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Petition to Ban Chromated Copper Arsenate (CCA) - Treated Wood in Playground Equipment (Petition HP 01-3)

United States Consumer Product Safety Commission

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March 28, 2003

I. Summary of Comments. The risk estimates used by the CPSC are based on extrapolations from the Taiwan data and policy judgments about extrapolation methods. The result estimates are highly uncertain. The best available data from several published epidemiological studies of U.S. and European populations (Lewis et al., 1999; Bates et al., 1995; Kurttio et al., 1999; Burchet and Lison, 1998) show no indication that the lung and bladder cancers risks are increased for U.S. populations exposed to arsenic concentrations lower than the Taiwan cohort. Because of the apparent differences between the arsenic risks observed in Taiwan and those observed in the U.S. and Europe, we believe the estimates of cancer risks should also be consistent with results of epidemiological studies conducted in the United States and Europe. In particular, we feel that more reliance should be placed on the Lewis et al. study conducted in the United States.

Several of the more important issues where policy judgment, or simple expediency, has prevailed should be reconsidered by the CPSC and the EPA; these are:

1. Choosing a mathematical exposure-response model that is linear at low arsenic concentrations, although the most plausible modes-of-action by which arsenic causes cancer all imply a sublinear (that includes threshold) shape at low arsenic concentrations. EPA noted in the June 22, 2000 proposal that there was considerable evidence for a sub-linear extrapolation of risks.

2. Selectively following or disregarding the recommendations of the NRC report (NRC, 1999). For example, the CPSC and EPA have disregarded the NRC recommendation "... that a range of feasible modeling approaches be explored. The calculated risk should be supported by a range of analyses over a fairly broad feasible range of assumptions" (NRC, 1999). Decision makers should be made aware of the range of estimated risks from different plausible risk models.

3. Not exploring the sensitivity of lifetime risk estimates using values other than the median arsenic concentration in a village as "representative" of the village. This is important because the median, by itself, provides no information about the dispersion of well tests within a village and dispersion is large in some villages (NRC, 1999, Table A10-1). This could be accomplished by using a Monte Carlo approach, or other procedures that takes dispersion of well tests within a village into account.

4. Disregarding results of epidemiological studies, especially the EPA Utah study in evaluating the results of the current risk assessment. Results of EPA's cancer risk assessment are statistically inconsistent with results of several epidemiological studies conducted in the U.S. and Europe. The Utah study's outcome should be compared to the outcome predicted by the model EPA is using as a basis for its proposed MCL revisions. The findings in the Utah study should also be allowed to influence the estimated exposure-

response curve for the U.S. that is now based solely on results of the Taiwan study.

The CPSC used results of an epidemiological study in Taiwan (Chen, 1992; Wu, 1989) to estimate internal cancer risks from arsenic in drinking water in the United States. The process included: (1) collecting epidemiological data from a region in Taiwan, including measurements of arsenic concentrations in village wells used for drinking and records on the cause of death from 1973-1986; (2) statistically fitting a mathematical model to these data to estimate the exposure-response relationship; (3) using the exposure-response relationship to estimate risk in Taiwan at lower arsenic concentrations; (4) extrapolating risks estimated in Taiwan to the U.S. population.

EPA has recently completed additional risk assessments for arsenic-related cancer, but the Taiwan data continue to be used as the basis for estimating cancer risks. Briefly, our concerns include: (1) the exposure data available for the Taiwan population are not by individual, but by the median well test in communities or villages that often contain wells with highly disparate arsenic concentrations; (2) EPA considers only a very narrow range of mathematical models to assess the sensitivity of the results to model choice; (3) for two equally plausible models, the extrapolation of arsenic-related risks observed at high exposures to risks at low exposures differ by over two orders of magnitude. There are no data from lower dose exposures other than the U.S. studies to evaluate the health effects at lower arsenic concentrations; (4) even if the true exposure-response relationship was known for the population studied in Taiwan, applicability to the U.S. (aside from the adjustment for weight, water consumption rate, and lifespan, and higher consumption of arsenic in food partially taken into account by EPA) is questionable because the people of the study region tend to be undernourished and have diets low in selenium. While EPA now recognizes several sources of bias that likely result in overestimates of risk when extrapolated to the U.S. population, it should not be assumed that the overestimates are small. Rather, we believe they may be considerable.

Ecological exposure data used for the EPA risk assessment. The accuracy and reliability of an exposure-response curve depend on both the quality of the exposure/health outcome data and the appropriateness of the model. The data on exposure are the results of well tests in 42 villages of the study area in Southwest Taiwan (NRC, 1999, Table A10-1), and the lifespan of persons in the study (all deceased). The mortality data, constructed from records of individuals, are grouped by village. These data are considered ecological, since specific exposures are not known for individuals who died. It is also not known which individuals in a village used which wells so the data have been treated as if everyone in a village was exposed to the median well concentration of the village. The median well test of a village is used as representative of the arsenic concentration of the village.

A problem arises with the well data because it is not known if all the wells used for drinking were tested. A question also arises because only one well was tested in about half of the villages (20 of the 42 villages). In those 20 villages, it us not known if there was only one well in the village, the more favorable outcome, or if there more wells but

only one was tested. In villages with more than one well test, it is not clear that all the well tests were of different wells, but it seems unlikely that many wells were tested more than once. If all of the well tests within a village were quite similar, the effect of not knowing who drank from which well would not be consequential. However, what is observed is that villages with more than one well test often display a very wide range of arsenic concentrations. Therefore, the assumption that the mean or median well water arsenic concentration is representative of the drinking water arsenic exposures for cancer cases is unlikely to be correct.

For example, in Table A10-1 of the NRC report (NRC, 1999) village O-G, with five wells represented at a median concentration of 30 μg/L, has two well tests at 259 and 770 μg/L and two at 10 μg/L. By using only the median value for each village, arsenic exposure of deceased residents of village O-G are treated as if all were exposed at 30 μg/L. The consequence is that excess cancers that occurred in village O-G (excess meaning above the background level, the cancer risk for those not exposed to arsenic) are counted as having occurred at 30 μg/L although they are more likely to have occurred at the two higher well concentrations. Village O-G is one of the more extreme cases, but wide spreads in the values of well tests within a village are not uncommon for villages with more than one well. Some further examples from Table A10-1 include villages O-E, O-I, 3-Q, 4-F, O-H, 4-I, 2-M, O-F, 3-R, and 3-M, with ranges (all in μg/L) of 10-686, 20-590, 148-458, 120-819, 50-1,752, 20-970, 435-950, 415-749, 397-1,010, and 221-1,411.

Exposure for an individual was assumed to be the median arsenic concentration from the well tests conducted in the individual's village, and exposure was assumed to remain unchanged for an individual from birth until death. Considering the high variability of well tests within ten villages, only one well test in 20 villages, and reported temporal variability in wells in the general study region (Tseng et al., 1968), it is apparent that exposure estimates are quite unreliable. People are not expected to always drink from the same water source from birth until death even though the study population was fairly stable. The relative usage of wells within a village is unknown; many people farm or work in salt fields where they might be expected to consume 4-5 liters of water per day in the hottest season of the year while other persons, or these same workers in other seasons, may consume much less water. EPA has assumed that U.S. adults consume two liters/day on average. While the exposure data used by EPA may be adequate for statistical tests to associate chronic exposure to arsenic with mortality trends, they are not suitable for the more demanding task of estimating risk at specific arsenic concentrations, either in Taiwan or the U.S. Statistical modeling of exposure-response cannot compensate for poor exposure data.

The ecological nature of the data arises from grouping data by village, and it is of interest to ask what can be said about the effect that grouping may have on estimation of the exposure-response curve. Figures 4 and 5 show the age-standardized mortality rate of bladder and lung cancer in the Taiwan study. There is a gap in the data from 126 μg/L up to 256 μg/L. There are wells within that range but no median village well concentration. To the left of that range, i.e., below 126 μg/L, are five villages with mortality rates of 40 and above, and there is no visible evidence of an exposure-response relationship below

126 μg/L. One reason for the dispersion of mortality rates between villages with similar well-test medians is that the data are discrete and the number of cancer cases is small, so a difference of only two or three cancer cases between villages can appear large. The other reason is that the median value for some villages is not a good measure of arsenic exposure in the village, i.e., the observed mortality could not be expected to occur at such a low concentration as the median. This latter possibility might occur if there are some quite large arsenic concentrations in a village with a relatively low median value.

Mathematical models. To estimate the exposure-response relationship, one has to decide on the correct mathematical family of curves. With exposure-response modeling of arsenic, it is not known what family of curves to use. There are many possibilities that would meet the basic requirements. The best choice, of course, is a model with suitable (but unknown) parameter values that would come closest to mathematically capturing the true exposure-response relationship. It is important to remember that the true dose-response relationship rests on biological underpinnings. Consequently, only families of curves that produce estimates consistent with plausible modes of action, i.e., consistent with what is known about the biological mechanisms, should be considered. Despite current evidence that the arsenic exposure-response relationship at low exposures is sublinear (with a threshold), EPA continues to assume that the relationship is linear or nearly linear at low exposures with no threshold. We strongly disagree with EPA's approach that assumes a linear relationship at low arsenic exposures.

There is biological support for sublinear exposure-response curves: "The NRC and EPA expert panel (US. EPA, 1997) reports examined several lines of evidence for various modes of action that might be operative. These included changes in DNA methylation patterns that could change gene expressions and repair, oxidative stress, potentiation of effects of mutations caused by other agents, cell proliferative effects, and interference with normal DNA repair processes. Further examination in both of these reports of dose-response shapes associated with these effects led to the conclusion that they involve processes that have either thresholds of dose at which there would be no response or sublinearity of the dose response relationship (response decreasing disproportionately as dose decreases)." (US EPA, 2000, p.38901).

At the Fourth International Conference on Arsenic Exposure and Health Effects, held recently (June, 2000), two research reports provide further support of a sublinear exposure-response curve. The results are not yet published, so the following quotes were taken from abstracts. "It is clear, however, that a linear extrapolation of risk based on exposure to high, toxic concentrations of arsenic cannot adequately predict response to low, subtoxic concentrations." (Snow et al., 2000). "Arsenic is clearly a 'threshold' type cancer promoter." (Menzel et al., 2000). Epidemiological data also suggest a possible threshold (Lewis et al., 1999; Bates et al., 1995; Kurttio et al., 1999; Burchet and Lison, 1998).

Given that biological plausibility is preserved, curves that provide the best statistical fit are candidates. The NRC report (1999) considered two families of curves, the Poisson and the Multistage-Weibull (MSW), with several variations on the Poisson such as

different transformations on arsenic concentration and age, and different comparison groups.

The MSW was used previously in EPA's skin cancer risk assessment of arsenic (US EPA, 1988) and was included in the NRC report (1999) and the article by Morales et al. (2000) for comparison with the Poisson. It is not clear that the Poisson is preferable to the MSW, and there is a large difference in the risk estimates at low arsenic concentrations, e.g., 50 μg/L and lower. With no comparison population, excess lifetime risk estimates for males at low concentrations using the MSW model are approximately two magnitudes lower than for the Poisson at 10 μg/L (NRC, 1999, Tables 10-7 & 10-11).

From a biological perspective, the MSW is preferable to the Poisson because it is sublinear at low arsenic levels (for female bladder and lung and male bladder, but not male lung, as determined from the values of Q_1 in Table 10-6, NRC, 1999) while the Poisson is virtually linear. As previously noted, the most plausible modes of action are consistent with sublinearity at sufficiently low arsenic concentrations. The Poisson model is considered to be more stable (less sensitive to subsets of the data being excluded than the MSW), which is a favorable statistical property but may not necessarily provide for a good estimate. For example, an arbitrary straight line is completely stable but is obviously not a good estimator. It can also be argued that the exposure-response curve should show some sensitivity to the data, particularly to inclusion/exclusion of villages from the limited number below 100 μg/L, the region of greatest interest.

