSFs) for quantifying the potential risks associated with ingestion of arsenic. The range of values reflects different methodologies used to interpret the available epidemiological data regarding the carcinogenicity of arsenic ingestion. Specific methodological differences include the carcinogenic endpoints considered, the model used to extrapolate results observed at relatively high exposures to predict risks associated with low level exposures, and approaches used to account for background risk levels and arsenic intake from other sources such as food. The numerical CSF values considered by CPSC range from 0.41 to 23 $(mg/kg\text{-}day)^{-1}$, spanning almost two orders of magnitude. This considerable numerical range of values reflects the substantial uncertainty inherent in efforts to quantify the carcinogenic risks associated with ingested arsenic and the impacts of alternative modeling approaches on quantitative potency estimates. As discussed below, however, available data indicate that all of the CSF values considered by CPSC staff in their risk calculations are likely to overestimate actual risks associated with arsenic ingestion, and that the high-end CSF (23 $[mg/kg\text{-}day]^{-1}$) is implausible, particularly when applied to evaluate potential risks in U.S. populations with low level arsenic exposures.

The specific CSF values used by CPSC staff in their risk assessment of CCA-treated wood were derived based on analyses of arsenic toxicity and carcinogenicity conducted by the U.S. Environmental Protection Agency (USEPA, 2001) and the National Research Council (NRC, 1999, 2001) as part of their evaluations of an appropriate maximum contaminant level (MCL) for arsenic in U.S. drinking water. While neither EPA nor the NRC explicitly published alternative CSF values for arsenic as part of these evaluations, CSF values can be calculated based on risk estimates presented in their reports, *i.e.*, risk summaries presented in the EPA report and maximum likelihood estimates of cancer-related deaths presented in the NRC report. It should be noted, however, that the NRC subcommittee never explicitly endorsed the use of the arsenic unit risk value reflected in its risk analyses. Instead, the subcommittee notes that, in accordance with its charge, it did not conduct a full-scale risk assessment and risk characterization for ingested arsenic. Instead, it provided an evaluation of the potential potency of arsenic intended for use in a "public-health context."

CPSC staff calculated CSF values based on the EPA assessment ranging between 0.4 and 3.7 $(mg/kg\text{-}day)^{-1}$, and a CSF value based on the NRC report of 23 $(mg/kg\text{-}day)^{-1}$. (As discussed in more detail below, it should be noted that the high end CSF estimate calculated by CPSC staff based on the EPA analyses (3.7 $[mg/kg\text{-}day]^{-1}$) appears to reflect an error in the CPSC staff calculations. Correcting the apparent error would reduce this estimate by approximately a factor of 2, to 1.9 $[mg/kg\text{-}day]^{-1}$.) This

range of CSF values was calculated using essentially the same set of epidemiological data. The primary differences in approach resulting in the broad range of potential CSF values were associated with the choices made regarding the appropriate comparison populations used to quantify excess cancer risks and the models used to extrapolate risks at low doses based on observations made in populations exposed to high doses of arsenic. The selected methodologies also differed in the assumptions made regarding arsenic intake in the Taiwanese study population from sources such as food and water.

Although CPSC staff treat this full range of possible values as equally plausible in their risk analyses, CPSC staff also note "the shortcomings of the available data" when addressing these values (CPSC, 2003). As discussed below, these "shortcomings" in the available data result in substantial uncertainties in all of the CSF values that have been derived for ingested arsenic. Moreover, numerous factors suggest that the available CSFs are likely to overestimate actual risks associated with arsenic ingestion at the low levels typically associated with exposure settings such as contact with arsenic from CCA-treated wood. The high end CSF derived based on the NRC analysis is particularly uncertain and is inconsistent with available epidemiological evidence.

To calculate a reasonable CSF for arsenic, it is necessary to accurately describe the dose-response relationship between arsenic exposure and consequent health effects. Often, EPA and other regulatory agencies develop CSF values using data from animal experiments conducted at high doses and extrapolating these results to predict possible human health effects at lower doses. By contrast, for inorganic arsenic, there are no reliable animal models to assess arsenic carcinogenicity; however, there is a large body of epidemiological data which has demonstrated an association between arsenic exposure through contaminated drinking water and a variety of different cancers in humans. While many epidemiological studies describing the relationship between arsenic and cancer exist in the scientific literature, only a few have sufficient data and quality controls to be useful for risk calculations. Even fewer contain a study design that would be useful for assessing potential health risks from low level exposures to arsenic from CCA-treated wood. In particular, none of the available epidemiological studies with adequate sample sizes and quality control procedures demonstrate adverse health effects of arsenic associated with low levels of exposure (*e.g.*, Kurttio *et al.*, 1999; Bates *et al.*, 1995).

The primary study used by EPA and the NRC to quantitatively assess cancer risks associated with arsenic ingestion in their evaluations of the MCL is a large-scale study conducted in Southwestern Taiwan in individuals exposed to arsenic in drinking water at levels that ranged from 10–1,752 µg/L

(Chen *et al.*, 1985; Chen *et al.*, 1992; Wu *et al.*, 1989). This study, which has been re-analyzed several different times, showed significant associations between arsenic exposure and cancer mortality from lung and bladder cancer, and weaker associations with cancer mortality from liver and kidney tumors. The NRC also used this study to derive a unit risk value for arsenic-induced cancer (*i.e.*, a value indicating the number of excess cases of bladder or lung cancer associated with intake of 1 μg/L of arsenic in drinking water over a 70-year lifetime). The NRC also took into consideration a study by Ferreccio *et al.* (2000). This study examined a South American population exposed to arsenic in drinking water (at concentrations ranging between 1 and 860 μg/L) and established an association between arsenic exposure and lung cancer.

In general, it is problematic to use these epidemiological studies directly to predict risks posed by arsenic to U.S. populations (Brown *et al.*, 1997; Chappell *et al.*, 1997; Guo *et al.*, 1998). For example, as discussed in more detail below, substantial problems exist in identifying the specific arsenic doses that the study participants experienced (Brown *et al.*, 1997). There are numerous areas of uncertainty in evaluating the toxicity and carcinogenicity associated with arsenic exposure based on epidemiological data (Abernathy *et al.*, 1999). The principal areas of concern involve defining an appropriate dose-response relationship, assessing the relevance and applicability of studies conducted in the poor agrarian society of the Southwestern Taiwanese to the U.S. population, and the uncertainty of the shape of the dose-response curve at low doses. Moreover, the types of risk levels observed in the Taiwanese and South American study populations have not been observed in comparable studies conducted in U.S. populations.

Similarly, available data do not indicate potential carcinogenic risks associated with the negligible arsenic exposure levels from contacts with structures built of CCA-treated wood or with the higher exposures experienced by various worker populations contacting CCA-treated wood. For example, a review by the Florida Physicians Arsenic Workgroup reports that there is no evidence of an epidemic or cluster of diseases resulting from contact with structures built of CCA-treated wood (FPAW, 2002). Moreover, while some clinical reports suggest an association between health risks (but not cancers) and high occupational levels of exposures to arsenic from CCA-treated wood, other more comprehensive studies have not shown increased health risks despite elevated exposures to arsenic from CCA-treated wood in occupational settings (Budy and Rashad, 1976; Decker *et al.*, 2002). If these factors are not considered carefully, extrapolating risks for U.S. populations based on data from current epidemiological studies conducted in Taiwan and South American could overestimate risks for U.S.

populations. Such extrapolations are particularly likely to overestimate potential risks associated with arsenic for populations exposed to structures built of CCA-treated wood.

Conservative Elements of EPA and NRC Slope Factor Calculations

While EPA and the NRC differ significantly in their methodologies for deriving a dose-response relationship for arsenic, certain features that are common to both analyses incorporate conservative assumptions and uncertainties into the evaluation. These conservative elements include the dose-response model assumed to extrapolate carcinogenic risks associated with low level arsenic exposures based on the higher exposure levels experienced in the epidemiological studies used to derive the cancer risk estimates. Specifically, both EPA and the NRC assumed a linear dose-response relationship for arsenic even at low doses (*i.e.*, they assumed that no dose of arsenic is without risk). In addition, both EPA and the NRC only considered the results of the Taiwanese epidemiological studies when quantifying potential arsenic risks and discounted the results of analyses conducted in arsenic-exposed populations in the U.S. Similarly, the EPA and NRC analyses failed to account for the poor nutritional status of the Taiwanese study population in a quantitative fashion and to address how this factor might increase their sensitivity to arsenic toxicity. The effects of these conservative elements mischaracterizes the actual potency of arsenic. Moreover, these conservatively derived toxicity values are likely to overestimate risks for U.S. populations where arsenic exposures (*e.g.*, from water and CCA-treated wood) are significantly lower and nutritional status is better. These conservative assumptions are each discussed in more depth below.

Non-linearity of Dose-response Relationship for Arsenic Carcinogenicity

The statistical models used by EPA and the NRC to quantify cancer risks associated with arsenic ingestion include the default assumption that the dose-response relationship is linear at low doses. This assumption implies that even very low dose of arsenic confer some excess cancer risk and that, as the dose increases, risk increases in a directly proportional fashion. Careful examination of the biological principles that govern arsenic toxicity indicate that this assumption is incorrect and that the true dose-response relationship is likely to be sub-linear or non-linear. Thus, from a toxicological perspective, low doses of arsenic would be relatively less harmful than higher doses, and may, in fact, be associated with zero risk.

A key fact that supports non-linearity for the arsenic dose-response relationship is associated with the way in which arsenic alters gene expression (USEPA, 1997; Clewell *et al.*, 1999). Specifically, arsenic does not interact directly with DNA to produce point mutations, but instead may modify gene transcription through one or more indirect mechanisms, including chromosome alterations, changes in DNA-methylation patterns, and perturbation of key regulatory enzymes. A description of possible mechanisms of arsenic-induced carcinogenesis is provided below. These mechanisms are not mutually exclusive and all are consistent with a non-linear dose-response relationship.