For its most recent risk estimate, EPA selected the Poisson model (the same as Model 1 in Morales et al.). EPA dismisses the MSW model in favor of a Poisson model by saying that the latter "had less variability in risks from regrouping the exposure intervals" (US EPA, 2000, p.38950). It is not clear, however, that such a characteristic is, necessarily, desirable. We are not proposing use of the MSW model *per se*, but attempting to illustrate what appears to be a very narrow and biased perspective by EPA.

Morales et al. (2000) provides three reasons why the Poisson model is preferable to the MSW model: 1) The MSW model appears to be more sensitive to outliers; 2) The hazard function for the MSW model involves a truncation that complicates estimation; 3) The inclusion of the power parameter k tends to give the fitted model a relatively sublinear shape that leads, in general, to higher benchmark exposure levels. These reasons are hardly compelling. Many analysts would argue that methods more sensitive to outliers are often preferable to those that aren't because they help to detect outliers and are, in general, more sensitive to the data. The second reason simply describes a mathematical inconvenience, something unrelated to the statistical properties or the biological appropriateness of the model. There are ways to surmount the mathematical inconvenience, as demonstrated by fitting the MSW model to the internal cancer data in the NRC report (NRC, 1999, Table 10-6). The third reason simply devalues the MSW model because it is relatively sublinear and leads to higher benchmark doses. This reason gives the appearance of a biased slant against sublinearity and the consequently higher benchmark dose.

One must also note that the problems with the original Taiwan study, as discussed above. These problems should encourage the EPA to use caution in making strong interpretations from any model that fits the data. Given the likelihood that the true exposure levels for cases from various villages are likely to be very different from the assumed median well water arsenic concentration for that village, a good statistical fit to flawed exposure-response data provides little assurance that the model reflects any external reality.

The objective should be to produce the most creditable model, and that should not exclude models that produce a sublinear fit to the data. The MSW model contains a linear term, which would produce linearity at low exposure if the coefficient were estimated to be positive, but the best fit of the model occurred with the linear coefficient at zero (for male and female bladder cancer, and female lung cancer, but not male lung cancer). This outcome is consistent with the widely held opinion discussed earlier that the most plausible mode(s)-of-action would lead to low-exposure sublinearity. EPA should explore not just the MSW model, but also other tenable models that are sublinear including threshold and "hockey-stick" models. Although not specifically mentioning sublinear models, the NRC "subcommittee recommends that a range of feasible modeling approaches be explored."(NRC, 1999, p.296). EPA has not followed this recommendation from the NRC.

If either Model 1 or the MSW provides a reasonably accurate estimate of lifetime risk at low arsenic concentrations, e.g. 5 μg/L, then one would expect that downward extrapolation a little further from the observable range to 0 μg/L would also be fairly accurate. The lifetime risk of bladder and lung cancer for males and females is shown in Figures 2 and 3 for Model 1 and the MSW. There are large differences between estimates at zero arsenic exposure from the two models. The estimate for male bladder cancer at zero arsenic exposure from Model 1 (MSW) is 22.8 (21.2) per thousand population, a difference of 1.6 per thousand which is quite large. The comparable figures for female bladder cancer are 22.8 (26.2) per thousand, with an even larger difference (and in the opposite direction) of 3.4 per thousand. It is apparent from Figures 2 and 3 of Morales et al. (2000), that these four estimates are very much larger than the comparable figures for either all of Taiwan or just the southwestern region. Although it would be possible to fit other models to the data and to make more comparisons there seems to be a basic problem with the data.

Risks from epidemiological studies in the U.S. The largest health study of arsenic in drinking water in the U.S., conducted on a cohort in Millard County, Utah, recently completed by EPA (Lewis et al., 1999), found no evidence of increased mortality due to lung, bladder, or liver cancer in the United States at arsenic concentrations ranging from 14 to 166 μg/L. In fact, for bladder and lung cancers, the study observed 39 deaths in the cohort when 63.5 were expected ($p<0.05$). Based on arsenic exposure levels and the new EPA risks, a total of 75 bladder and lung cancer deaths would have been expected compared to only 39 observed ($p<0.01$).

The Utah study results are preferable to those from Taiwan because individual exposure histories are known and it was conducted in a U.S. population where results are unlikely to be confounded or biased by the use of alcohol or tobacco, both known carcinogens. EPA has dismissed results of its own study, and others, in estimating risks possibly associated with arsenic in U.S. drinking waters. EPA has not even compared the outcome of the Utah study or other studies with what it would predict from the same model it is using to predict cancer risks at the low arsenic concentrations actually observed in the Utah study. That should be done and an explanation provided as to why the results of epidemiological studies in the U.S. and Europe are inconsistent with risks estimated from the Taiwan data. In addition, the results of the Utah study should be allowed to influence results of the Taiwan data. These data can be used to develop a revised exposure-response relationship.

Although not as large as the Taiwan study of bladder and lung cancer, the Utah study does has sufficient statistical power to detect risks if the risks are as great as estimated by Morales et al. and EPA. The study also has some distinct characteristics: it was conducted in the U.S.; data were collected on individuals; a high percentage of the study population is Mormon (Church of Jesus Christ of Latter-day Saints) who, as a group, have low rates of consumption of caffeine, alcohol, and tobacco, because of their religious beliefs. Unless EPA argues that added arsenic-related risks only occur among current and former cigarette smokers, the Utah cohort with a low background occurrence of bladder and lung cancer should be the ideal study population.

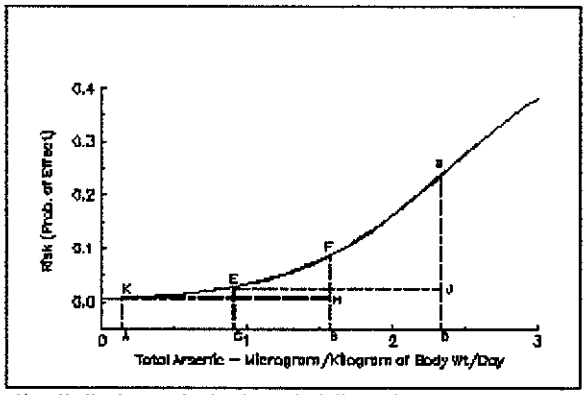
By the end of data collection in 1996, 2,203 cohort members were deceased and included in the data analysis. An exposure index score was constructed for each individual based on the number of years of residence in the community and the median arsenic concentration of drinking water in the community. More specifically, the exposure index of an individual was the product of arsenic concentration in each community of residence, times the duration of exposure there, summed over all communities of residence. The exposure index is stated in terms of ppb-years (equivalently, μg/L-years). Exposure indices were then grouped into low (<1,000 ppb-years), medium (1,000-4,999 ppb-years), and high (∃5,000 ppb-years). The expected arsenic-related health outcomes occurred less often in both genders for all malignant cancers, digestive organs and peritoneum, respiratory system cancer, and bladder and urinary cancers was not significant in either gender. Since no evidence was found of an association between arsenic exposure and death from bladder cancer or death from lung cancer, these results appear to be counter to what might be predicted by the EPA Model 1.

It is interesting to note that the EPA feels that Athe urban Taiwanese population is not a comparable population for the poor rural population (Taiwanese) used in this study.@ Yet in dismissing the findings of the Utah study in the June 22, 2000 proposal, the EPA stated that the Utah cohort is, because of the lack of cigarette smoking, not representative of the U.S. population. EPA has also stated that there may be issues in comparability between the Taiwanese cohort and the U.S. population. Beyond this brief mention of a serious problem, there was no further discussion of how differences between the population may affect extrapolation of risks. If the Taiwan cohort is not representative of

the Taiwan population in terms of cancer risks, how can it be representative of the U.S. population? The logical extension of the EPA=s discussion of the differences between the Taiwanese study cohort and the urban Taiwanese populations should be extended to explain the differences between the Taiwanese cohort and the U.S. population. This is especially important because of the huge differences in risk observed for the Taiwanese and U.S. arsenic health effects studies. Unless we are missing some important information, one might conclude that Utah Mormons are more representative of the U.S. population than the Taiwanese study cohort. If so, the cancer risks from the Utah study may better reflect the true risks, at least for nonsmokers, than the extrapolated risks from the Taiwanese population as discussed in the current NODA.

Arsenic in food. Although EPA's most recent risk estimate considers the impact of using high arsenic water for cooking rice and potatoes, it does not consider differences in exposures to arsenic in foods between Taiwan and U.S. populations. Thus, risks continue to be overstated by EPA. Estimates of arsenic in the diet of people in the study region indicate much higher dietary consumption of arsenic than people in the United States. Schoof et al. (1994) calculates an average of 84 μg/day, with the lowest measured food arsenic at 61.6 μg /day and the highest at 292 μg/day. For the U.S. the average male receives 10 μg arsenic per day.

The higher foodborne arsenic exposures in Taiwan presents two problems. First, if the high foodborne arsenic levels are associated with high waterborne arsenic levels, then the foodborne arsenic exposure would be counted as a drinking water arsenic exposure. This would confound the epidemiological results. Second, if the exposure-response relationship is non-linear between arsenic and health effects, then the contribution of any source of arsenic exposure depends on the baseline level of exposure. For example, if the exposure-response relationship is relatively flat at low doses, then an exposure to 50 μg/L of arsenic in drinking water will have relatively little health effects if the background exposure to arsenic is low. However, if the exposure-response relationship is non-linear, the same 50 μg/L drinking water exposure would have a much greater health effect if the baseline exposures were high. Note that moving from K to E produces very little increase in risk of adverse health effects whereas moving from E to F or F to G produces a much larger increased risk. Since the baseline exposure to arsenic from food in Taiwan is much higher than for the U.S., the estimated health effect from a 50 μg/L exposure would be higher for a Taiwanese population than for a U.S. population. EPA's insistence that non-linear dose-response relationships not be considered is a policy decision and not a scientific decision. Unfortunately, by precluding discussion of non-linearity of the exposure-response relationship and failure to adequately consider other sources of arsenic exposure, such as food, the EPA may have greatly over-estimated the risk of ingested arsenic. This causes further confusion since the linear model can not reconcile the greatly different results of U.S. versus Taiwan epidemiological studies (e.g Bates et al., Lewis et al versus the Taiwanese studies)..



Hypothetical example showing calculations of excess risk

Nutritional status of Taiwan study population. There is considerable evidence from various sources to suggest that poor nutritional status of the study population in Taiwan may be a factor in risk of cancer from ingestion of arsenic. It is unknown just how undernourishment might affect the exposure-response curve, or how large the effect might be. To some, the potential effect is sufficiently large that it is not advisable to extrapolate arsenic health risks from the study region of Taiwan to the U.S. For example, it is the opinion of the nutritionist on the NRC subcommittee, Dr. Walter Mertz, (retired) Director of Beltsville Human Nutrition Research Center in Rockville, MD, that "It is not permissible to extrapolate risks from a nutritionally deficient area to the U.S., particularly an area with very low selenium levels such as Taiwan". (personal communication). The potential of the undernourishment effect, dietary sources of arsenic, and how these might affect the exposure-response curve is one of the reasons EPA's Utah study is important.

Some of the earliest published evidence that undernourishment in the study region of Taiwan might be a significant factor in risk from arsenic appears in Hsueh et al. (1995). They found that risk of arsenical skin cancer in Taiwan increased with duration of consuming dried sweet potato as a staple food, with a history of working in the salt fields (which may simply increase water consumption), and in chronic HBsAg carriers with liver dysfunction. More recently, Chen et al. (2000) have reported a similar result. They found an association between long-term consumption of dried sweet potato chips and/or the low serum level of antioxidant vitamins, used as an indicator of undernourishment, and arsenic-induced health hazards.

Dietary intake of selenium is of particular interest because it is well-established that "arsenic and selenium reduce each other's toxicity" (NRC, 1999, p.240). Although the strong arsenic-selenium interaction has been shown in animals but not directly in humans, the NRC committee stated that the selenium status in the study population of Taiwan "should be considered a moderator of arsenic toxicity and taken into account when the Taiwanese data are applied to populations with adequate selenium intakes" (NRC, 1999, p.240). The problem, however, is how to take selenium into account in extrapolation of risk estimates from Taiwan to the U.S. and, in particular, how to quantify an effect on the exposure-response curve. For example, the effect might be that a

reduced number of people are at risk of bladder or lung cancer; that the same number of peopled are at risk but at a reduced risk level; or that the onset of cancer is just later in life. Nevertheless, daily selenium intake may be as low as 12-16 μg/day, on average, in some regions of Taiwan, among the lowest in the world. This compares with a daily intake of 60-159 μg/day in the U.S., where the recommended dietary allowance for selenium in the U.S. is 55 and 70 μg/day for females and males, respectively (as reported, with supporting references, in NRC, 1999, p.242).

Xia et al. (2000) recently reported that both laboratory tests and clinical symptoms showed that organic selenium has therapeutic effects on the patients with chronic arsenicism. They found that the selenium-treated group in their study increased selenium levels and decreased the arsenic levels in blood (59% of controls), urine (57%) and hair (54%) when treated with 200 μg/day of selenium over a period of 14 months. Kenyon et al. (2000) concluded that "Further studies to evaluate the potential toxicological consequences of As (arsenic) exposure in selenium deficiency are warranted, as is consideration of population selenium status in the design and interpretation of epidemiological studies".

Increased arsenic-related cancer risks among smokers. Missing from the EPA's statement of limitations and uncertainties in their risk estimates is the role of exposure to other carcinogens. Since laboratory data suggest that arsenic at high doses acts as a promoter rather than an initiator of cancer, exposures to other carcinogens may be critical in assessing the risk. A recent presentation (Irva Hertz-Picciotto. Interactions between arsenic and other exogenous exposures in relation to health outcomes. Abstract 4th International Conference on Arsenic Exposure and Health Effects, San Diego, CA June 18-22, 2000.) suggests that much of the risk, if any, from waterborne arsenic exposure would likely occur among current and former smokers. Epidemiological studies also suggest interactions between arsenic and smoking with risks observed only in smokers (Lewis et al., 1999; Kurttio et al., 1999; Burchet and Lison, 1998). This is an important consideration in estimating population risks. In fact, the low smoking rates for the Utah cohort was cited by the EPA in the June 22, 2000 report as a reason for not observing elevated cancer risks from the Mormon participants. If the adverse effects occur primarily among cigarette smokers, then the population at risk for adverse consequences is greatly reduced. Also less expensive approaches to risk reduction can be considered.

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Epidemiology: The Science of People

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Posted Apr. 23, 1996 / Revised Feb. 7, 2000
Sources: A Journalist's Handbook on Environmental Risk Assessment

Epidemiology is the most direct method of assessing risk to humans, but like any scientific method, it has its own limitations and problems of interpretation. Knowing the principles and pitfalls of epidemiology will help you interpret epidemiological studies.

What is Epidemiology?

Epidemiology is the study of patterns of disease in human populations*. Because epidemiological studies look directly at humans rather than extrapolate from animals, they provide the most compelling evidence for measuring environmental risks to humans.

> Most recent studies that have convincingly linked environmental factors to human diseases were epidemiological studies.

Most studies in recent decades that have linked environmental factors to human diseases were designed using principles of epidemiology.

Epidemiological studies have provided the critical evidence to link:

- toxic shock syndrome to tampon use.
- leukemia to on-the-job exposures to benzene.
- heart attacks to cholesterol.
- lung cancer, heart attacks, and low birth weight to cigarette smoking.
- Legionnaires' disease to contaminated cooling units.

Epidemiological studies provide evidence, not proof. Uncertainty is inherent in the tools that epidemiologists use. While the uncertainty can be very small, it can never be zero, because epidemiologists cannot be absolutely sure that the effect they see corresponds to the suspected cause.

I. Epidemiological Research

Epidemiologists compare two or more groups of people to determine what characteristics distinguish groups who get disease from groups who do not.

These distinguishing characteristics are then examined to determine how and why they are associated with disease.

Some of the characteristics epidemiologists look at are:

- consumption of certain foods.

- contact with bacteria, chemicals, or viruses.
- gender, race, or socioeconomic status.
- daily activities and behaviors.
- genetic background.
- metabolic characteristics, such as cholesterol level and blood pressure.

Risk Factors and Exposures

Epidemiologists prefer not to use the word "cause" when looking for clues to disease, because many characteristics associated with disease are not true causes.

Epidemiologists prefer the term "risk factor" rather than "cause" to describe anything that increases the risk of disease.

For example, cigarette smoking is associated with heart attacks because chemicals in the smoke trigger the attacks. Race, gender, and socio-economic status also are strongly associated with heart attacks, not because they directly cause the attacks, but because they are proxies for many hard-to-define behaviors, environmental factors, and genetic factors that increase the risk of heart disease.

So epidemiologists use the term "risk factor" to describe anything that in-creases the risk of disease. Cigarettes, race, and socio-economic status all are risk factors for heart disease.

Risk factors also are called exposures. A person with a risk factor is said to be exposed; a person without that particular risk factor is unexposed.

(However, it is not usual to describe risk factors that are inherent characteristics of an individual, such as sex and race, as exposures.)

II. Types of Epidemiological Studies

Epidemiologists favor two types of studies for searching out risk factors for disease, case-control studies and.; cohort studies.

Case-control studies look at the histories of cases and controls for clues to what causes disease in the cases.

Case-Control Studies

Epidemiologists survey a group of people with disease (cases) and a group without disease (controls) about their histories. The survey may involve direct questioning or examination of medical or other records.

The basic question: *What differs in the histories of these two groups that could explain why one is diseased and the other is not?*

Example of a case-control study: In the spring of 1980, U.S. doctors diagnosed hundreds of cases of toxic shock syndrome (TSS), a potentially fatal, previously rare disease. Most cases occurred in young women during their menstrual periods. Investigators at the Centers for Disease Control questioned 50 women with toxic shock syndrome (cases) about their use of sanitary products in the month before they got sick. Then they asked each woman for the names of three friends who did not have TSS (controls), and asked them the same questions. Women with TSS were more likely than their friends to have used

tampons; in particular they were almost 8 times as likely to have used one brand: Rely. This brand was withdrawn from the market in September 1980, and the incidence of TSS decreased dramatically.

Cohort Studies (Follow-up Studies)

A cohort study begins with a group of people who do not have the disease being studied. Group members differ on one or more characteristics suspected of causing the disease (for example, some may smoke while others do not). The group is followed over time to see if members with the suspect characteristic are more likely to develop the disease.

Cohort studies follow groups through time to determine whether group members with a suspected risk factor are more likely to get disease.

The basic question: *Are the people with the suspect characteristic at greater risk of getting disease?*

Example of a cohort study: To evaluate the effect of environmental lead exposure on children's IQs, researchers followed 516 children in the lead-smelting town of Port Pirie, Australia, from birth to age seven, periodically taking blood samples to measure lead levels. At age seven, children with highest blood lead levels over the years had the lowest IQs.

Which Kind of Study is Better?

Case-control studies are more common than cohort studies because they are faster and cheaper. Also, for relatively uncommon diseases like childhood leukemia, they often are the only practical way to look for causes of disease.

Cohort studies are more convincing for two reasons:

Case-control studies are more common, but cohort studies are generally more convincing.

- they provide a much better opportunity to establish a cause-effect relationship because they begin with the exposure (cause) and move forward in time to the disease (effect). In contrast, case-control studies begin with the disease (effect) and look back to the exposure (cause). It is not always clear that the identified cause actually did come first.
- case-control studies are more prone to certain study design problems, such as bias or chance (see Chapter 5).

But cohort studies have their own drawbacks:

- they are very expensive.
- they take a long time (because they start with well people and wait for them to get sick).
- they are difficult to conduct properly because study subjects tend to drop out of the study over time.

Two other types of epidemiological studies-cross-sectional studies and clinical trials-are often in the news. While these studies serve valuable purposes, epidemiologists generally do not use them to investigate risk factors for disease.

Cross-Sectional Studies

The cross-sectional study identifies a population of interest (people in a particular neighborhood, people coming to a clinic) and asks its members about current diseases and current exposures.

Cross-sectional studies help identify whether a problem exists that warrants further study. They are not useful for determining cause and effect.

Cross-sectional studies offer epidemiologists a quick way to determine whether a problem exists that warrants further study-whether, for example, workers in a particular industry have an unusually high rate of disease.

But this kind of study is not useful for establishing cause and effect because it is difficult to determine whether the exposures actually caused the disease.

Example of misinterpretation from a cross-sectional study: It is well known that cigarette smoking increases the risk of a heart attack. But if researchers did not know this and surveyed a city's residents to determine who had heart disease and who smoked, they might find that healthy people smoke more than people with heart disease. The real reason for this result is that people tend to quit smoking after they are diagnosed with heart disease. (In effect, the outcome is influencing the cause.) However, to the researchers it might appear that cigarette smoking protects against heart disease. Many cross-sectional studies suffer from this chicken-egg problem.

Clinical Trials

A clinical trial is a study done to test the effectiveness of a drug or other treatment.

Patients with a particular disease are randomly assigned to receive either the treatment under study or an inactive placebo (or the standard treatment, if one exists). Patients are then followed for a specified period to determine whether patients receiving the new treatment do better than those getting the standard treatment or the placebo.

Clinical trials are the best of epidemiological studies in terms of the quality of the information they provide. However, as a rule, they can't be used to explore causes of disease because it is unethical to assign people to be exposed to suspected toxins. However, such trials may be very useful for studying preventive measures, such as vaccines.

Example of a clinical trial

III. Estimating Risk

At the end of a study, researchers calculate the risk ratio or relative risk, by comparing the occurrence of disease in two groups-one group with a suspect characteristic, and one group without. This is the source of statements like "people who smoke are 10 times as likely to get lung cancer as people who do not."

Epidemiologists use risk ratios to describe the effect a characteristic has on disease.

Risk ratio close to 1 suggests the characteristic has no effect on disease.

Risk ratio greater than 1 suggests the characteristic increases risk of disease.

Risk ratio less than 1 suggests the characteristic protects against disease.

Example of risk ratios: In a landmark study, scientists followed 34,445 British male physicians from 1951 to 1961 to see if those who smoked had a higher rate of lung cancer. At the end of 10 years, the statistics looked like this:

Lung cancer death rate:

- among nonsmokers: 7 per 100,000
- among those smoking up to a half pack daily: 54 per 100,000
- among those smoking up to a pack daily: 139 per 100,000
- among those smoking more than a pack daily: 227 per 100,000

Dividing rates among smokers by the rate among nonsmokers yields ratios which show that, compared to nonsmokers:

Smokers of up to a half pack daily were almost **8 times** as likely to die of lung cancer-(54/7=7.7; **the risk ratio** was 7.7). Smokers of up to a pack a day were almost **20 times** as likely to die of lung cancer-(139/7=19.9; **the risk ratio** was 19.9).

Smokers of more than a pack a day were more than **32 times** as likely to die of lung cancer-(227/7=32.4; **the risk ratio** was 32.4).

IV. Causation Criteria

If an association has been observed between an exposure and a disease, and bias, confounders, and other possible errors have been reasonably accounted for (see Chapter 5), then researchers can address the question of whether the association is likely to reflect a true cause-effect relationship. Some commonly used criteria are:

If the data indicate an association, the researcher must explore whether a cause-effect relationship truly exists.