- Arsenic has conclusively been shown to induce chromosome damage. Clastogenic effects in response to arsenic have been observed in both *in vivo* and *in vitro* test systems. Some alterations include chromosomal deletions (Hei *et al.*, 1998), induction of micronuclei (Noda *et al.*, 2002; Wang and Huang, 1994) and aneuploidy (Vega *et al.*, 1995). Although chromosomal alterations are only one proposed mode of action of arsenic carcinogenesis, the NRC concluded that the "most accepted explanation for the mode of action for arsenic carcinogenicity is that it induces chromosomal abnormalities without interacting directly with DNA" (NRC, 1999).
- Arsenic affects the methylation status of DNA, which can affect gene transcription. For example, chronic exposure of rat skin cells in culture to arsenic caused reduced DNA methylation with impacts on gene transcription (Zhao *et al.*, 1997). These changes were associated with malignancy as reflected by the production of tumors when cells were injected into mice. Additionally, the effect of arsenic on perturbing DNA methylation may depend on the nutritional status of the affected individual. In particular, individuals who have diets low in selenium might be more sensitive to arsenic-induced perturbation of DNA methylation (USEPA, 2001; Slayton *et al.*, 1996; ATSDR, 1998). Conversely, this mode of arsenic carcinogenesis would not be expected to be a factor in well-nourished individual.
- Arsenic is known to inhibit enzymes through interaction with thiol-rich groups embedded in proteins, causing alterations to protein structure and function. In particular, DNA ligase is inhibited in the presence of arsenic exposure (Li and Rossmann, 1989). Inhibition of DNA repair enzymes is consistent with a non-linear mode of carcinogenesis.
- Arsenic-induced carcinogenicity may also be induced by modulation of cell signaling pathways responsible for cell growth. Particularly, exposure to arsenic has been seen to activate the c-Src dependent epidermal growth factor receptor (EGFR) pathway and the mitogen-activated protein kinase (MAPK) pathway (Luster, 2003). These pathways are involved in the regulation of cell proliferation. Perturbation of this pathway can result in unregulated cell growth commonly associated with the effects of tumor promotion.
- Recently, a role has been suggested for the metabolites of inorganic arsenic (*i.e.*, monomethylarsinic acid [MMA] and dimethylarsinic acid [DMA]) to generate reactive free oxygen radicals that can result in DNA damage (Kitchin and Ahmad, 2003; Mass *et al.*, 2001). As a contributing factor in carcinogenesis, oxidative injury is consistent with a non-linear mode of action for the purposes of human health risk assessment. A living organism endures constant oxidative attack. Protective pre-emptive mechanisms, such activation of anti-oxidants, as well as post-damage DNA repair systems are well prepared to combat many types of oxidative injury (Sancar, 1994; Modrich, 1994). Thus,

there likely exists a threshold under which oxidative damage generated by trivalent organo-arsenicals (*e.g.*, arsenic metabolites) can be counteracted by antioxidants and DNA repair systems.

- Treatment of human cells with micromolar concentrations of arsenic can induce protective cellular mechanisms such as the upregulation of glutathione and induction of heat shock proteins (Del Razo *et al.*, 2001; Schuliga *et al.*, 2002). These mechanisms will protect cells from arsenic induced-damage and are also consistent with a non-linear dose-response relationship.
- Luster (2003) suggests that arsenic acts as a co-mutagen by inhibiting DNA repair. This mechanism, together with others including those mentioned above, "suggests the likelihood that the dose-response for arsenic may be non-linear in the low dose region."

Based on available data including the above proposed modes of action, arsenic does not appear to be an initiating carcinogen (*i.e.*, the type of carcinogen for which a linear dose-response relationship is plausible). Instead, arsenic likely acts late in the carcinogenic process as a tumor progressor (Lee *et al.*, 1988; Germolec *et al.*, 1997). A progressor acts by enhancing (through increased cell proliferation) the progression to malignancy of already initiated cells (*i.e.*, cells which have had some initial DNA damage). For this enhancement to occur, the progressor must be present at sufficiently high doses for an adequate period of time. This conclusion is consistent with that of an expert panel convened by EPA to evaluate the shape of the arsenic dose-response relationship (USEPA, 1997). The NRC also concluded that "a sublinear dose-response curve in the low-dose range is predicted, although linearity can not be ruled out" (NRC, 1999).

In addition, there is evidence that low levels of arsenic may have a protective or anti-carcinogenic effect. For example, subtoxic concentrations of arsenic have been shown to increase viability, induce stress response genes, alter redox capacity, and induce DNA repair activity in cultured human cells (Snow *et al.*, 1999). Similarly, chronic exposure to arsenic in cultured rat cells induced resistance to higher levels of arsenic (Romach *et al.*, 2000). In addition, results in rats suggest that administration of arsenic alone and in chemical mixtures antagonizes the development of glutathione s-transferase positive foci tumor precursor lesions in rats (Pott *et al.*, 2001).

Despite the overwhelming evidence that arsenic does not exert its toxicity in a linear fashion, both the EPA and the NRC have used linear models to estimate human risks at low arsenic exposures. This decision was made based on a 1996 EPA guidance document which states that, in the absence of definitive mode of action, a linear default assumption will be utilized. Thus, the decision to reject a non-linear or threshold model for arsenic carcinogenesis was a decision based on policy and not the most

biologically plausible model. Because the EPA quantitative carcinogenic assessment for ingested arsenic is based on a linear dose-response relationship, and the true dose-response is likely to be non-linear, use of the CSF generated based on the EPA analyses is likely to overestimate cancer risks at some exposure levels lower than those experienced in the Taiwanese study.

This conclusion is further supported by results in a number of epidemiology studies in which associations between arsenic exposure and carcinogenic effects were only observed at the higher exposure levels present in the study population. For example, the NRC 2001 report discusses five recent studies that found an association between the occurrence of cancer and exposure to arsenic in drinking water. Four of these studies show no effects of arsenic until arsenic concentrations in drinking water were significantly greater than the present drinking water standard (*i.e.*, the maximum contaminant level or MCL, of 10 μg/L). The first study notes that the relative risk for urinary cancer and transitional cell carcinoma in a northeastern Taiwanese study population (based on a National Taiwan comparison group) was statistically significant only at arsenic concentrations in drinking water greater than 100 μg/L (Chiou *et al.*, 2001). In the second study (Morales *et al.*, 2000), the original data from Southwestern Taiwan were re-analyzed. Using a southwestern Taiwanese comparison group, a recalculation of the relative risks for lung and bladder cancer showed a dose-response relationship only at arsenic concentrations in drinking water that were greater than 400 μg/L. In the third study (Lewis *et al.*, 1999), using a general Utah comparison group, the relative risk for lung and bladder cancer in a population of in Utah was not found to be significantly greater than the background risk at mean concentrations of arsenic in drinking water ranging to 191 μg/L. In the fourth study (Tucker *et al.*, 2001), which was a cross-sectional study of a population from Inner Mongolia, skin cancer was observed only in individuals exposed to peak concentrations of 150 μg/L or greater.

Based on a Chilean population, the fifth study alleges effects at arsenic concentrations in drinking water that are less than the MCL (Ferreccio *et al.*, 2000); however, as discussed in more detail below, this study has serious limitations that preclude its use for quantifying risks, *e.g.*, changing exposure group categories in different analyses. Although the NRC 2001 report acknowledges the limitations of this study, the NRC nevertheless used the study to quantify estimates for the Chilean study population, and to justify performing similar extrapolations based on the Southwestern Taiwanese data. Again, this approach ignores important available data and is likely to lead to overestimates of potential risks associated with low-level arsenic exposures.

Failure to Consider Results of Epidemiological Studies of U.S. Populations

As noted above, the EPA and NRC analyses also failed to reflect the results from studies in U.S. populations which suggest that the incidence of cancer in these groups is less than would be predicted based on the Taiwanese or South American studies. Several well-designed epidemiological studies have been conducted in U.S. populations with elevated arsenic exposures; however, in contrast with the Taiwanese studies, results from these studies have been mostly negative. For example, EPA sponsored and directed a large-scale study of arsenic diseases that was conducted in several communities in Utah with elevated arsenic concentrations in their drinking water (Lewis *et al.*, 1999). This study found no convincing evidence of carcinogenic or noncancer effects at average arsenic concentrations in drinking water ranging to 191 μg/L, which is significantly greater than the MCL of 10 μg/L. The study included a high percentage of participants who were members of the Mormon Church. This population generally has lower rates of alcohol and tobacco consumption doe to religious beliefs. As a result, measures of lung and bladder cancers from this study are minimally confounded by use of alcohol and tobacco. While the Lewis *et al.* study has some limitations, it possesses many strengths, including better exposure history information for study participants than has been available for other studies.

Furthermore, several other studies of U.S. populations have also failed to identify a relationship between arsenic exposure and increased cancer risks (Moore *et al.*, 2002; Tollestrup *et al.*, 2002; Valberg *et al.*, 1998; Bates *et al.*, 1995; Engel and Smith, 1994; Morton *et al.*, 1976). These studies have examined bladder, lung, and skin cancer risks, including both childhood and adult exposure periods, for populations with elevated arsenic exposures (*e.g.*, with arsenic drinking water concentrations as high as 400 μg/L). The results from these studies thus present the possibility that no diseases associated with arsenic exposure have occurred at exposure levels typical of U.S. exposures. This finding suggests that the number of cancer cases reduced in the U.S. as the result of reducing any already low level arsenic exposures (*e.g.*, *via* arsenic in drinking water or associated with contacts with CCA-treated wood structures) may be unrecognizably small or nonexistent. The results of this and other studies of U.S. populations are discussed in more detail below.

The advantage of analyzing arsenic-induced cancer effects in U.S. populations is apparent. Using results obtained from more relevant study populations avoids the many confounding factors that distort extrapolation of results observed in populations residing in areas of the world that differ significantly from U.S. populations in characteristics such as their nutritional status and other aspects of their lifestyle.

Using study populations that have similar diets, a higher standard of living, and are exposed to levels of arsenic that are of current concern in the U.S. will generate a more realistic picture of anticipated risks for U.S. populations. These factors should be considered when selecting a CSF for estimating potential cancer risks and when interpreting the risk estimates derived from using specific CSF values.

Failure to Consider Role of Nutritional Status in Susceptibility to Arsenic Carcinogenicity

Studies of arsenic-exposed populations in Taiwan and India provide evidence that nutritional deficiencies enhance responsiveness to arsenic (Mazumder *et al.*, 1997; Mazumder *et al.*, 1998; Hsueh *et al.*, 1997). For example, in an Indian population exposed to arsenic in their drinking water, individuals who were 80% below the standard body weight for their age and gender had an increased prevalence of skin keratoses, a condition associated with arsenic exposure (Mazumder *et al.*, 1998). The role of malnourishment in enhancing susceptibility to arsenic has a mechanistic explanation. Believed to be an important detoxification pathway for inorganic arsenic in the body, methylation is dependent on the availability of methyl donors groups (*e.g.*, methionine, choline, and cysteine). Arsenic has also been shown to be methylated nonenzymatically by methylvitamin B_{12} and glutathione (Zakharyan and Aposhian, 1999). Poor nutritional status (such as a diet low in protein, selenium, or vitamin B_{12}) may result in a reduced ability to detoxify arsenic (NRC, 1999; Slayton *et al.*, 1996; Kitchin, 2001).