Strength of association. The exposure is associated with a large increase (or decrease) in the risk of disease. (The stronger the association, the less likely it is to be due to bias or an unknown confounder.)

Dose-response relationship. Higher doses of the exposure are associated with higher rates of disease.

Biologic credibility. A plausible biologic mechanism is available to explain how the exposure causes disease.

Consistency. Other studies done in different ways and in different populations have found the same association.

Time sequence. The exposure can be shown to occur before the disease. Specificity . The exposure is associated with a specific disease. The above criteria are guidelines, not rules. Some toxicants that clearly cause disease do not meet all the above criteria. For example, cigarette smoking does not meet the specificity criterion, for it is associated with many diseases. [Back to top]

V. Cancer Clusters

When contamination is discovered in a community, citizens often look for health effects. They may notice a lot of people with cancer and conclude that this represents an unusually high incidence of disease. Public health agencies are often called upon to investigate the reported cluster-a group of individuals living in a limited area and manifesting a particular disease.

Epidemiologists usually find that suspected clusters do not represent anything unusual.

In many instances, scientists find that people have underestimated the background incidence of cancer and that the number of cancers is really just what would be expected.

In other situations, it is clear from the variety of cancers occurring that there is not a cluster that can be associated with a particular source. In the vast majority of cases, public health epidemiologists find that the suspected clusters do not represent unusual events.

Some cases are more complex than described on the previous page and it may not be possible to determine whether a cluster is present. Reasons why a firm conclusion is not possible include:

Sometimes, it is not possible to determine if a cluster is present, due to small sample size and limited information.

- the population is so small that any variations from population averages may be due to chance.
- it is usually impossible to reconstruct past exposures to the agent of concern to determine which cancer victims have been exposed and how much they have been exposed.
- the history of individual exposures to other possible cancer-causing agents, such as workplace chemicals or radon, cannot accurately be determined. In summary, investigations of cancer clusters are very unlikely to establish a relationship between a local contaminant and the disease. However, public health epidemiologists often undertake cancer cluster analyses in response to strong public reaction to contamination incidents and deep public fear of cancer.

VI. Conflicting Studies

What if researchers do not agree? Reporters frequently are faced with conflicting studies. (A recent example is the question of whether alcohol consumption increases the risk of breast cancer; some studies say yes, some say no.)

> The answers to complex questions come slowly through the accumulation of study findings that eventually tip the balance in favor of a particular answer.

One possible explanation is that one study was larger and therefore had more power to find an effect. Other possibilities are bias or confounding in one or both studies. (See Chapter 5 for discussion of how to evaluate the validity of competing studies.)

Often, there is no obvious resolution to the conflicts; they reflect the frustrating fact that most diseases have complex, intertwined causes that are difficult to tease apart. The answers come slowly, through the accumulation of research results that eventually tip the balance in favor of a particular explanation.

MORTALITY IN CHILDREN RESIDING NEAR THE ASARCO COPPER SMELTER IN RUSTON, WASHINGTON

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BACKGROUND

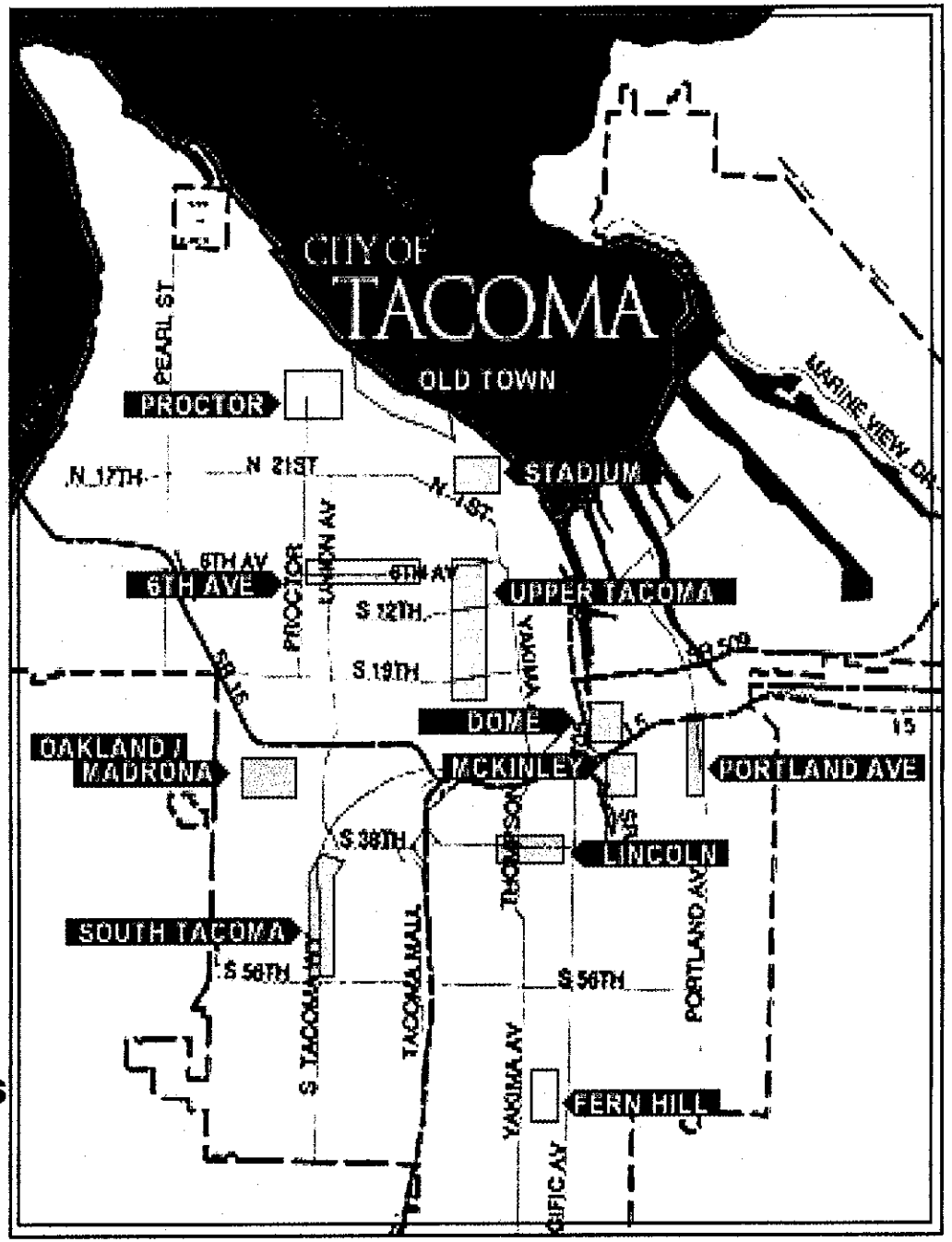
Arsenic has been known to be a poisonous substance for centuries. Numerous occupational studies have linked airborne arsenic exposure to excess skin, respiratory and other internal organ cancers. Other community studies have found a strong association between high waterborne arsenic levels (up to 1120 mg/L) and mortality due to lung, liver, bladder, kidney, prostate, and skin cancers, as well as increased mortality for vascular disease, ischemic heart disease, and diabetes. However, other community studies of populations exposed to low-level drinking water arsenic have generally failed to find similar adverse effects. The results of these occupational and community studies have generated concern that populations living close to arsenic emitting industrial plants may be at an increased risk of mortality due to lung and bladder cancer as well as other conditions.

ASARCO COPPER SMELTER IN RUSTON, WASHINGTON

The American Smelting and Refining Company (ASARCO) copper smelter operated in the town of Ruston, Washington from the late 1890's until the smelter was closed in 1985 (Map). In the 1970's and 1980's, soil and ambient air arsenic concentrations in the community were measured and found to increase with decreasing distance from the smelter stack. Ambient air sampling, done in 1974, showed the same uniformly decreasing arsenic concentrations as seen in the soil. The highest air concentrations were observed south and southwest of the smelter.

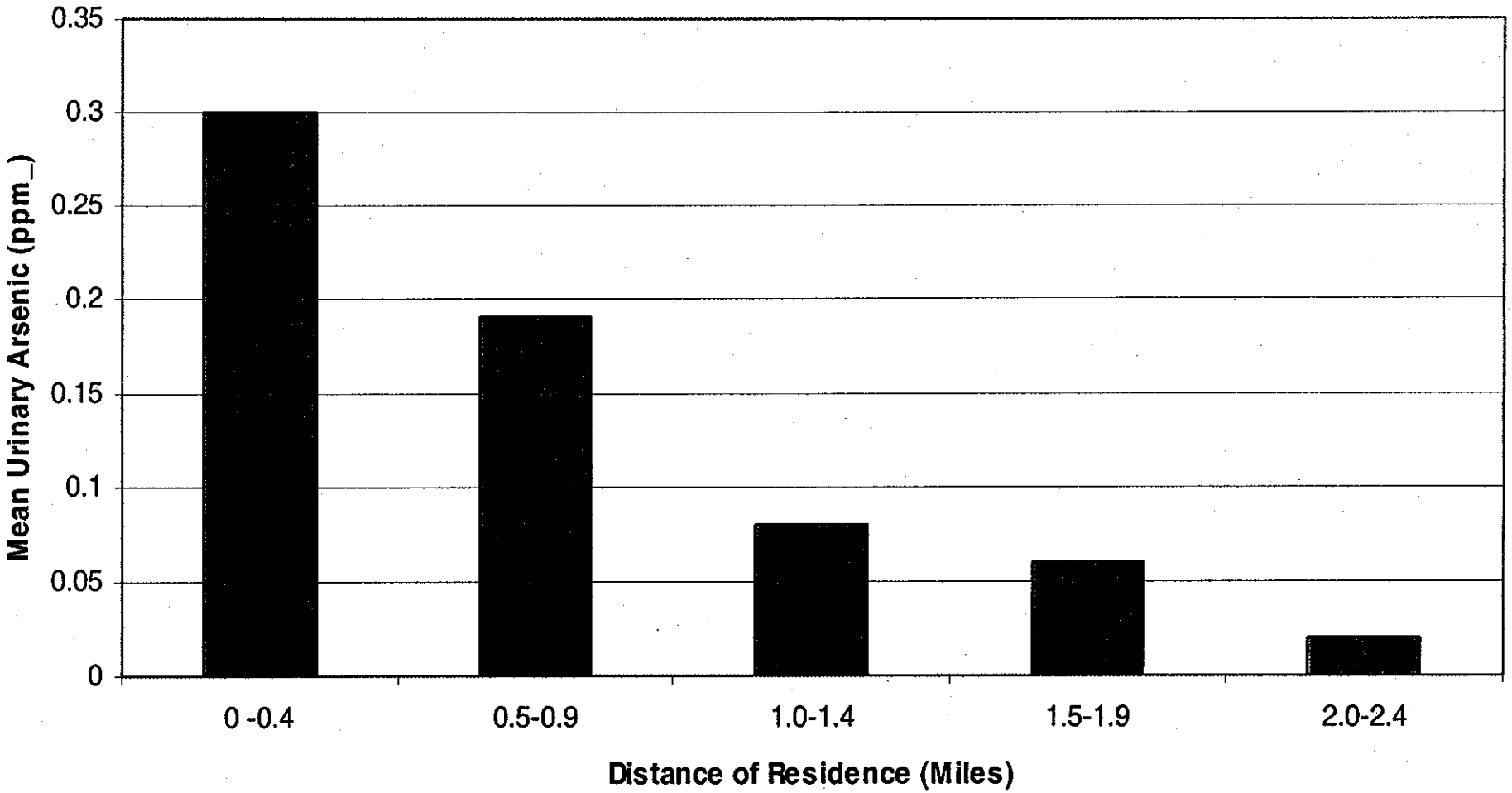
Urinary arsenic concentrations of residents near the smelter also followed this same pattern (Figure 1).