As another example, in a case/control study in Taiwan, a synergistic interaction for risk of ischemic heart disease was reported between low serum carotene levels and consumption of water containing arsenic (Hsueh *et al.*, 1998).[1] Lower serum beta-carotene levels were also found to be associated with increased skin cancer risks (Hsueh *et al.*, 1997). These findings suggest that inadequate carotene intake and/or overall poor nourishment increases susceptibility to arsenic-related health effects.

Therefore, populations with severe malnutrition (such as the Taiwanese and Indian populations exposed to elevated concentrations of arsenic in their drinking water) may have a higher susceptibility to the adverse effects of arsenic than people living in the United States, where such severe malnutrition is unlikely to occur. As noted by EPA, "there is a concern of the applicability of extrapolating data from the Taiwanese to U.S. populations because of different background rates of cancer, possibly genetically determined, and differences in diet other than arsenic (*e.g.*, low protein and fat and high carbohydrate)" (USEPA, 2001). Individuals in the U.S., who are generally well nourished, are likely to be less

[1] Alpha- and beta-carotene are antioxidants found in many fruits and vegetables.

responsive to arsenic than individuals from other, less developed nations. Again, this factor increases the likelihood that quantitative risk estimates derived based on data from study populations where malnutrition was a significant concern (*e.g.*, the Taiwanese study population) will overestimate actual risks in typical U.S. populations.

Deficiencies in Procedures Used to Derive Specific CSF Estimates

Although EPA and the NRC used some of the same information and considerations when estimating the carcinogenic potency of low level arsenic exposures, many of the assumptions applied in the analyses differed. In its analysis of benefits associated with adopting a new MCL for arsenic in drinking water (USEPA, 2001), EPA developed both lower- and upper-bound estimates of excess risk associated with a variety of arsenic concentrations in drinking water. Based on these risk estimates presented by EPA, CPSC staff calculated lower- and upper-bound CSFs for arsenic ingestion of 0.4 $(mg/kg\text{-}day)^{-1}$ and 3.7 $(mg/kg\text{-}day)^{-1}$. As noted above, examination of CPSC staff calculations suggests that the upper-bound value may be in error and may, in fact, be 1.9 $(mg/kg\text{-}day)^{-1}$, based on the procedures applied by CPSC staff. This range reflects use of different assumptions regarding variations in U.S. water consumption rates and total estimated arsenic intakes in the Taiwanese population. The NRC reanalysis of the same data was used by CPSC staff to estimate a much greater CSF value of 23 cancer cases per mg/kg-day, suggesting that the carcinogenic potency of ingested arsenic is 6 to 60 times greater than indicated by the EPA analyses (NRC, 2001). While the NRC considered alternative methodologies to calculate arsenic potency, they did not present their estimates as a range. Instead, only the risks associated with their preferred approach were presented. The substantial discrepancy between the EPA and NRC values is based on a number of factors that must carefully be considered when using the results of the EPA and NRC risk analyses to assess potential carcinogenic risks associated with arsenic ingestion. Differences in the analyses are discussed below. These differences indicate that, while the CSF values resulting from EPA analyses reflect many of the conservative elements discussed above, by comparison with the NRC evaluations the EPA values reflect a more reasonable and scientifically-sound approach for estimating the carcinogenic potency of ingested arsenic.

Studies Used to Calculate Cancer Risks

As mentioned above, both EPA and the NRC based their risk analysis on studies of Taiwanese populations with elevated arsenic concentrations in their drinking water (Chen *et al.*, 1985, 1992; Wu

et al., 1989). In particular, the Chen *et al.* (1992) study included extensive data collection and information on multiple cancer endpoints. Data regarding cancer mortality and arsenic concentrations in well water samples were collected from 42 villages in southwestern Taiwan from 1973-1968. This data collection program provided ample data to establish a significant relationship between arsenic intake and deaths due to bladder and lung cancers. The central shortcoming of this study was that it was an ecologic assessment that attempted to correlate median arsenic concentrations in well water to cancer incidence in the villages. This approach is problematic because a specific individual who developed cancer is unlikely to have been exposed to the median arsenic concentration. Instead, such individuals are more likely to have been to exposed to higher arsenic concentrations in the more contaminated wells.

As a result, the doses for the studied individuals were imprecisely characterized. For example, in one of the villages, the median arsenic concentration measured in the well water samples was 30 µg/L; however, the range of concentrations observed in the five wells sampled in that village ranged from 10 µg/L to 770 µg/L (with specific concentrations for the sampled wells of 10 µg/L, 10 µg/L, 30 µg/L, 259 µg/L, and 770 µg/L). Observed cancer cases in this village are more likely to be associated with the exposures to the wells with the higher concentrations (*i.e.*, 259 µg/L or 770 µg/L) rather than with the wells with the lower concentrations (*i.e.*, 10 µg/L or 30 µg/L). It is not possible to develop a reliable and accurate dose-response relationship from this information because of the uncertainties inherent in the available exposure data. Therefore, while the Taiwan studies provide qualitative evidence of a relationship between arsenic ingestion and cancer risk, these studies do not provide definitive support for developing a quantitative carcinogenic potency value.

As noted elsewhere in these comments, even if the Taiwanese data were more applicable for establishing a quantitative dose–response relationship for Taiwanese populations, other factors indicate that the data derived from the Taiwanese population do not provide an appropriate basis for quantifying arsenic-related risks in the U.S. First, the standard of living in the southwestern Taiwanese study region was considered to be below average for Taiwan and is not comparable to the typical U.S. standard of living. Most of the study population subsisted on a diet consisting primarily of sweet potatoes and rice, with limited intake of fresh vegetables and animal protein (Wu *et al.*, 1989). As discussed above, this confounding variable of nutritional status may have greatly contributed to the excess cancer risk observed in the studied population. Second, the arsenic concentrations in drinking water that the Taiwanese were exposed to were very high (*i.e.*, ranging from 10 µg/L to 1,752 mg/L). As a result, only a small fraction of the studied individuals were exposed to arsenic concentrations that are relevant for exposures in the

U.S. Lifetime exposure to arsenic associated with CCA-treated wood is expected to be even less than that associated with drinking water in the U.S. Thus, the discrepancy between the arsenic exposures experienced by the Taiwanese study population and those that are likely to occur for the U.S. population of interest is even greater when assessing potential risks associated with contacts with structures built of CCA-treated wood. Because toxicological and epidemiological data suggest that the dose-response curve for arsenic carcinogenicity is non-linear, the differences between the exposure levels of the Taiwanese and U.S. populations require particular attention when attempting to extrapolate potential risks for U.S. populations based on the Taiwanese data.

Both EPA and the NRC also identified additional limitations in the Taiwanese study and subsequent analyses. Specifically, both EPA and NRC recognized that the data analyses presented in the original study were insufficient for drawing conclusions regarding potential risks for a U.S. population because these analyses did not account for arsenic exposure sources other than arsenic in drinking water (*e.g.*, arsenic in food and air). Also, EPA and the NRC noted that the original data analyses used an unreliable comparison control population to model the study data.

In addition to the Taiwanese study, the NRC subcommittee also examined a study of arsenic exposures in three regions in Chile as a potential source of information regarding the dose-response relationship between arsenic in drinking water and health effects (Ferreccio *et al.*, 2000). In selecting this study for evaluation, the NRC identified the following advantages of this study: adequate nutritional status of the participants, unbiased assessment of exposure, a lengthy exposure period, and consideration of confounders such as smoking in the analysis. In contrast with the ecological design of the Taiwanese study, NRC also noted that the Chilean study used a case-control approach. Despite these study advantages, this study also has significant limitations that raise serious concerns regarding the NRC's use of the study to quantify risks associated with low level exposures to arsenic. As detailed in a recent review (Mandel and Kelsh, 2001), the weaknesses of this study include inconsistencies in how doses were estimated and how cases and controls were selected. Specifically, the selected dose ranges vary in different analyses and the numbers of individuals included in the control groups differed from the numbers intended in the study design. Some of these weaknesses are commonly found in case-control studies. The authors themselves observe that the control selections could bias the study results, with risks being overestimated at low arsenic levels and underestimated at high arsenic levels. Thus, it is inappropriate to use this study in a quantitative manner. In choosing to evaluate the Ferreccio *et al.* study, the NRC analysis did not significantly alter the dose-response relationship for arsenic and lung cancer.

Instead, consideration of this study qualitatively confirmed the dose-response relationship between arsenic exposure and cancer that was observed in the Taiwan studies.

Choice of Cancer Endpoint

Both EPA and the NRC used lung and bladder cancers as health effect endpoints to calculate the carcinogenic potency of arsenic. This approach reflects a departure from earlier analyses conducted by both EPA and the NRC which had previously used skin cancer as the principal carcinogenic endpoint. This decision was rationalized by stating that internal caners were a more sensitive endpoint and a greater health concern, especially in the U.S.

Model Choice

Accurately quantifying potential health risks depends on both the quality of the data used to assess the risks and the model selected to estimate risk levels. Both EPA and the NRC relied heavily on the data obtained from the southwestern Taiwanese studies. Both organizations reviewed a number of potential approaches for statistically modeling the empirical data and extrapolating the results observed at high exposure levels to estimate the potential risks expected at low doses. As discussed earlier, based on policy considerations, both organizations chose to apply a linear approach to estimate potential effects at lower exposures despite substantial evidence that arsenic does not directly interact with DNA and, thus, arsenic-induced carcinogenesis may have a threshold or may best characterized by a sublinear dose-response curve.

When assessing the form of the dose-response relationship for arsenic, both EPA and the NRC reviewed an article by Morales *et al.* (2000). This article reanalyzes the data from the Taiwanese study using 10 different mathematical models, which were applied using three different comparison populations. For its risk calculations, EPA used the exhaustive statistical analyses of the Taiwanese data presented in Morales *et al.* (2000), as further reanalyzed by EPA. NRC also considered the statistical analyses and data presented in Morales *et al.* (2000), but expanded its analyses to consider lung cancers and models that were not originally considered in the Morales study. Specifically, NRC explored models that included either linear or quadratic dose terms, whereas Morales *et al.* (2000) only considered exponential linear and exponential quadratic dose terms.