Map of Tacoma, Washington:



The ASARCO Copper Smelter is Located in the Square Box at the End of Pearl Street

Mean Urinary Arsenic Levels by Distance of Residence from the ASARCO Smelter Stack



PURPOSE OF STUDY

The current study was undertaken to determine the health effects of childhood exposure to ambient arsenic during the time period from 1907 – 1932 in cohort of children who lived near the ASARCO copper smelter in Ruston, Washington (Table 1).

Table 1. Characteristics of Cohort of Children Living Near the ASARCO Copper Smelter

	Boys (n = 1827)		Girls (n=1305)	
	N	%	N	%
Year of birth:				
1895 – 1901	221	12.1	258	19.8
1902 – 1906	262	19.3	252	19.3
1907 – 1912	414	22.7	364	27.9
1913 – 1917	387	21.2	232	17.8
1918 – 1925	543	29.7	199	15.2
Age at first exposure:				
0-2 yr	691	37.8	434	33.3
3 – 5 yr	347	19.0	278	21.3
6-10 yr	518	28.4	386	29.6
11-18 yr	271	14.8	207	15.8
Year of first exposure:				
1907 – 1912	512	28.0	527	40.4
1913 – 1917	331	18.1	336	25.8
1918 – 1924	663	36.3	353	27.0
1925 – 1932	321	17.6	89	6.8
Exposure intensity:				
0 – <1.0 yr	640	35.0	308	23.6
1.0 – 3.9 yr	486	26.6	365	28.0
4.0 – 9.9 yr	399	21.8	301	23.1
10 or more yr	302	16.6	331	25.3
Follow-up status on 12/31/90:				
Deceased	712	39.0	362	27.8
Alive	365	20.0	285	21.8
Alive between 1932-1990	116	6.3	51	3.9

RESULTS

- 39.0% (712) of boys and 27.8% (363) of girls were deceased by December 31, 1990.

- The cause of death with the highest crude mortality rate for both boys and girls in all exposure groups was ischemic heart disease. The second highest crude mortality rates were for malignant neoplasms (Figures 2 and 3).

- Hazard ratios for lung cancer were not elevated in any exposure group for both boys and girls (Tables 2 and 3).

- Adjusted hazard ratios for all causes of death, ischemic heart disease, and all external causes were significantly elevated in boys for the highest exposure intensity group (10 or more years at less than 1.0 mile from the smelter).

- No significantly elevated hazard ratios for girls were observed for any exposure group for any cause of death.10

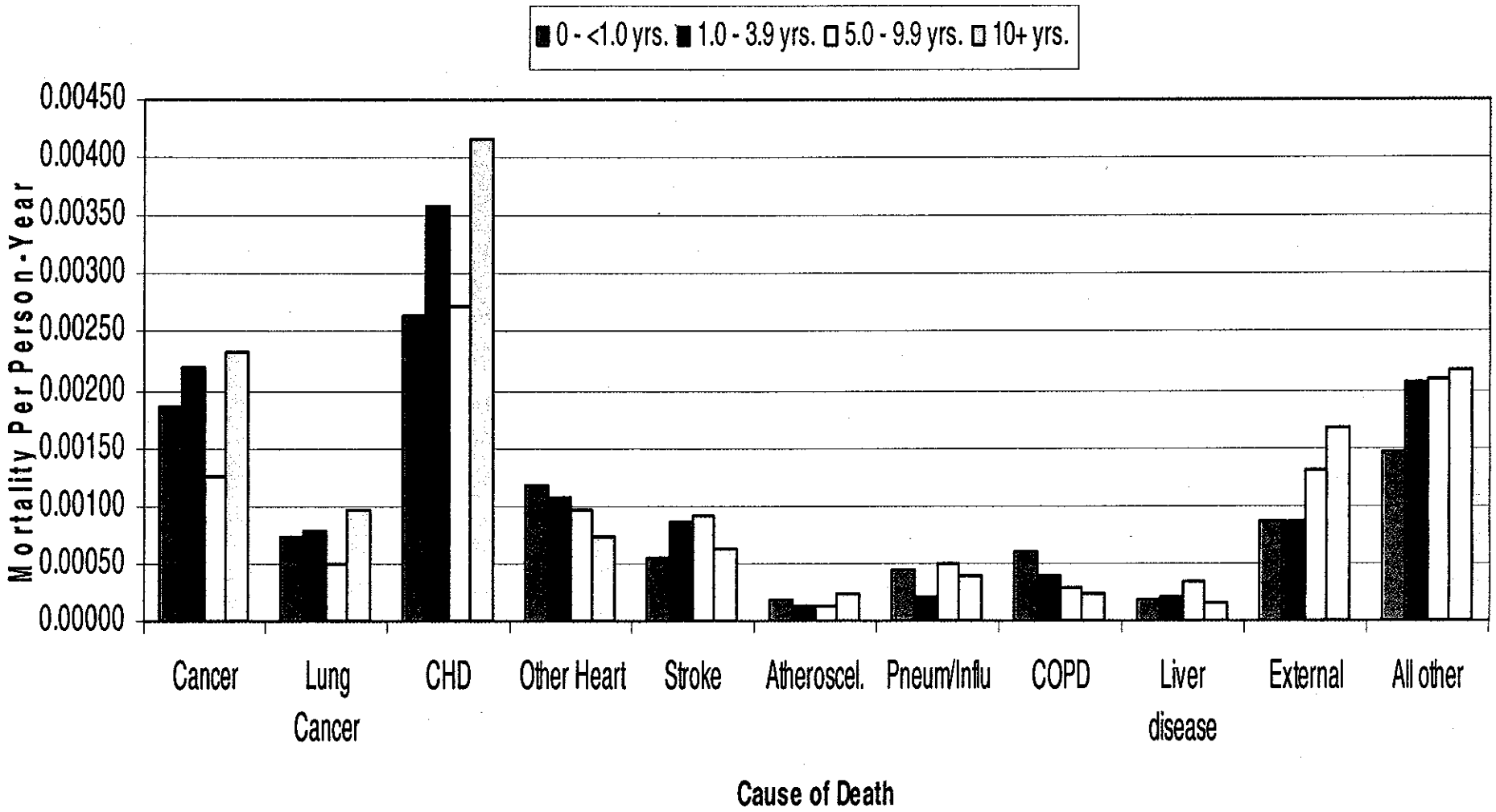


Figure 2. Crude Mortality Rates in Males

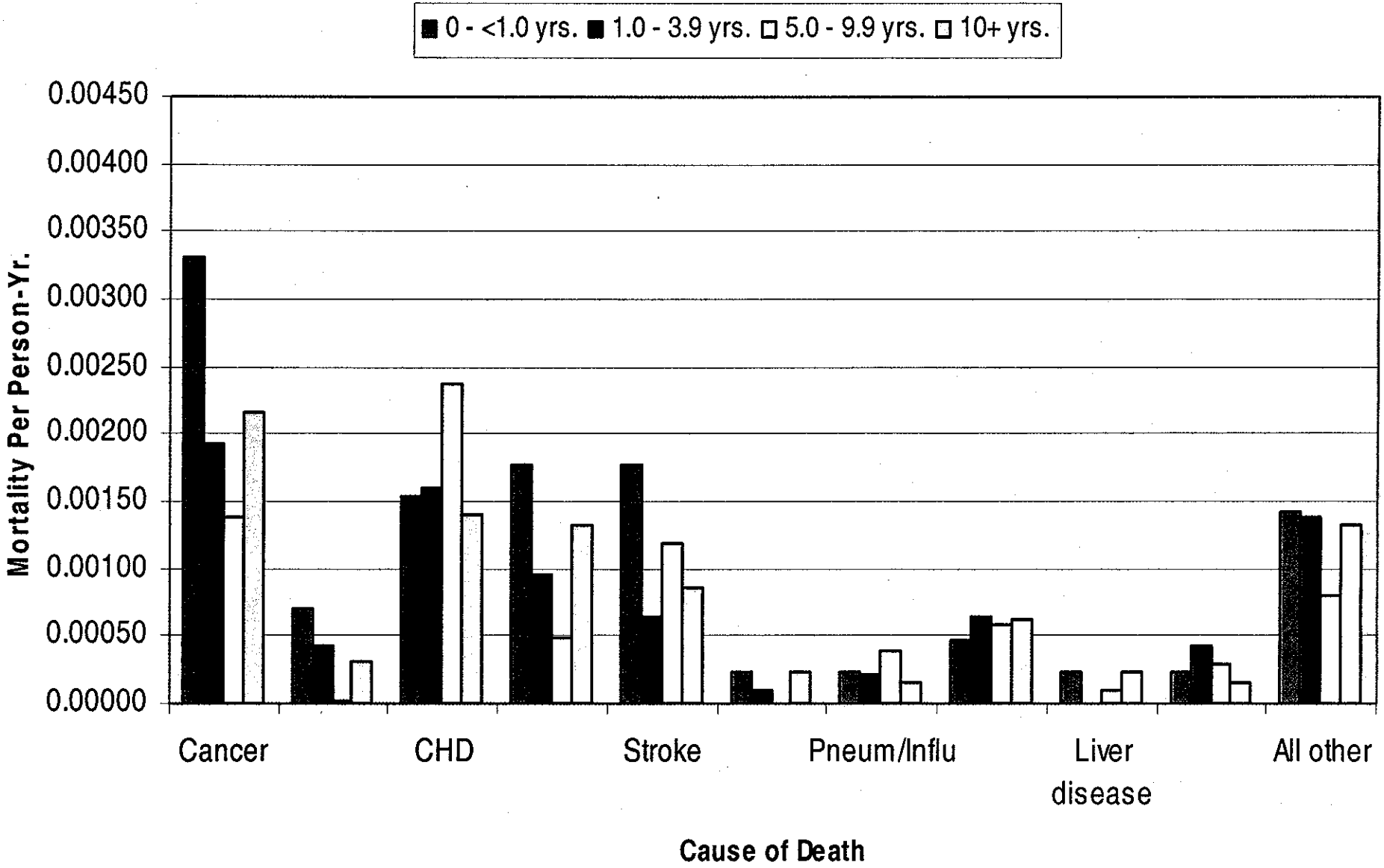


Figure 3. Crude Mortality Rates in Females

Table 2. Hazard Ratios Adjusted for Year of Birth for Selected Causes of Death for Males in the ASARCO Children's Cohort

Cause of Death	0 – <1.0 yr	1.0 – 3.9 yr		4.0 – 9.9 yr		10 or more yr	
	H.R.	H.R	95% C.I.	H.R.	95% C.I.	H.R.	95% C.I.
All Causes of Death	1.00	1.06	0.87, 1.29	0.98	0.80, 1.21	1.52	1.23, 1.86
Malignant Neoplasms	1.00	1.08	0.68, 1.71	0.64	0.37, 1.12	1.51	0.93, 2.44
Lung Cancer	1.00	1.05	0.49, 2.22	0.66	0.27, 1.61	1.54	0.72, 3.28
Bladder Cancer	1.00	0.59	0.05, 6.79	0.78	0.07, 8.79	0.00	
Ischemic Heart Disease	1.00	1.27	0.88, 1.85	0.98	0.65, 1.47	1.77	1.21, 2.58
Other Heart Conditions	1.00	0.80	0.43, 1.49	0.77	0.40, 1.48	0.77	0.36, 1.66
Atherosclerosis	1.00	0.73	0.13, 3.99	0.81	0.14, 4.60	3.27	0.65, 16.52
External Causes	1.00	0.98	0.48, 1.99	1.50	0.79, 2.84	1.93	1.03, 3.62