These models differ significantly in the way they fit the Taiwanese data. Only one model that was originally applied in the Morales analyses permitted non-linearity at low dose arsenic exposures, *i.e.*, the multistage-Weibull model (MSW). In the examples provided in the original Morales *et al.* article and in NRC's subsequent work, the nonlinear models performed as well as or better than linear models according to the various measures of fitness that were examined (*e.g.*, Akaike Information Criteria (AIC) and Bayesian Posterior Model Probabilities (PMP)). In fact, statistical tests comparing the PMPs would be unable to distinguish between several of the best fitting models, which frequently included the MSW model. Thus, the analysis by Morales *et al.* (2000) shows that the dose-response relationship at low doses of arsenic is highly unstable and that this relationship is poorly described by a linear model. Both the EPA and NRC reports acknowledge the instability of the simply linear model. As previously described, there is a scientific basis for employing other models that are non-linear and which would likely indicate lower risks than those presented in NRC (2001). At a minimum, because of the uncertainty regarding the comparison populations, the instability of the model fits, and the relative equivalence of various proposed models in fitting the data, the NRC and EPA reports should have considered multiple plausible model forms simultaneously to establish a range of valid dose-response relationships and, therefore, a more comprehensive range of potential doses of concern. Instead, EPA's and NRC's characterization of the range of valid dose-response relationships has been distorted by their focus on thoroughly describing a single functional form.

There are two differences between the functional form of the dose-response relationship for arsenic as described by EPA and NRC. As described below, the first difference is the choice of a comparison population. The second difference relates to the shape of the dose-effect relationship. Following the example of Morales *et al.* (2000), EPA assumed an exponential linear dose-effect relationship. This choice implies the use of a multiplicative model. In contrast, NRC departed from any example presented by Morales *et al.* (2000) and assumed a linear dose-effect relationship. This choice implies an additive model. All of the remaining aspects of the dose-response model were identical between the modeling approaches selected by EPA and NRC. These model elements included: the regression methods used to fit the data to the model, the transformations of the dose term, and the age effect. The dose-response model elements selected by EPA and NRC are compared in the following table.

Table B-1
Summary of EPA and NRC Model Elements

Terminology	EPA, 2001	NRC, 2001
Regression Method	Poisson	Poisson
Comparison Population	None	Southwestern Taiwan
Age Effect $h_0(t)$	Quadratic $\exp(\alpha_0+\alpha_1 t+\alpha_2 t^2)$	Quadratic $\exp(\alpha_0+\alpha_1 t+\alpha_2 t^2)$
Dose Transformation	Linear x=μg/L	Linear x=μg/L
Model Choice	Multiplicative	Additive
Dose effect $g(x)$	Exponential Linear $\exp(\beta_1 x)$	Linear $\beta_1 x$

Comparison Population

One of the major reasons that the original analysis by Chen *et al.* (1992) was inconclusive was because background cancer rates for all of Taiwan were compared with the cancer deaths observed in the study regions with elevated arsenic concentrations in their drinking water. This approach inherently assumes that the baseline cancer risks in the southwestern Taiwan study population are the same as those for populations residing in the more urban areas of Taiwan. In addition, the use of an external comparison population by Chen and co-workers assumes that arsenic exposures in areas of Taiwan that are not within the study area are essentially zero. Both of these assumptions are problematic and will lead to overestimates of the carcinogenic potency of ingested arsenic.

According to Morales *et al.* (2000), the choice to use an internal control population (*i.e.*, a comparison group from within the study population) rather than an external control population (*i.e.*, a comparison group selected from outside the exposed group of interest) substantially effects the shape of the exposure-response relationship for arsenic. In fact, in many cases, choosing an external comparison population causes the dose-response curve to appear supra-linear, *i.e.*, exposures to low doses of arsenic would be expected to result in proportionately more cancer deaths than exposures to high doses. This model prediction is inconsistent with the likely mode of action of arsenic carcinogenicity and with the results of numerous epidemiological studies that have shown no adverse health effects from exposure to arsenic at low doses.

For its ultimate risk analyses, EPA chose to use a linear model (Model 1 from the Morales study) that did not compare the observed cancer mortality to an external control population (USEPA, 2001). As noted above, this decision was based on the observation that use of external comparison populations resulted in a supra-linear dose-response relationship which the EPA correctly assessed was biologically implausible. By comparison, the NRC selected an external control population, stating that the cancer

rates for the southwestern study region and Taiwan as a whole do not differ significantly when normalized for arsenic exposures. This approach ignores differences that exist between urban and rural areas of Taiwan with respect to education, health care access, and diet. The NRC notes that the supra-linear dose-response relationship is probably an artifact of poor data collection and inability to control for confounding factors.

Drinking Water Intakes in Taiwan

The carcinogenic potency of arsenic that is estimated based on the Taiwanese studies is sensitive to the total arsenic intake of the study participants. The primary source of arsenic intake that was the focus of the Taiwanese studies was direct intake resulting from consuming drinking water containing elevated arsenic concentrations. The study populations also were exposed to additional arsenic from specific components of their diet (*e.g.*, rice and yams) and from the use of arsenic-containing water in cooking. Both EPA and the NRC assumed that the average Taiwanese study participant would drink relatively more water than a citizen of the U.S. EPA assumed the average Taiwanese male would consume 3.5 L of water per day while a female would ingest only 2.0 L/day. The NRC subcommittee assumed an average water intake of 2.2 L/day for both males and females. This element of the NRC approach would tend to increase the estimated carcinogenic potency of ingested arsenic relative to the EPA calculations because a smaller amount of ingested arsenic was associated with the observed carcinogenic effects.

If arsenic exposure sources (other than drinking water) are not correctly accounted for, the arsenic dose that the Taiwanese study population experienced will be underestimated. As a result, the risks associated with arsenic exposures will be overestimated. The original analyses presented by Chen *et al.* (1985) were criticized because food-borne arsenic was not accounted for when estimating arsenic doses. This omission was particularly problematic for this study because the primary food staples of the Southwestern Taiwanese study population (*i.e.*, rice and yams) can take up relatively large amounts of arsenic during cultivation. Schoof *et al.* (1998) estimated that yam and rice consumption in this area of Taiwan may contribute more than 50 µg of arsenic per day to an individual's arsenic intake. In addition, rice and yams can take up arsenic from water used in the cooking process. To accurately determine arsenic intake, this additional water intake should be characterized and added to the total arsenic dose.

To account for arsenic in the diet, the NRC suggested that a correction factor of 30 µg/day be added to the total arsenic dose for an individual. This adjustment was intended to include the water used

to cook the food as well as the food itself. In light of the estimates presented in Schoof *et al.* (1998), EPA's assumption is likely to significantly underestimate arsenic intake associated with arsenic in food sources and arsenic uptake from water during cooking. By contrast, EPA took a more reasonable approach when developing a lower-bound estimate of arsenic risk. To account for water absorbed into food during cooking, EPA assumed that 1 L of water should be added to both male and female water consumption (bringing the total water consumption to 4.4 L/day for males and 3 L/day for females). EPA also assumed that an additional 50 μg per day was available for ingestion in raw food.

EPA's approach for accounting for arsenic in the diet has more scientific merit as it incorporates available data regarding food-borne arsenic intake values for the Taiwanese study population and also makes adjustments for water absorbed during the cooking process. Because the NRC is likely to have underestimated the amount of dietary arsenic intake for the Taiwanese study population, their approach will underestimate the total arsenic intake for the study population and consequently will overestimate the carcinogenic potency of ingested arsenic, particularly at low doses.

Overall Comparison of the EPA and NRC Approaches

In almost all of its assumptions, the NRC took a very conservative approach towards assessing the carcinogenic potency of ingested arsenic. These choices led to risk estimates suggesting a CSF of 23 $(mg/kg\text{-}day)^{-1}$, a figure that ignores applicable biological data and relies upon unsubstantiated ecological data. This unreasonably inflated value arises from a variety of sources. Most importantly, the use of an external comparison population for determining likely baseline cancer rates in the study population distorted calculations of excess cancer risks associated with arsenic exposure. In particular, choosing a large external population and imposing a linear constraint on the dose-response model greatly enhanced the steepness of the apparent dose-response relationship between arsenic and cancer mortality. In addition, the Taiwanese intake of arsenic from food and cooking water was underestimated, causing the associated value for the carcinogenic potency to be overestimated. EPA's analyses of arsenic carcinogenicity also included many conservative elements, *e.g.*, focusing solely on linear dose-response models and overlooking adjustments for nutritional deficits in the Taiwanese populations. Overall, however, EPA's modeling efforts were more scientifically sound and better reflect currently available information.

Overall, the range of CSFs derived from the analyses of EPA and the NRC differed by a factor of almost 60-fold. This discrepancy is not simply a reflection of any variability or sensitivity in the analysis,

but instead represents important and incompatible differences in scientific and mathematical methodologies. By accepting both analyses unconditionally, CPSC staff significantly misrepresent the uncertainty surrounding the carcinogenic potency of ingested arsenic. CPSC staff expressly state that their rationale for electing to use both analyses is that " both quantitative assessments by the EPA (2001) and the NRC (2001) are reasonable and appropriate." In fact, in light of the substantial uncertainties that exist in quantifying the carcinogenic potency of ingested arsenic, both assessments are likely to overestimate the potential carcinogenic risks associated with low-dose arsenic exposures in the U.S. Moreover, the CPSC staff analysis corresponds to a quantitative CSF value that is implausible and reflects numerous flawed assumptions which should preclude its use in quantifying potential risks associated with typical U.S. exposures to ingested arsenic.

Apparent Error in CPSC Staff CSF Calculations

As noted above, review of the CSF values derived by CPSC staff based on the EPA and NRC risk analyses suggests that the CSF calculated based on the upper-bound EPA risk estimates reflects a calculation error. This review suggests that the value calculated by CPSC staff is 2-fold greater than the actual value and should be 1.9 $(mg/kg\text{-}day)^{-1}$ rather than 3.7 $(mg/kg\text{-}day)^{-1}$ as indicated by the CPSC staff report. When combined with the uncertainties indicating that the high-end CSF applied by the CPSC staff in their risk analyses is unsuitable for risk calculations, correction of this error indicates that the high-end CSF value that CPSC staff should use in their risk calculations should be reduced by a factor of 12, from 23 $(mg/kg\text{-}day)^{-1}$ to 1.9 $(mg/kg\text{-}day)^{-1}$. This change would reduce the corresponding risk estimates by a similar amount. The basis for these conclusions is described below.

In its January 22, 2001 Final Rule regarding arsenic in drinking water, EPA reported a range of cancer incidence risks for U.S. populations associated with various options for drinking water MCLs. EPA derived this range of risks based on the following considerations:

- Risks were estimated for bladder and lung cancer combined, males and females combined.
- Cancer risks were calculated for MCL options of 3, 5, 10, and 20 µg/L.
- Risks were calculated for two estimates of "community tap water" ingestion:
  - Mean exposure level (*i.e.*, 1 L of water intake per person per day)
  - 90th percentile exposure level (*i.e.*, 2.1 L of water intake per person per day)

Alternatively, risks were also calculated for two estimates of "total water" ingestion, which includes sources such as bottled water. The daily "total water" ingestion was estimated as 1.2 L for the mean exposure level and 2.3 L per person per day for the 90th percentile exposure level.

- Upper- and lower-bound cancer risks for each combination of *i)* MCL option, *ii)* type of drinking water ingestion, and *iii)* quantile of the exposure level, included adjustments for food and cooking water intakes in the Taiwanese diets. These adjustments decreased the cancer risk estimate for the U.S. population, yielding the lower-bound estimate. Upper-bound estimates were calculated by omitting the adjustments for arsenic in food and cooking water.

EPA defines the CSF as an upper bound on the increased risk of cancer incidence resulting from a lifetime of exposure to an agent. CSF values are usually expressed in units of the proportion of a population affected per mg/kg-day of exposure. In presenting these risks in its documentation, EPA never explicitly states the CSFs that were used to calculate the risk estimates for U.S. populations. By reapplying the particular assumptions used to estimate the range of cancer risks for U.S. populations, however, the range of CSFs may be derived using the following equation:

Equation 1: Derivation of Carcinogenic Slope Factor from EPA Estimates of Risk Associated with Various MCL Options

$$CSF = RISK \div \left(\frac{MCL \cdot IR}{BW} \right),$$

where:

CSF	=	carcinogenic slope factor (in units of $[\mu g/kg\text{-}day]^{-1}$)
RISK	=	lifetime cancer risk for a population exposed at a particular MCL (unitless)
MCL	=	arsenic concentration in drinking water assumed in deriving a specific estimate of RISK (in µg/L),
IR	=	drinking water ingestion rate for a given exposure level (*i.e.*, the mean *vs.* 90th percentile) and water type (*i.e.*, community tap water *vs.* total water) (in L/day)
BW	=	average adult body weight (in kg).

In their assessment of cancer risks associated with exposures to arsenic from playground structures built of CCA-treated wood, CPSC staff calculated CSFs based on EPA's analysis that ranged from 0.4 to 3.7 $(mg/kg\text{-}day)^{-1}$. CPSC staff describe this range as based on EPA's risk estimates at a specified MCL, for either community tap water or total water ingestion, for either the mean or the 90th percentile exposure levels, and as reflective of both upper- and lower-bound estimates. CPSC staff do not provide the details of their calculations. To derive this range of values, however, CPSC staff must have

employed assumptions regarding average adult body weight and water ingestion rates, presumably equivalent to what EPA employed in its original risk estimates.

If one assumes, as EPA indicates, that an average adult weighs 70 kg, that mean and 90th percentile "community tap water" intakes are 1 and 2.1 L/day respectively, and that the mean and 90th percentile "total water" intakes are 1.2 and 2.3 L/day respectively, one cannot reproduce the full range of values for the CSF derived by CPSC staff. Applying these assumptions, Tables 1 and 2 summarize calculations based on EPA's lower and upper-bound risk estimates, for either community tap water or total water ingestion, for both mean and 90th percentile exposure levels. The CSFs derived in this way range between 0.4 and 1.9 (mg/kg/day)$^{-1}$. Two examples of these derivations (both assuming ingestion of total water) are also described in detail, using the framework established in Equation 1.

Table B-2
Summary of Lower-Bound Calculations of Arsenic CSF, Using EPA 2001 Data

Drinking Water Exposure Level	**Mean**		**90th %tile**	
Water Type	**Community**	**Total**	**Community**	**Total**
MCL (µg/L)	10	10	10	10
Risk @ MCL (USEPA, 2001, Table III.D-2(b))	*$6.30x10^{-5}$*	*$7.60x10^{-5}$*	*$1.32x10^{-4}$*	*$1.54x10^{-4}$*
Ingestion Rates (L/d)	1.0	1.2	2.1	2.3
Adult body weight (kg)	70	70	70	70
CSF (mg/kg/d)$^{-1}$	0.44	0.44	0.44	0.47

Table B-3
Summary of Upper-Bound Calculations of Arsenic CSF, Using EPA 2001 Data

Drinking Water Exposure Level	**Mean**		**90th %tile**	
Water Type	**Community**	**Total**	**Community**	**Total**
MCL (µg/L)	10	10	10	10
Risk @ MCL (USEPA, 2001, Table III.D-2(a))	*$2.41x10^{-4}$*	*$2.99x10^{-4}$*	*$5.23x^{10-4}$*	*$6.09x10^{-4}$*
Ingestion Rates (L/d)	1.0	1.2	2.1	2.3
Adult body weight (kg)	70	70	70	70
CSF (mg/kg/d)$^{-1}$	1.69	1.74	1.74	1.85

Example 1: Lower-bound CSF, for Mean Level of Exposure to Total Water

Using the data in Table 1, this CSF is calculated as follows:

$$CSF_L = 7.6\times10^{-5} \div \left(\frac{10\mu g/L \cdot 1.2L/day}{70kg}\right) = 0.00044(\mu g/kg/day)^{-1} = 0.44(mg/kg/day)^{-1}$$

Therefore, based on EPA's risk estimates, the CSF for the lower-bound estimate of the mean level of exposure to total arsenic in all sources of water is 0.44 $(mg/kg/day)^{-1}$. This value is virtually identical to all estimates of the lower-bound arsenic CSF, regardless of water types or drinking water exposure level.

Example 2: Upper-bound CSF, for the 90th Percentile Level of Exposure to Total Water

Using data in Table 2, this CSF is calculated as follows:

$$CSF_U = 6.09\times10^{-4} \div \left(\frac{10\mu g/L \cdot 2.3L/day}{70kg}\right) = 0.0019(\mu g/kg/day)^{-1} = 1.9(mg/kg/day)^{-1}$$

Therefore, based on EPA's risk estimates, the CSF for the upper-bound estimate of the 90th percentile level of exposure to total arsenic in all sources of water is 1.9 $(mg/kg/day)^{-1}$. This value is slightly greater than all other estimates of the upper-bound arsenic CSF, regardless of water types or drinking water exposure level.

Although the documentation provided by CPSC staff does not specifically describe their CSF calculations based on EPA's 2001 risk estimates, CPSC staff appear to have erroneously used the mean "community tap water" and mean "total water" intakes of 1 and 1.2 L/day, respectively, to derive the CSF estimates for both the mean and the 90th percentile levels of exposure. Thus, the calculation of the CSF based on the lower-bound risks in the mean exposed population is approximately correct, but the CSF based on the upper-bound risks at the 90th percentile of exposure is overestimated by almost two-fold. Thus, it seems that the risks associated with this 90th percentile exposed population were accounted for; however, their actual increased water consumption was not. Table 3 summarizes the assumptions that CPSC staff appear to have used in generating CSF estimates based on EPA's risk analyses. Table 3 also shows the resulting apparently erroneous CSFs.

Table B-4
Potential CPSC Staff Calculation of Lower- and Upper-Bound CSFs, Using EPA 2001 Data

Drinking Water Exposure Level	Mean (Lower Bound)		90th %tile (Upper Bound)	
Water Type	Community	Total	Community	Total
MCL (µg/L)	10	10	10	10
Risk @ MCL (USEPA, 2001, Table III.D-2(a))	$6.30x10^{-5}$	$7.60x10^{-5}$	$5.23x10^{-4}$	$6.09x10^{-4}$
Ingestion Rates (L/d)	1.0	1.2	1.0	1.2
Adult body weight (kg)	70	70	70	70
CSF $(mg/kg/d)^{-1}$	0.44	0.44	3.66	3.55

Based on this review, the correct values for the range of CSFs that are implicit in EPA's 2001 presentation of upper- and lower-bound risks from exposure to arsenic should range from 0.44 to 1.9 $(mg/kg/day)^{-1}$.

Lack of Evidence of Elevated Cancer Risk in U.S. Epidemiological Studies

Several well-designed epidemiological studies have been conducted in U.S. populations with elevated arsenic exposures; however, in contrast to the Taiwanese studies, results from these studies have been mostly negative.[2] Table B-2 summarizes findings from the best available epidemiological studies of U.S. populations with elevated arsenic exposures, including two with high childhood exposures. Short descriptions are also provided below for several of the more recent, larger studies. Despite the existence of elevated arsenic exposures in these populations, these studies do not show evidence of increased excess bladder, lung, or skin cancer risk associated with arsenic exposures in U.S. populations. These studies provide evidence that ingestion of arsenic in drinking water—at the levels found in the U.S—is unlikely to cause cancer. Concentrations that are considered to be elevated arsenic exposures among U.S.

[2] Two recent European studies of chronic arsenic exposure (Kurttio *et al.*, 1999; Buchet and Lison, 1998) also provide little or no evidence of increased lung and bladder cancer risks; however, both of these studies have significant limitations. Specifically, Kurttio *et al.* conducted a population-based case-cohort study in Finland of 61 bladder cancer and 49 kidney cancer cases examining low concentrations of arsenic in drinking water (*i.e.*, typically less than 0.5 µg/L). These researchers reported no association between arsenic exposures *via* drinking water and kidney cancer; however, increased bladder cancer risks were observed for smokers at higher arsenic exposure levels. Chance observation and/or unmeasured bias has been cited as a possible explanation for these findings (NRC, 2001), given the small number of cases. Possible exposure misclassification error is also thought to play a role in these observations because the study failed to account for dietary arsenic exposures that likely would have contributed to total daily arsenic intakes. Buchet and Lison conducted a broad ecological study of Belgian populations with moderately increased arsenic intakes (*i.e.*, 0.3 $\mu g/m^3$ in air and 20-50 µg/L in drinking water). These researchers, concluded that their study failed to identify an effect of arsenic exposure on cancer mortality. Potential sources of bias in this study include confounding, as well as the use of questionable geographic comparison populations.

populations are substantially less than those of the Taiwanese and South American populations where excess lifetime bladder, lung, and skin cancer risks have been observed. As a result, these U.S. epidemiological studies support the non-linearity of the arsenic dose-response relationship and are suggestive of a possible threshold for arsenic carcinogenicity. Furthermore, as discussed in more detail below, findings from these studies indicate that the use of a CSF based on studies of cancer occurrence (*i.e.*, bladder, lung, and skin) in highly exposed Taiwanese populations is likely to overestimate arsenic-related cancer incidence in the United States.