Table 3. Hazard Ratios Adjusted for Year of Birth for Selected Causes of Death for Females in the ASARCO Children's Cohort

Cause of Death	0 – <1.0 yr	1.0 – 3.9 yr		4.0 – 9.9 yr		10 or more yr	
	H.R.	H.R	95% C.I.	H.R.	95% C.I.	H.R.	95% C.I.
All Causes of Death	1.00	0.63	0.46, 0.86	0.80	0.59, 1.08	1.23	0.96, 1.69
Malignant Neoplasms	1.00	0.51	0.28, 0.94	0.45	0.24, 0.87	1.00	0.58, 1.71
Lung Cancer	1.00	0.50	0.14, 1.81	0.14	0.02, 1.16	0.54	0.15, 1.98
Ischemic Heart Disease	1.00	0.92	0.43, 1.95	1.78	0.90, 3.52	1.69	0.81, 3.51
Other Heart Conditions	1.00	0.48	0.21, 1.11	0.32	0.12, 0.91	1.31	0.64, 1.69
External Causes	1.00	1.67	0.29, 9.48	1.50	0.24, 9.11	1.02	0.14, 7.42

METHODS

- **Description of the study area. The study area included all residences within approximately 2 miles of the ASARCO Copper Smelter, Ruston, Washington. Four elementary schools served this area during the period of interest: three public schools (Ruston, Point Defiance, and Sherman Elementary Schools) and a Catholic School (Holy Cross School).**

- **Identification of the cohort. Study members were born between 1895 - 1925 and resided in the study area for at least 2 years before age 14 years. Annual elementary school censuses from 1910 - 1932 were used to identify potential cases.**

- **Exposure information. Exposure was computed as a function of duration of residence at a particular address and its distance from the smelter stack. The number of years of residence at each address was calculated for each study member for the 25-year study period. Geographic coordinates for each residential address were identified and used to calculate the distance to the smelter stack. Exposure intensity was calculated as the total number of days at residences less than one mile from the smelter stack. Exposure intensity was grouped into four categories by length of time at residences less than one mile from the smelter stack: 0 - <1.0 years, 1.0 - 3.9 years, 4.0 - 9.9 years, and 10 or more years.**

- **Follow-up. A total of 1827 boys and 1305 girls were included in the cohort. The National Death Index (NDI) from 1979-1989 and death records from Washington (1900-1990), Oregon (1971-1979), and California (1960-1990) were used to locate deaths of cohort members. For those were not deceased, the last date they were known to be alive was collected from the Washington State Department of Licensing records (1985-1991), local church records, Tacoma Polk City directories (1895-1932), Tacoma News Tribune articles, the informant listed on a spouse's death certificate, and interviews with relatives, friends, and schoolmates.**

CONCLUSIONS

- **This is the first study to examine long-term effects of childhood exposure to ambient arsenic using a large community-based cohort. We found no consistent patterns of adverse health effects, including excess mortality rates due to lung and bladder cancer. Our results are comparable to other studies of health effects in communities exposed to high levels of ambient air arsenic.**

- **An elevated risk for ischemic heart disease has also been observed in a few studies of occupational cohorts exposed to airborne arsenic and communities exposed to high waterborne arsenic levels.**

  - **Some authors have suggested that arsenic exposure increases the risk of ischemic heart disease due to its effect on cardiovascular risk factors (diabetes, hypertension) and atherosclerosis.**

  - **However, in our study, although ischemic heart disease mortality was elevated in the highest exposure group, there was no significant elevation in mortality due to diabetes, stroke or atherosclerosis.**

  - **This exposure group also had the highest percentage of participants with known follow-up status at the end of the study period. Because members of this exposure group remained in Washington State, they may differ from the other groups in important socioeconomic and behavioral characteristics that are associated with ischemic heart disease mortality such as smoking, alcohol use, obesity, etc.**

- **The findings of this study were limited by several factors. Actual individual exposure measures such as urinary arsenic levels were not available for the cohort. Instead, an indirect measure of exposure intensity was calculated based on the time at a residence and the residence's distance from the smelter stack.**

Exponent

EXTERNAL MEMORANDUM

TO: CPSC Commissioners

FROM: Joyce Tsuji

DATE: March 27, 2003

SUBJECT: Additional Information on Dietary Exposures to Arsenic

This memorandum provides additional information on dietary exposures to inorganic arsenic in support of my previous comments regarding potential exposure for children playing on CCA-treated wood play structures relative to exposure through naturally occurring background sources of arsenic.

The recent estimates of dietary inorganic arsenic intake by children that I presented in my previous comments were summarized in a poster presentation at the International Conference on Arsenic Exposure and Health in July 2002 (Yost et al. 2002). The full analysis will be submitted for publication soon. This work is in follow-up to and relies on previous work by Yost et al. (1998) and Schoof et al. (1999b). These articles are provided in Attachment 1.

Yost et al. (1998) presented estimates of inorganic arsenic intake in U.S. diets of 9.4 μg/day for toddlers and 14 μg/day for adults. These estimates were considered preliminary, however, because of the limited number of foods for which inorganic arsenic concentrations were available. The inorganic arsenic data were those of 13 foods analyzed by the Ontario Ministry of the Environment. Estimates of U.S. food consumption patterns were based on U.S. Food and Drug Administration market basket surveys including consumption rates for 11 general food groups for 1982 through 1990. Because of the limited number of foods with inorganic arsenic data, assumptions on concentrations had to be made based on data from related food types.

Schoof et al. (1999a) developed more refined estimates of dietary inorganic arsenic intake in adults based on analyses reported in Schoof et al. (1999b). Schoof et al. (1999b) analyzed inorganic arsenic levels in 40 foods estimated to make up 90 percent of the inorganic arsenic intake in the diet. Schoof et al. (1999a) used these data to calculate inorganic arsenic intakes of 3.2 μg/day on average for adults in the United States with a 99th percentile of 23 μg/day.

Yost et al. (2002) used the inorganic arsenic data of Schoof et al. (1999b) and the U.S. Department of Agriculture Continuing Survey of Food Intake by Individuals (1998 data on children; USDA 2000) to model arsenic intake probabilistically using a dietary analysis software system (FARE^{TM}) developed by Novigen Sciences (now part of Exponent). FARE^{TM} translates food consumption data (e.g., spaghetti) into its ingredients, which can then be related

to the food types (e.g., tomatoes, wheat, beef) with inorganic arsenic data. The model then incorporates dietary consumption patterns of survey respondents with the inorganic arsenic data of the ingredients making up these diets to develop chemical intake distributions for the population. The resulting estimates are an average dietary inorganic arsenic intake for children ages 2–5 years of 3.2 μg/day with a 99th percentile of 9.4 μg/day. Foods contributing the most inorganic arsenic to these estimated intakes were rice, other grains, and fruit.

These estimates are expected to underestimate background exposures to inorganic arsenic because the water concentration of arsenic used in food preparation was assumed to be 0.8 μg/L, whereas, as noted in the CPSC risk assessment, average levels in drinking water in the United States are around 1–2 μg/L. Some U.S. populations are exposed to higher concentrations near and above the new drinking water standard of 10 μg/L (ATSDR 2000). In addition, the inorganic arsenic content of raw rice samples analyzed by Schoof et al. (1999b) (74 ng/g) were lower than samples measured in other studies (range of 83–101 ng/g) summarized in Schoof et al. (1999b).

By comparison, inorganic arsenic intake by Asian populations would be considerably higher because of their greater consumption of rice and fish than the U.S. population. Although most of the arsenic in fish is in the organic rather than the inorganic form, a high seafood consumption rate can contribute to greater inorganic arsenic intake. Tsuji and Robinson (2002) note a dietary inorganic arsenic intake by adults in a subsistence population in Southeast Asia of 20 μg/day, based on average food intake rates and average inorganic arsenic concentrations. Mohri et al. (1990) report an average inorganic arsenic intake of 14 μg/day in a 3-day duplicate diet survey of six Japanese men and six Japanese women. The range was 1.2 to 32 μg/day. Although estimates for children are unavailable, the greater arsenic intake by adults indicates that inorganic arsenic intake for Asian children would also be considerably higher than in the United States. There is no evidence in the scientific literature that this amount of arsenic intake is associated with increased risk of arsenical cancers in Japan. For example, IARC Worldwide Cancer Incidence Statistics[1] report an average age-standardized incidence rate for bladder cancer in Japanese women of 2.1 per 100,000 for six prefectures (range of 1.5 to 2.8 per 100,000) and a higher incidence in the United States of 6.2 per 100,000 for white women and 4.3 per 100,000 for black women. Bladder cancer rates for men show similar trends and are much higher for both countries, likely because of greater smoking rates in men.

Thus, the arsenic intakes estimated by the CPSC risk assessment for children playing on CCA treated wood (1.4 μg/day over a year and 0.09 μg/day over a lifetime) are fractions of the background dietary intake of naturally occurring inorganic arsenic in food.

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[1] http://jncicancerspectrum.oupjouirnals.org/cgi/statContent/cspectfstat; 102.

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Attachment 1

Articles

Exponent®

Estimation of Dietary Intake of Inorganic Arsenic in Children

L.J. Yost[1], S.H. Tao[2], S.K. Egan[2], L.M. Barraj[3], N.J. Rachman[3], R.A. Schoof[4], and M. Garry[1]
[1] Exponent, Bellevue, WA; [2] FDA Washington, DC;
[3] Exponent,Washington, DC (formerly Novigen);
[4] Gradient Corporation, Mercer Island, WA.

Presented at:
Fifth International Conference on Arsenic Exposure and Health Effects
July 14-15, 2002, San Diego, CA

Introduction

Arsenic is a natural component of our environment, and is known to be ubiquitous in soils and in the diet. Accurate dietary intake estimates for inorganic arsenic are needed to establish background levels of exposure to inorganic arsenic. Previous investigations have estimated dietary intake in adults ranging from 1 to 20 μg/day with an average of 3.2 μg/day, based on a comprehensive market basket survey in which 40 commodities anticipated to provide at least 90 percent of dietary inorganic arsenic intake were analyzed for inorganic arsenic content (Schoof et al. 1999a,b). Four samples of each commodity were collected. Total arsenic was analyzed using an NaOH digestion and inductively coupled plasma-mass spectrometry (ICP-MS). Separate aliquots were analyzed for arsenic species using an HCl digestion and hydride atomic absorption spectroscopy (Schoof et al. 1999a). In addition, intake in the U.S. was previously estimated using a more limited number of foods analyzed for inorganic arsenic (Yost et al. 1998), to derive an estimate of 9.4 μg/day in children and 12.7 μg/day for an adult.

This poster describes derivation of an estimate for intake in children using the more robust dataset for inorganic arsenic and the dietary intake estimates derived by the U.S. Department of Agriculture (USDA) as applied in the Foods and Residue Evaluation Program (FARE™) model developed by Novigen (now Exponent). A mean dietary intake estimate of inorganic arsenic of 3.2 μg/day was derived for children ages 2 to 5 years, with estimates of 1.7 μg/day and 6.2 μg/day at the 10th and 95th percentiles, respectively. Because previous estimates suggested uncertainties regarding inorganic arsenic in milk, lower-end estimates based on trivalent arsenic alone were calculated, resulting in a mean estimate of 2.9 μg/day, with estimates of 1.4 μg/day and 5.8 μg/day at the 10th and 95th percentiles, respectively. Because dietary exposure to inorganic arsenic occurs naturally and is unavoidable, this intake estimate provides useful context in risk management of arsenic exposure.