Table B-5
Summary of Epidemiological Studies of Cancer Risks in U.S. Populations with Elevated Arsenic Exposures

Study Type	Study Location	Study Population(s)	As Drinking Water Levels (µg/L)	Estimated Daily As Intakes (µg/kg-day)	Key Findings on Cancer Health Effects	Reference
Lifetime/Adult Exposures						
Retrospective Cohort	Millard County, UT	4,058 Adults	Medians ranging from 14 to 166	0.3 to 3.3 (based on median water levels, 1.4 L/day ingestion rate, and 70 kg body weight)	No elevated death rates from bladder or lung cancers have been observed for those who died through November 1996, and death rates show no association with exposure level. For bladder and lung cancers together, the authors observed 39 deaths when 63.5 were expected ($p<0.05$).	Lewis *et al.*, 1999
Meta-analysis	Utilized studies of Fallon, NV (Vig *et al.*, 1984), Fairbanks, AK (Harrington *et al.*, 1978), and Millard County, UT (Southwick *et al.*, 1983)	105 for Fallon, 79 for Fairbanks, and 145 for Millard County	100 for Fallon, 76-401 for Fairbanks, and 208 for Millard County	2.9 for Fallon, 1.5-4.6 for Fairbanks, and 6.0 for Millard County	No skin cancers were found in the exposed populations in each study location. This study further examined whether an absence of risk in U.S. populations or random variability from a predicted risk was the more likely explanation for the study findings. Likelihood ratio analysis showed that no effect of arsenic on skin cancer prevalence is about 2.2 times more likely than an effect of arsenic exposure on skin cancer prevalence as predicted by EPA's current arsenic cancer potency factor of 1.5 $(mg/kg/day)^{-1}$.	Valberg *et al.*, 1998
Case-control	88 towns in Utah	117 cases, 266 population-based controls	Range of 0.5 to 160, with a mean of 5 (81 out of 88 towns <10 µg/L; 1 town >50 µg/L)	0.01 to 3.2 (based on range of water levels, 1.4 L/day ingestion rate, and 70 kg body weight)	No association found between bladder cancer risk and arsenic exposure for two exposure metrics- total cumulative exposure (<19 up to >53 mg) and intake concentration. Analyses indicated increased bladder cancer risks for smokers, although authors could not rule out possible bias in data.	Bates *et al.*, 1995

Study Type	Study Location	Study Population(s)	As Drinking Water Levels (µg/L)	Estimated Daily As Intakes (µg/kg-day)	Key Findings on Cancer Health Effects	Reference
Ecologic	30 U.S. counties with population-weighted mean arsenic levels 5 µg/L or greater	Residents of 30 U.S. counties between 1968-1984	Range of means of 5.4 to 91.5, with 5 counties with mean greater than 20	0.1 to 2 (based on range of water levels, 1.4 L/day ingestion rate, and 70 kg body weight)	The standardized mortality ratios (SMRs) for both all cancers and lung cancers were 1.0 for counties with drinking water levels of 5-10 µg/L, while the SMRs were nearly all less than 1.0 for those with higher drinking water levels (10-91.5 µg/L)	Engel and Smith, 1994
Ecologic	Lane County, Oregon	190,871 total study population	Averages of 16.5 and 4.8 in all rural and urban regions, respectively, with a maximum recorded conc. of 33	Averages of 0.3 and 0.1 for rural and urban regions, respectively (based on average water levels, 1.4 L/day ingestion rate, and 70 kg body weight)	Did not detect any excess risk of skin cancer associated with arsenic exposures up to 33 µg/L (note 19,063 people were exposed at this maximum concentration). Among the 3,237 skin-cancer cases identified in the study, only three had evidence of arsenic keratosis. Based on results, authors concluded that "it seems safe to conclude that our data showed no evidence of water arsenic influence on skin cancer incidence in Lane County over this 14-year period."	Morton *et al.*, 1976
Childhood Exposures						
Ecologic Study	Entire State of Nevada, including Churchill County and Fallon, Nevada, where a recent leukemia cluster has been reported	327,947 children between 0-19 years of age	0-7.8 in low-exposure group, 10-24.6 in medium-exposure group, 35.9-91.5 in high-exposure group	0.9 to 2.4 in high-exposure group (based on 1 L/day ingestion rate, and 38 kg body weight)	No evidence of excess childhood leukemia incidence for even elevated arsenic exposures (~90 µg/L with over 5,500 children at this exposure level). In fact, only 2 cases of leukemia were observed during the study period (1979-1999).	Moore *et al.*, 2002

Study Type	Study Location	Study Population(s)	As Drinking Water Levels (µg/L)	Estimated Daily As Intakes (µg/kg-day)	Key Findings on Cancer Health Effects	Reference
Retrospective Cohort	Ruston, Washington in vicinity of American Smelting and Refining Company (ASARCO) copper smelter	3,132 children residing near smelter between 1907-1932	Not reported in study (note that ambient air exposures are considered to be the primary exposure source)	Not known during 1907-1932 exposure period, although elevated urine As levels observed in 1970s following improvements in smelter processes	Despite extremely elevated childhood As exposures, no elevated incidence of bladder or lung cancer mortality observed in 1,075 deceased members of cohort as of 12/31/90.	Tollestrup *et al.*, 2002

Summary of Lewis *et al.* (1999)

Building upon an earlier EPA study, Lewis and colleagues (1999) report the results of a larger and more powerful EPA study to investigate the health effects of chronic consumption of arsenic in drinking water by a cohort of Millard County, Utah residents. This study examined 4,058 individuals, more than 70% of whom had attained the age of 60 years at the end of the follow-up period or by the time they were deceased. As a result, this study is the largest and best-designed study of arsenic in drinking water conducted to date in a U.S. population. This study examined the relationship between arsenic concentrations in drinking water and mortality outcome, with analyses focusing on the 2,203 deceased members of the cohort. Several features of the study design resulted in a high statistical power of this study to detect risks if they are as high as those estimated by NRC (2001). These factors include the large size of the cohort population, the high arsenic concentrations in drinking water, and a population drawn from records of the Mormon Church. This group is unlikely to have significant alcohol or tobacco exposures, two known carcinogens and potential sources of confounding and bias in studies of bladder and lung cancer.

For the seven communities included in the study, median drinking water concentrations ranged from 14 to 166 µg/L, with slightly higher average concentrations of 18 to 191 µg/L. Maximum detected concentrations ranged as high as 620 µg/L. Table B-3 shows the distribution of cohort member residences and arsenic concentrations in drinking water from historical and recent arsenic measurements in the study communities. As shown in this table, almost 30% of the cohort resided in the town with the highest median arsenic drinking water concentration, and more than 25% of the deceased study subjects were also residents of Hinckley (Lewis *et al.*, 1998). A population-weighted mean concentration of almost 100 µg/L can be estimated using the data shown in Table B-3. (This calculation assumes that cohort members are evenly distributed in the five communities that together are reported to make up 41.2% of the enrolled cohort.) Together with information on the residence history of the cohort members, the median drinking water concentrations were used by the researchers to establish three arsenic exposure indices: low (<1,000 ppb-years), medium (1,000-4,999 ppb-years), and high (≥5,000 ppb-years). The study authors justify the selection of these cumulative arsenic exposure classifications by noting that 20 years of exposure is a reasonable period for most cancers to become manifest, and 20 years of exposure to drinking water with 50 µg/L (or ppb) of arsenic or greater yields a cumulative arsenic exposure of 1,000 ppb-years. Exposures for a significant portion of the cohort occurred over a full lifetime. In particular, nearly 44% of the deceased subjects in the high-exposure category were members of the cohort for more

than 70 years, while more than 60% were followed for more than 60 years. Almost 60% of the deceased members of the cohort were more than 70 years old at the time of their deaths.

Table B-6
Distribution of Cohort Member Residences and Arsenic Concentrations in Drinking Water in the Lewis *et al.* (1999) Utah Study

Community	% of Enrolled Cohort	Arsenic Concentrations in Drinking Water (µg/L)			
		Average	Median	Min	Max
Hinckley	29.4	164.4	166	80	285
Deseret		190.7	160	30	620
Abraham		134.2	116	5.5	310
Sugarville	41.2	94.5	92	79	120
Oasis		91.3	71	34	205
Sutherland		33.9	21	8.2	135
Delta	29.4	18.1	14	3.5	125

Despite elevated exposures to arsenic in drinking water, Lewis *et al.* (1999) found no relationship between bladder and lung cancer and exposure to arsenic in drinking water in the Utah cohort. Risks of bladder and lung cancer mortality were actually found to be statistically significantly lower in the study population than for the general population in Utah. Specifically, 39 bladder and lung cancer deaths were observed in the study cohort compared to an expected value of 63.5 deaths ($p<0.05$). Based on their findings, the authors conclude that "Whereas the studies in Taiwan and Argentina reported high exposures to drinking water arsenic, this study population was exposed to much lower levels, perhaps indicating that bladder cancer occurs in response to higher arsenic concentrations."

Summary of Other U.S. Studies of Lifetime and Adult Exposures

In addition to the Lewis *et al.* (1999) study, Table B-2 also describes several other studies of U.S. populations with elevated lifetime or adult exposures to arsenic in drinking water. These studies include two ecologic studies of large populations (*i.e.*, Engel and Smith, 1994; Morton *et al.*, 1976), one meta-analysis of U.S. epidemiological studies of skin cancer incidence (Valberg *et al.*, 1998), and one case-control study (Bates *et al.*, 1995). None of these studies reported a significant relationship between arsenic exposure and increased cancer risk, with arsenic concentrations ranging as high as 401 µg/L.

Engel and Smith (1994) conducted an ecologic study examining the relationship between the population-weighted mean arsenic concentration in public drinking water supplies and a variety of mortality endpoints, including all cancer and lung cancer mortality, for the period 1968 to 1984. They included 30 counties in the study, each with population-weighted mean arsenic levels of 5 μg/L or greater. Although the study included counties with mean arsenic levels ranging as high as 92 μg/L, the authors report standardized mortality ratios (SMRs) for all cancers and lung cancer that are almost all less than 1.0 for communities with higher arsenic drinking water levels (10 to 91.5 μg/L). Morton *et al.* (1976) also performed an ecological study, focusing on skin cancer incidence in Lane County, Oregon, where arsenic concentrations as high as 33 μg/L have been found in drinking water. Based on their analyses, these authors concluded that "it seems safe to conclude that our data showed no evidence of water arsenic influence on skin cancer incidence in Lane County over this 14-year period."

Bates *et al.* (1995) evaluated bladder cancer risks based on a case-control study involving 117 bladder cancer cases and 266 controls in the state of Utah. Arsenic concentrations in drinking water ranged from 0.5 to 160 μg/L in the 88 towns included in the study. Eighty-one towns had arsenic concentrations in drinking water of less than 10 μg/L and only 1 town had arsenic concentrations exceeding 50 μg/L. Overall, this study reported no association between bladder cancer risk and arsenic exposure for two exposure metrics, *i.e.*, total cumulative exposure (from <19 to >53 mg) and intake concentrations. Analyses suggested that smokers had increased bladder cancer risks, but the study authors could not rule out possible biases in the data as an explanation for this finding.

Valberg *et al.* (1998) examined whether an absence of risk in U.S. populations or random variability from a predicted risk was the more likely explanation for the lack of observed skin cancer cases in U.S. epidemiological studies of populations with elevated arsenic exposures. This analysis was conducted using a likelihood ratio approach that evaluated which of two hypotheses was the more likely explanation for the lack of observed skin cancer cases in the studies of U.S. populations. The two hypotheses evaluated were that an arsenic effect exists in the evaluated studies that is as large as predicted by the EPA CSF and, alternatively, that no arsenic effect exists. For their analysis, Valberg *et al.* identified three studies that had studied the effect of elevated arsenic concentrations in drinking water on the prevalence of skin cancers, and had provided detailed information on exposure levels and health outcomes. These studies included evaluations of populations in Fallon, Nevada (with typical exposure levels of 100 μg/L); Fairbanks, Alaska (with a range of exposure levels form 76-401 μg/L); and Millard County, Utah (with typical exposure levels of 208 μg/L). This analysis showed that the hypothesis that

arsenic has no effect on skin cancer prevalence was approximately 2.2 times more likely than the hypothesis that an effect of arsenic exposure on skin cancer prevalence is exists and is as large as predicted by EPA's CSF of 1.5 $(mg/kg/day)^{-1}$, the value presented in EPA's Integrated Risk Information System (IRIS) database (USEPA, 2003). This study thus indicates that using a CSF based on a study of elevated arsenic exposures in the Taiwanese population may result in overestimates of skin cancer prevalence in the U.S. population.

Summary of Studies of Exposed Children

Several recent epidemiological studies of cohorts of U.S. children with elevated childhood arsenic exposures also do not show elevated incidence of bladder or lung cancer mortality. Specifically, Tollestrup *et al.* (2002) studied 1,827 boys and 1,305 girls who resided near the ASARCO Ruston copper smelter between 1907 to 1932. Exposure intensity was grouped into four categories based on the length of time of residence less than one mile from the smelter stack, *i.e.*, 0 - <1.0 year, 1.0 - 3.9 years, 4.0 - 9.9 years, and 10 or more years. Using a Cox proportional hazard model, the study investigators found no evidence of elevated bladder or lung cancer mortality risks in the highest three arsenic exposure categories.

Although arsenic exposure levels during the 1907-1932 period are uncertain, urine samples collected during the 1970s showed that children living near the smelter had significantly elevated urinary arsenic levels. For urine sampling conducted in 1972, children residing less than half a mile from the smelter were found to have average total arsenic concentrations in urine of 0.3 mg/L, compared to an average of 0.08 mg/L for children living 1 to 1.4 miles away (Milham and Strong, 1974). Polissar *et al.* (1990) measured a median urinary inorganic arsenic concentration of 0.044 mg/L with a 95th percentile of 0.120 mg/L in children ages 0 to 6 years old living in close proximity to the smelter. Because emission controls were installed in the 1970s and 1980s and ASARCO significantly improved their arsenic recovery in the 1930s and 1940s, exposures during the 1907-1932 exposure period were likely much higher than those measured in the 1970s. Most importantly, exposures were also substantially higher than any exposures likely to result from current children's contacts with structures built of CCA-treated wood.

Moore *et al.* (2002) investigated the relationship between childhood cancer incidence and arsenic exposure in drinking water in Nevada. This study was prompted by a recent leukemia cluster in Churchill County, Nevada, where elevated concentrations of arsenic in drinking water are found. This study is one of a small number of studies that have examined arsenic-associated risks for childhood cancers. Such

cancers have not yet been investigated in any of the arsenic endemic areas of the world (*e.g.*, Taiwan, Argentina, or Chile).

The study population included all children within the state of Nevada, with population-weighted arsenic concentrations in drinking water in the 17 Nevada counties ranging from <10 μg/L to up to 90 μg/L. In Churchill County, 89% of residents (including 5,525 children included in this study) were found to drink water containing approximately 100 μg/L of arsenic. This county includes the town of Fallon and the recent cluster of 15 cases of childhood leukemia.

Standardized Incidence Ratios (SIRs) were calculated for all cancers, leukemia only, and all cancers excluding leukemia for three exposure groups: high exposure (35-90 μg/L, with more than 11,000 children), medium-exposure (10-25 μg/L), and low-exposure (<10 μg/L). Key findings included no evidence of excess childhood leukemia incidence for any exposure group, including elevated arsenic exposures (~90 μg/L). In fact, only 2 cases of leukemia were observed during the study period (1979-1999). A small (but statistically non-significant) excess in non-leukemia cancer incidence was observed for the high-exposure counties. These included bone cancers for 5 to 9-year-old and 10 to 14-year-old children, and lymphomas for 15 to 19-year-old children. This finding does not provide convincing evidence for increased risks for non-leukemic childhood cancers. Moreover, the authors caution that confirmation in other studies is required before conclusions can be drawn.

Implausibility of High End CSF and Inconsistency with Epidemiological Data

The high end CSF of 23 $(mg/kg\text{-}day)^{-1}$ used by CPSC staff in their risk analyses was not explicitly calculated by NRC (2001) in its analysis of excess lifetime risk of lung and bladder cancer for the U.S. Population. CPSC staff estimated this value, however, based on U.S. lung and bladder cancer risks for males and females combined, using the data available in the NRC (2001) report. This value is implausible and inconsistent with the best available epidemiological evidence from U.S. populations.

Derivation of the CPSC Staff High-End CSF

CPSC staff derived the high-end CSF based on the following assumptions: the theoretical maximum likelihood estimates of excess lifetime risk for individuals consuming drinking water containing arsenic concentrations of 10 μg/L, a body weight of 70 kg for U.S. adult residents, a drinking

water ingestion rate of 1 L/day in the U.S., and U.S. background cancer incidence rates based on cancer registry data (NCI, 2002). The excess lifetime risks in NRC (2001) were reported separately for males and females, and separately for bladder and lung cancer. These individual estimates are summarized in Table B-4.

Table B-7
Theoretical Maximum Likelihood Estimates of Excess Lifetime Risks (Incidence per 10,000 people) of Lung Cancer and Bladder Cancer for U.S. Populations, for Arsenic Concentrations in Drinking Water of 10 µg/L.

Cancer Endpoint	Bladder		Lung	
	Females	Males	Females	Males
Individual Genders/ Endpoints	12	22.5	18	13.5
Combined Genders (Females & Males)	17.25		15.75	
Combined Endpoints and Genders (Bladder & Lung, Males & Females)	33			

It should be noted that these excess lifetime risks calculated in NRC (2001) are based on relative risks, which reflect the background lung or bladder cancer rates in the population of interest. Because the background rates of bladder and lung cancer are several times higher in the U.S. than they are in Taiwan, the U.S. excess risks are correspondingly greater than the Taiwanese excess risks for comparable drinking water concentrations.

The CPSC documentation does not specifically describe how CPSC staff derived a single CSF for combined incidence of both lung and bladder cancer, for both genders; however, the CSF value presented by CPSC staff (*i.e.*, 23 $[mg/kg\text{-}day]^{-1}$) appears to have been calculated as follows:

- Average the excess lifetime risks of cancer across genders for each endpoint (17.25/10,000 for bladder cancer and 15.75/10,000 for lung cancer)
- Add the excess risks across endpoints (33/10,000 for [bladder or lung] cancer) to estimate the combined risk
- Convert the excess combined risk of cancer incidence across endpoints and genders to a CSF using the following formula and assumptions:
  - 33/10,000 combined risk = 10 µg/L arsenic in water * 1 L/day water ingestion rate / 70 kg body weight
  - 0.0033 = 0.14286 µg/kg-day
  - 0.0231 = 1 µg/kg-day
  - 23.1 $[mg/kg\text{-}day]^{-1}$ = CSF

The CSF derived by CPSC staff using this general approach was then used by them to extrapolate excess risk for a population exposed to arsenic on the basis of absolute risk.

The combined probability of having either a bladder or lung cancer (P(bladder) $\cup$ P(lung)) is statistically defined as being equal to the sum of their individual probabilities minus the probability of having both tumors simultaneously (*i.e.*, this probability is the product of the two probabilities if the events are independent of one another). Because U.S. tumor registries record only one primary tumor site for an individual, one cannot directly estimate the probability that an individual has both a lung and bladder tumor. Because the probability of both tumors occurring in the same individual is very small, however, no correction factor is likely to be required to adjust the estimated combined excess risk of having either a lung or bladder cancer to account for the possibility of developing both types of cancer.

Comparison of CSF with Available Epidemiological Data

The results of Lewis *et al.* (1999) and other studies of highly-exposed U.S. populations clearly do not support the presence of an arsenic-induced epidemic in the United States, even among populations with elevated arsenic levels in drinking water. Areas with elevated arsenic exposure levels do not have death rates that stand out from other areas and demand public health concern. If cancer risks associated with arsenic were as high as those predicted using the CPSC staff high-end CSF of 23 $(mg/kg/day)^{-1}$, such risks would have been apparent in a study as well-designed and as large as the Lewis *et al.* (1999) Utah cohort study. Several lines of evidence support this conclusion.