Background

Arsenic has been detected in most foods tested. Although arsenic may be present in foods in a variety of organic as well as in inorganic forms, most studies have reported only total arsenic concentrations. A number of investigators have reported dietary intake of total arsenic (Dabeka et al. 1993; Gunderson 1995; Tsuda et al. 1995; Tao and Bolger 1999; Egan et al. 2002). Inorganic arsenic intake has been previously estimated for adults (Schoof et al. 1999b; Meacher et al. in press), but intake estimates for children have only been calculated based only on limited data on inorganic arsenic in foods (Yost et al. 1998). In this investigation, arsenic speciation analyses in 40 foods (Schoof et al. 1999a) and dietary intake information from the U.S. Food and Drug Administration are applied to estimate inorganic arsenic intake in children.

Materials and Methods

Market Basket Design and Sample Collection

A market basket approach was used to collect and analyze speciated arsenic in foods using methods described in detail in Schoof et al. (1999a). Food consumption data from the USDA *Continuing Surveys of Food Intakes by Individuals* (CSFII) (USDA 1992, 1993, 1994), surveys of total arsenic in food (Dabeka et al. 1993; FDA 1997), and estimates of inorganic arsenic concentrations in food (Yost et al. 1998) were used to select 40 commodities that were predicted to account for at least 90 percent of the dietary inorganic arsenic in the U.S. The USDA consumption data were used to determine the foods consumed in the largest quantities. Total arsenic levels in foods from the total diet studies conducted in the U.S. and Canada were adjusted to reflect predicted inorganic arsenic levels and used to identify foods likely to have the highest inorganic arsenic levels. All foods thus identified (high consumption and/or expected high levels of inorganic arsenic) were included in inorganic arsenic dietary intake analyses for the U.S. The estimated intakes for the foods (consumption rate x inorganic arsenic concentration) were ordered from highest to lowest; the foods that together contributed the top 90 percent of inorganic arsenic intake were selected for the market basket survey.

A modified market basket survey method was used to collect four samples of each commodity. The food samples were collected during October 1997 from large supermarkets in two towns in Texas. Tap water was also included in the study; samples were collected in a hotel and in restaurants. The food samples were prepared in accordance with Appendix B from *Appendices for the 1990 Revision of the Food and Drug Administration's Total Diet Food List and Diets* (Pennington 1992), with some exceptions. Rice samples were not cooked (raw rice was tested to facilitate comparisons with arsenic concentrations reported in previous studies). Vegetables were cooked in a microwave oven, instead of being boiled in water. Further detail is provided in Schoof et al. (1999a).

Sample Analyses

All samples were analyzed at Battelle Marine Sciences in Sequim, Washington. Total arsenic was analyzed in food commodities after NaOH digestion by ICP-MS. Approximately 1 in every 10 samples was analyzed in triplicate. For the digestion of liquids (milk, juices, and water), NaOH was added to 8 g of liquid to produce 2N NaOH solution. This solution was heated for 16 hours at 80°C. For the digestion of solid food, either 1 or 2 g of food was digested in 13 mL of 2N NaOH for 16 hours at 80°C. In preparation for ICP-MS analysis, 1 mL of digestate was diluted with 9 mL of 2 percent concentrated HNO_3. A model Elan 5000 Perkin-Elmer ICP-MS was operated using the stock cross-flow nebulizer. Several ions were monitored to evaluate polyatomic interference from ^{40}Ar and ^{35}Cl, which have the same mass as arsenic. When interference occurred, the manufacturer's correction factor was used to reduce the interference.

Arsenic speciation was determined in food samples digested with HCl. Between 0.5 and 2 g of food was digested with 13 mL of 2N HCl at 80°C for 16 hours. The digestates were stored at 4°C before analysis by EPA Method 1632 (U.S. EPA 1996). A 2-mL aliquot of the digestate was analyzed for As^{3+} by arsine generation at pH 6 with the reducing agent sodium borohydride. The hydride was collected on a cryogenic column before quantification by atomic absorption (AA) using a quartz tube with an air-hydrogen flame positioned in the light path.

The quantification of total inorganic arsenic, monomethyl arsenic (MMA), and dimethyl arsenic (DMA) was conducted similarly to that of As^{3+}, except that arsines were generated at pH 1. The three arsines (arsine, methylarsine, and dimethylarsine) were collected on the cold column, then quantified by AA when the column was heated. The different column retention times of the arsines allow quantification of inorganic arsenic, MMA, and DMA. The concentration of As^{5+} is determined by the difference between inorganic arsenic and As^{3+}. Every fourth sample was analyzed in triplicate.

The data were blank-corrected by subtracting the mean of the procedural blanks. The mean blank concentrations are shown in Table 1. The method detection limits were determined from the variance in triplicate analyses of food samples containing low but detectable arsenic. The standard deviation was multiplied by the Student's t-value for 95 percent confidence level. The method detection limits are shown in Table 1.

Table 1. Arsenic Analysis Methods in Food[a]

Speciation	Digestion Method	Time Period	Analysis Method	Mean Blank Concentrations	Method Detection Limit (ng/g) wet weight
Total As[b]	2N NaOH	16 hours @ 80°C	ICP-MS	4.57	3.6
As_i	2N HCl	16 hours @ 80°C	EPA Method 1632	1.96	2
As^{3+}	2N HCl	16 hours @ 80°C	EPA Method 1632	<1	1
As^{5+}	The concentration was determined by the difference between As_i and As^{3+}			1.96	2
MMA	2N HCl	16 hours @ 80°C	EPA Method 1632	<1	1
DMA	2N HCl	16 hours @ 80°C	EPA Method 1632	<2	2

Note:
As_i - Inorganic arsenic
Further description in Schoof et al. (1999a).

[a] Analyses of 40 commodities predicted to account for at least 90 percent of dietary As_i in U.S (see Schoof 1999a).
[b] For liquid foods, NaOH was added to 8 g of liquid to produce 2N NaOH solution; for solid foods, either 1 or 2 g of food was digested in 13 mL of 2N NaOH.

If no arsenic was detected (after blank-correcting), one-half the value of the method detection limit was given with a "*U*" designation. One-half the detection limit was used in subsequent calculations. Mean values have a "*U*" qualifier if all values used to calculate the mean were "*U*" qualified. When the concentration of arsenic in food (after blank-correcting) was detected above the blank concentration but below the method detection limit, the value was given a "*J*" designation. The same rule as was used for the "*U*" designated values was also applied in assigning "*J*" qualifiers to mean values. Additional detail on analyses is provided in Schoof et al. (1999a).

Results

Total and Inorganic Arsenic Concentrations

Total arsenic was detected in two or more samples of 35 of the 40 commodities (i.e., all of the commodities except butter, soybean/vegetable oil, salt, whole milk, and green beans). Inorganic arsenic was detected in two or more samples of 34 of the 40 commodities (i.e., all commodities except soybean/vegetable oil, whole and skim milk, chicken, tuna, and orange juice). Inorganic arsenic concentrations were either undetected or qualified with "*J*" in approximately half of the samples, suggesting that the detection limits achieved in this study are just sufficient to characterize inorganic arsenic concentrations in a wide variety of foods. The percentage inorganic arsenic present was calculated relative to the total arsenic concentration. Table 2 shows mean concentrations of total and inorganic arsenic for the 40 commodities analyzed. The data from the two towns from which food samples were collected did not differ significantly. Consequently, the data for all four samples of each commodity were averaged. Table 2 also shows estimates of dietary intake of inorganic arsenic. Specifically, the percentage of inorganic arsenic in the 40 commodities analyzed was applied to adjust dietary intake estimates of total arsenic.

Table 2. Arsenic Concentration in Foods and Estimates of Dietary Intake in Infants and Toddlers

Food Type	Arsenic Concentrations and Speciation[a] Total Arsenic[b] (ng/g)	Total Inorganic Arsenic[b] (ng/g)	Percent Inorganic Arsenic
Meat, fish, poultry			
Beef	51.5	0.39 *J*	0.7
Chicken	86.4	0.89 *J*	1.0
Pork	13.5	0.67 *J*	4.9
Average inorganic arsenic in meat (applied to all other meat and meat mixture categories)			2.2
Freshwater finfish	160	1.0 *J*	0.6
Saltwater finfish	2356	0.55 *J*	0.0
Shrimp	1890	1.9 *J*	0.1
Tuna	512	1.0 *U*	0.2
Average inorganic arsenic in seafood			0.2
Milk, yogurt, cheese			
Milk (applied to all milk products)	2.2	1.0 *U*	46.2
As^{3+} percentage (applied to all milk products)			8.32
Eggs			
Egg	20	0.98 *J*	4.9
Legumes, nuts, and seeds			
Peanut butter (applied to legumes, nuts, and seeds)	43.7	4.7	10.8
Grain and grain products			
Corn (meal)	38.6	4.4	11.5
Flour	39.2	10.9	27.8
Rice	303	73.7	24.3
Average inorganic arsenic in grain products (applied to all grain categories)			21.2
Fruits and fruit juices			
Orange	1.6	2.5	152.8
Orange juice	4.8	1.0 *U*	20.7
Average inorganic arsenic in oranges			86.7
Apple, raw	4.8	1.8 *J*	37.4
Apple, juice	7.6	2.8	37.6
Grape juice	14.1	9.3	65.5
Average inorganic arsenic in noncitrus juices			51.5
Banana	2.3	0.65 *J*	27.6
Grapes	10.2	3.7	35.9
Peaches	3.4	2.3	66.8
Watermelon	6.7	2.1	31.9
Average inorganic arsenic in other fruits			40.5
Potatoes			
Potatoes	2.8	0.82 *J*	29.2
Vegetables and vegetable products			
Tomato	9.9	0.92 *J*	9.3
Green beans	2.1	1.2 *J*	60.7
Lettuce	1.4	1.5 *J*	104.1
Peas	4.3	4.5	103.1
Spinach	5.1	6.1	119.1
Average inorganic arsenic in dark green vegetables		96.8	
Carrots	7.3	3.91	53.7
Inorganic arsenic in deep yellow vegetables			53.7
Corn (kernel)	1.6	1.1 *J*	72.0
Cucumber	9.6	4.12	43.0
Onions	9.6	3.3	34.4
Average inorganic arsenic in other vegetables			49.8
Condiments, fats, oils			
Butter	1.8 *U*	1.17 *J*	64.7
Soybean oil	1.5	0.81 *J*	54.6
Salt	4.8	0.84 *J*	17.4
Average inorganic arsenic in condiments			45.6
Sugars and adjuncts			
Beet sugar	12.2	3.5	28.5
Cane sugar	23.8	4.44	18.7
Corn syrup	6.0	0.44 *J*	7.4
Average inorganic arsenic in sweets (applied to sweets and soft drinks)		18.2	0.36

Note:

J - Estimated

U - Undetected

[a] Data analyzed by Battelle Marine Sciences Laboratory, 1529 W. Sequim Bay Rd., Sequim, WA 98382-9099. Each food type represents an average concentration of 4 samples, with one of the four samples in each food category analyzed in triplicate (Schoof et al. 1999a).

[b] Undetected samples have been included at 1/2 the detection limits. All averaged values were computed as follows:

- If all values to be averaged were non-detects, the minumum detection limit was reported
- If one or more, but not all values to be averaged was non-detected, 50% of the detection limit(s) was used incalculating the average concentration.

E^x

Dietary Exposure Estimates

Dietary intake of arsenic was estimated using Exponent's FARE™ software, and data from USDA's CSFII. The CSFII consumption data used were collected from 1994 through 1996 and 1998 for the Supplemental Children's Survey data (USDA 1995, 1996, 1998). The amount of inorganic arsenic present in a food, based on values provided in Table 2 data, was multiplied by the distribution of the amount of food consumed (based on estimates from the CSFII database).

USDA developed recipes to translate foods reported in the survey "as eaten" into their component ingredients for purposes of nutrient analysis. The recipes in FARE™ are based on USDA's, but have been made more user-friendly for use in additional kinds of intake analyses, including ingredients, additives, or contaminants. Per capita and per "user" food consumption algorithms and calculations in FARE™ are the same as those used by USDA.