First, a recent peer-reviewed sample size calculation indicates that studies such as the Lewis *et al.* study of Millard County, Utah, have sufficient power to detect the postulated health risks associated with arsenic exposures if they are indeed as high as those predicted based on observations in the Taiwanese study populations (Frost *et al.*, 2002). Specifically, for an arsenic concentration in drinking water of 100 µg/L, Frost *et al.* (2002) demonstrated that a sample size of approximately 1,400 would be sufficient to detect elevated bladder cancer incidence, if the excess risk of bladder cancer was as high as estimated by Morales *et al.* (2000) in their re-analysis of the Taiwanese data that are the basis of the high-end CSF calculated by CPSC staff.

Second, the Lewis *et al.*, (1999) Utah study cannot be directly compared to the CSF derived by CPSC staff, in part because the CSF is based on data regarding tumor incidence whereas the Lewis *et al.* study examined tumor mortality. By adjusting the excess tumor rates based on survivorship patterns seen both in Utah and in the total United States, however, the CSF may be transformed into a slope factor reflecting cancer mortality. The lifetime excess cancer mortality risks in the Lewis study may then be evaluated based on this adjusted factor.

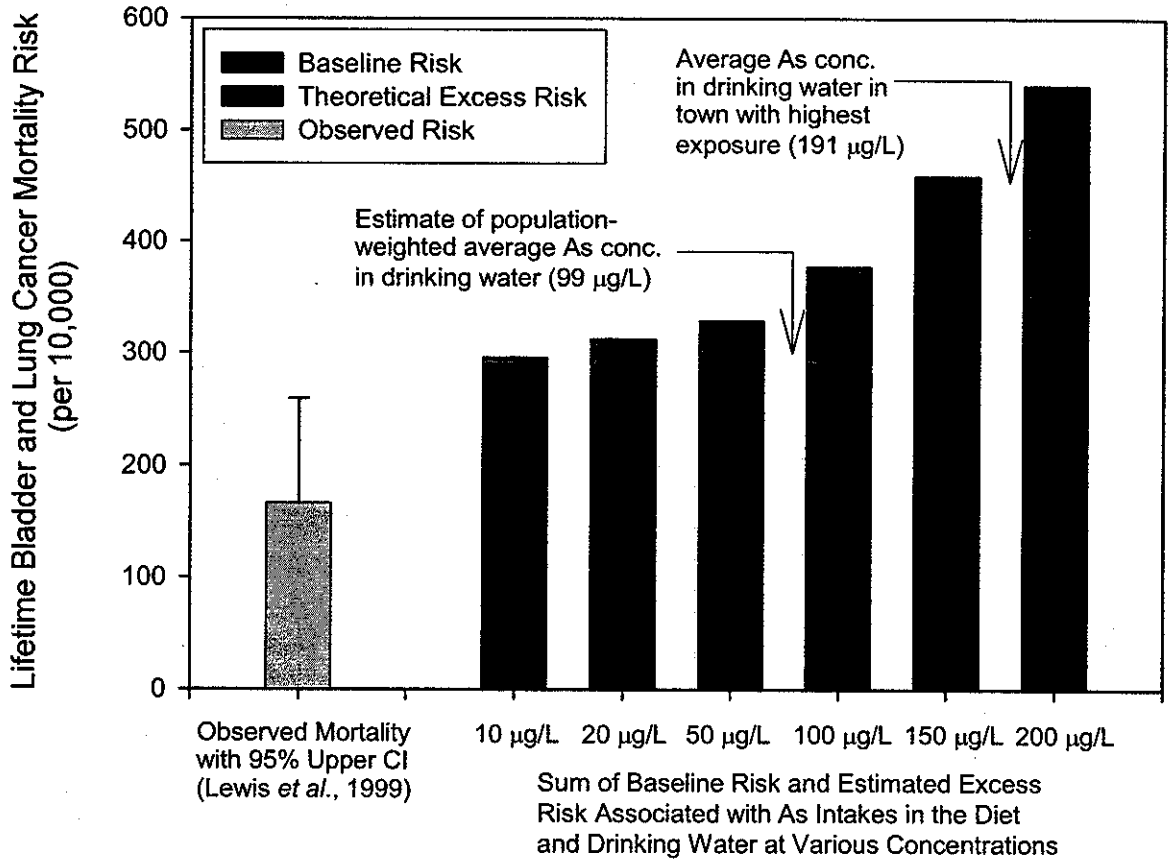
A CSF consistent with the cancer incidence data can be derived by examining the combined excess mortality from both lung and bladder cancer, for both genders. Based on data from U.S. tumor registries (NCI, 2002), a reasonable estimate of the proportion of all tumors that are fatal is 20% for bladder cancer and 80% for lung cancer. By applying these adjustments to the data in Table B-4, an estimate of the slope factor reflecting cancer mortality can be derived as follows:

- Average the excess lifetime risks of mortality from cancer across genders for each endpoint, (3.5/10,000 for bladder cancer and 12.6/10,000 for lung cancer)
- Add the excess risks across endpoints (16.1/10,000 for [bladder or lung] cancer) to estimate the combined risk of mortality
- Convert the excess combined risk of cancer mortality across endpoints and genders to estimate a slope factor reflecting cancer mortality using the following formula and assumptions:
  - 16.1/10,000 combined risk = 10 μg/L arsenic in water * 1 L/day water ingestion rate / 70 kg body weight
  - 0.00161 = 0.14286 μg/kg-day
  - 0.0113 = 1 μg/kg-day
  - 11.3 $[mg/kg\text{-}day]^{-1}$ = Slope factor for cancer mortality

Again, a similar adjustment for the probability of simultaneous mortality from both a lung and a bladder tumor would have a minimal impact on an estimate of the combined risks of mortality associated with both tumor types. Nevertheless, these excess mortality rates attributable to exposure to arsenic can be used in the larger context of adding to baseline lifetime cancer mortality rates. In Utah during the period 1995-1999, these rates were 0.37% for bladder cancer and 2.54% for lung cancer, with a sum of 2.91% (NCI, 2002). This rate is the baseline risk for this combined endpoint in the absence of arsenic exposures.

Figure B-1 clearly shows that observed bladder and lung cancer mortality risks in the Lewis *et al.* study are significantly less than those predicted by the high-end CSF derived by CPSC staff. As discussed earlier, the Lewis *et al.* (1999) Utah study followed a cohort of 4,058 individuals exposed to median drinking water arsenic levels that ranged from 14 to 166 μg/L (with average levels ranging from 18 to 191 μg/L). Nearly 1,200 of these individuals resided in the community with the highest median drinking water arsenic level of 166 μg/L. Despite these elevated arsenic concentrations in drinking water, no elevated death rates from bladder or lung cancers were observed for those who died through November 1996 (2,203 cohort members). Moreover, death rates were not elevated among the cohort members with the highest concentrations of arsenic in their drinking water. Both of these findings are inconsistent with the large excess cancer risks that would be predicted using the high-end CSF developed by CPSC staff.

Figure B-1
Comparison of Observed Bladder and Lung Cancer Mortality Risk with Combined Baseline and Excess Lifetime Mortality Risks Predicted Based on CPSC High-end CSF



The observed mortality risk for combined lung and bladder cancer, averaged across males and females in the cohort, and the two-sided 95% upper confidence limit on this risk estimate (calculated according to the Poisson distribution) are displayed in Figure B-1. Estimated excess lifetime mortality risks defined by a comparison population of Utah (1995-1999) are presented for a range of water concentrations that span the average concentrations measured in the seven towns included in the Lewis *et al.* study. Arrows indicate relevant exposure levels for the population as a whole (*i.e.*, 99 μg/L, which is an estimate of the population-weighted mean drinking water level) and for the most exposed members of the population (*i.e.*, 191 μg/L, which is the average measured drinking water concentration in the town of Deseret).

For an arsenic concentration in drinking water of 100 μg/L (which is just slightly greater than the estimate of the population-weighted mean drinking water level), the baseline and theoretical predicted excess lifetime bladder cancer mortality risk greatly exceeds the observed mortality rates. This disparity between the observed and estimated cancer mortality risks is even larger for greater exposures to arsenic. Specifically, for an arsenic concentration of 100 μg/L, the predicted cancer mortality risk is approximately 380 deaths per 10,000, more than two times greater than the observed death rate of approximately 170 per 10,000. For an arsenic concentration of 200 μg/L, which is slightly greater than the highest average drinking water concentration measured in the seven towns included in the study (191 μg/L), the predicted cancer mortality risks were more than three times greater than the observed cancer mortality risk based on the Lewis *et al.* findings.

In summary, as demonstrated in Figure B-1, findings from the Lewis *et al.* study of a Utah cohort are clearly inconsistent with the CPSC staff high-end CSF of 23 $(mg/kg/day)^{-1}$. This high-end CSF is based on studies of a heavily-exposed Taiwanese population where arsenic exposure levels were substantially greater than those of exposed U.S. populations. The observed cancer mortality risks in the Lewis *et al.* study are not only substantially less than those that are predicted using the CPSC staff high-end CSF for the cohort exposures, but they are also less than the baseline cancer mortality risks predicted for the general population of Utah. This finding is observed even with arsenic drinking water concentrations that, on average, were as high as 191 μg/L, and at times exceeded 600 μg/L. These findings indicate the implausibility of such a high CSF for U.S. populations, where even exposures considered to be highly elevated are far less than those of the Taiwanese population that is the basis for the CPSC staff high-end CSF.

These studies indicate that the use of the CPSC staff high-end CSF of 23 $(mg/kg/day)^{-1}$ in arsenic health risk assessments will significantly overestimate cancer risks in U.S. populations, even where elevated arsenic concentrations are present in drinking water supplies. Even under worst-case conditions, children's arsenic exposures associated with contacts with structures build of CCA-treated wood will be less than those for populations with elevated arsenic concentrations in their drinking water. Thus, the CPSC staff high-end CSF is also likely to overestimate cancer risks for this population. In summary, the best available scientific evidence does not support the widespread application of the staff CPSC high-end CSF to estimate potential cancer risks for U.S. populations exposed to arsenic *via* ingestion. Moreover, available evidence regarding the non-linearity of the dose-response relationship for carcinogenicity of ingested arsenic indicates that use of the CSF values applied by CPSC staff in their risk analyses is likely to overestimate potential carcinogenic risks for U.S. populations exposed to low levels of arsenic (*e.g.*, such as the levels estimated by CPSC staff to be associated with contacts with structures built of CCA-treated wood).