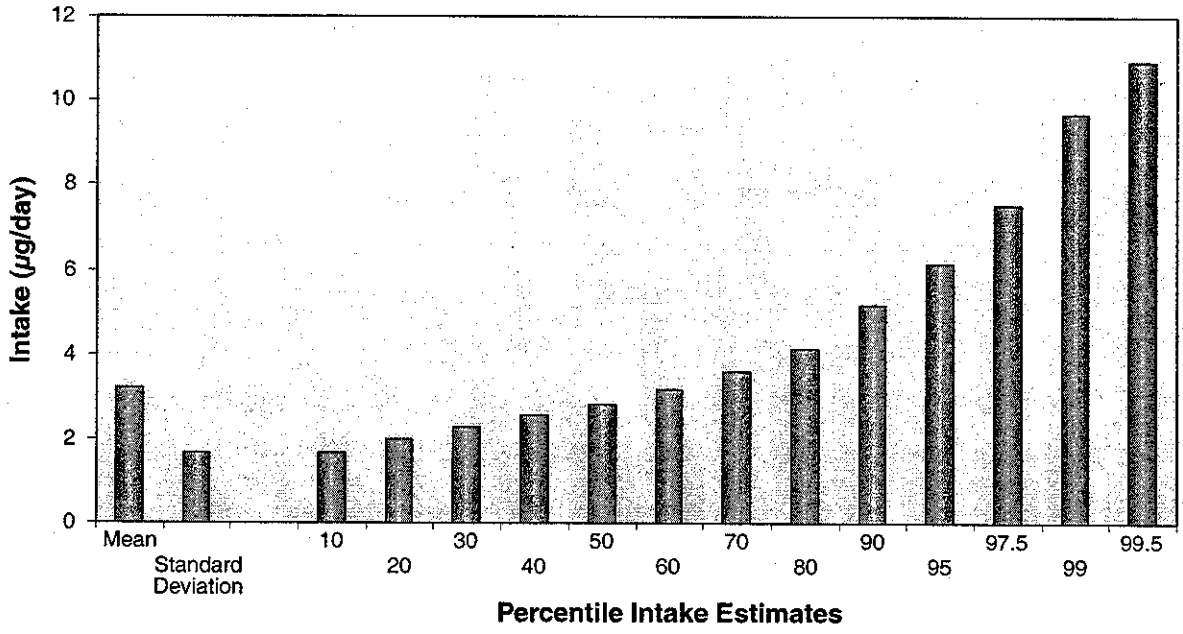
Provided the ingredient/contaminant of interest is not an acute toxicant or teratogen, it is appropriate to average exposures over a longer period than one day. Therefore, these estimates were based upon each respondent's food consumption averaged over the two days of the CSFII survey. For example, if someone reported consuming 100 grams of bread on day 1 and 150 grams of bread on day 2, his/her 2-day average bread consumption would be 125 grams ([100+150]/2).

A 2-day average typically overestimates long-term (chronic) intake; however, only two nonconsecutive days' worth of food consumption data are available in the most recent CSFII survey database. Although the 1989–1991 CSFII included food consumption diaries on three nonconsecutive days, which might better support estimation of chronic daily intake, rapidly evolving trends in diet and the pace of introduction of new foods call into question the representativeness of the older data for today's consumers. This estimate was therefore based on the most recent consumption data in our assessments.

Discussion

Inorganic arsenic was found at ng/g concentrations in most foods tested. The intake of inorganic arsenic in children ages 2–5 was estimated to have a mean of 3.2 μg/day with percentile estimates ranging from 1.7 μg/day to 6.2 μg/day (Figure 1), at the 10th and 95th percentiles, respectively. The concentration of inorganic arsenic in milk products was previously identified as an uncertainty in this estimate (Yost et al. 1998). Total

Figure 1. Dietary intake of inorganic arsenic in children ages 2–5 years



inorganic arsenic was undetected in milk at a detection limit of 2 ng/g and was included in the estimate at one half of the detection limit (i.e., at a concentration of 1 ng/g). There was indication that inorganic arsenic was present. Specifically, trivalent arsenic (As3+) was also detected in milk at a concentration of 0.18 ng/g. Application of the percentage of inorganic arsenic in milk based on As^{3+} alone had little effect on the estimates, yielding a mean total dietary inorganic arsenic estimate of 2.9 μg/day with estimates of 1.4 μg/day and 5.8 μg/day, at the 10th and 95th percentiles, respectively. These estimates also incorporated intake related to use of water in food preparation based on a water concentration of 0.0008 μg/mL. Due to the relatively high use of water in the preparation of food, individuals with higher arsenic concentrations in water likely also have higher dietary intake of arsenic.

Although the 40 commodities tested provided a more robust basis for analysis than had been previously available, there is still some uncertainty related to foods not analyzed, or key dietary items that were undetected. Where foods were not analyzed they were evaluated though application of the foods thought to be most representative. Thus, some uncertainty is introduced by the methods in which the foods are grouped in the estimates.

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Human and Ecological Risk Assessment: Vol. 4, No. 1, pp. 137-152 (1998)

Intake of Inorganic Arsenic in the North American Diet

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ABSTRACT

Dietary intake of inorganic arsenic, previously assumed to be an insignificant source of arsenic exposure in humans, was estimated for Canadian and United States populations. Input data included arsenic contents of various food groups, a limited historical database from the Ontario Ministry of the Environment measuring the percent inorganic arsenic in food groups, and food consumption data. Estimated daily dietary intake of inorganic arsenic ranges from 8.3 to 14 μg/day in the United States and from 4.8 to 12.7 μg/day in Canada for various age groups. These data suggest that between 21% to 40% of total dietary arsenic occurs in inorganic forms. Uncertainties regarding total arsenic in dairy products in the data set applied here may account for observed differences between United States and Canadian estimates. While estimates provided here are preliminary because of limitations in data on the proportion of inorganic arsenic in foods, this analysis suggests that dietary intake of inorganic arsenic is higher than is currently assumed. Additional research is needed to more fully characterize inorganic arsenic concentrations in foods. Future study is also needed on the variability of total and inorganic arsenic in foods and the bioavailability of dietary inorganic arsenic.

Key Words: United States, Canada, food, speciation, metals exposure assessment, arsenic

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1080-7039/98/$.50

INTRODUCTION

As the 20th most abundant element in the Earth's crust, arsenic has been detected in virtually all foods evaluated (NAS, 1977; Irgolic, 1992). Speciation analyses of arsenic have focused primarily on marine animals; less data are available for marine plants and less yet are available for terrestrial biota and foods as consumed (Irgolic, 1992; Phillips, 1994). (A separate manuscript [Schoof *et al.*, 1998] has been submitted presenting results of speciation analyses of arsenic in yams and rice collected in Taiwan. The results of these analyses are new data that can be used to evaluate arsenic concentrations in yams and rice.) Arsenic in marine biota has been shown to occur predominantly in nontoxic organic forms (*i.e.*, arsenobetaine and arsenocholine). Because of the widespread belief that most dietary arsenic also occurs in nontoxic organic forms, dietary intake of inorganic arsenic is typically considered to be insignificant (Gunderson, 1995). This may not be the case.

A preliminary study of speciated arsenic in food was conducted by the Ontario Ministry of the Environment (OME). Results have been circulated in internal memoranda (OME, 1987), but they have never been published. A review of the OME (1987) data in light of reports evaluating the data shows that these data have been widely misinterpreted because of an inaccurate table in a widely cited U.S. Environmental Protection Agency (EPA) report (USEPA, 1988).[1] For example, although OME did not analyze any potatoes or vegetables, the data have been cited as indicating that arsenic in yams (USEPA, 1988) and vegetables (Mushak and Crocetti, 1995) occurs primarily in organic forms. This paper presents the findings of the 1987 OME study and applies them to provide preliminary estimates of inorganic arsenic intake in typical United States and Canadian diets.

SPECIATION ANALYSES CONDUCTED BY OME

To identify the relative proportions of inorganic and organic arsenic in foods, OME analyzed 15 samples of food for total arsenic and for inorganic and organic arsenic forms. These analyses were carried out by the Ontario

[1] Table E-1 of USEPA (1988) cites the OME study presented here as the source of estimates of the percentage of inorganic arsenic in food groups that EPA applied in deriving toxicity values for arsenic. None of the EPA inorganic arsenic percentages match those detected by OME. EPA estimates for saltwater fish (0%), rice (35%), and cereals (65%) are close to those detected by OME (*i.e.*, EPA estimates are within 5–10 percentage points of those predicted by OME data). However, EPA estimates for milk (75%) and poultry (65%) appear to be the inverse of those detected by OME for milk (26%) and poultry (41%), EPA estimates for fruit (10%) does not agree with the percent suggested by OME data (73%), and there were no OME analyses for potatoes or vegetables and thus these EPA estimates (of 90% and 95%, respectively) are unexplained.

Research Foundation (ORF) for the OME. Method development was reported in one technical memorandum (OME, 1986) and results in a second (OME, 1987).[2]

Methods

Total and speciated arsenic were measured in 15 homogenized food samples (OME, 1986). Although only one sample was analyzed for each food, all but four of the food samples were analyzed in duplicate or triplicate (*i.e.*, all except sole, tuna, apple juice, and cigarettes).

For total arsenic measurements, aliquots of 1 to 7 g (depending on moisture and fat content) were measured into 125-ml flasks, 20 ml concentrated nitric acid was added, and samples were warmed until the initial reaction subsided. Sulfuric acid (2 ml) was then added, and the solutions were evaporated to light fumes of sulfuric acid. When necessary to prevent charring or loss of sample, nitric acid was added. Perchloric acid (2 ml) and nitric acid (5 ml) were then added, the mixture was evaporated to destroy residual organic material and expel remaining perchloric acid, and samples were allowed to cool. Deionized water (10 ml) and hydrochloric acid (5 ml) were then added. The solutions were warmed to dissolve precipitated salts, cooled, and diluted to volume (25 ml). Finally, the solutions were reduced from the pentavalent to the trivalent state using potassium iodide and analyzed for total arsenic by hydride atomic absorption.

Analyses for speciated arsenic began by digesting subsamples of the foods analyzed for total arsenic using hydrochloric acid (25 ml of a 50% solution) and hydrobromic acid (1 ml) and then refluxing samples in a Bethge distillation apparatus for 5 to 15 minutes until 20 ml of distillate could be collected. Then an additional 20 ml of hydrochloric acid was added, and 20 ml more of the distillate was collected. Condensers and receivers were rinsed, and the rinsate was added to the combined distillate.

Inorganic arsenic was reduced to the trivalent state during distillation and codistilled with the acid mixture. Distillates containing the inorganic arsenic were combined with nitric acid (5 ml) and sulfuric acid (2 ml), and the solutions were evaporated to fumes of sulfuric acid. After cooling, water (10 ml) and hydrochloric acid were added and the solutions were diluted to 25 ml for hydride generation atomic absorption analysis.

Organic arsenic was determined by taking the residues in the distillation flask; adding concentrated nitric (approximately 20 ml), sulfuric (2 ml), and perchloric (5 ml) acids; evaporating to fumes of perchloric acid; diluting; and detecting with hydride generation atomic absorption. OME (1986) mentions possible breakdown of organic arsenic during the distillation step and notes that evaporating the distillation flask to dryness could cause further decomposition of organic compounds.

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[2] The principal investigator, Roland Weiler, has retired and could not be contacted, consequently, some details of the procedures are unknown.

Results

Total arsenic concentrations in the foods analyzed ranged from 0.011 mg/kg in pastry flour to 4 mg/kg in sole (Table 1; all sample results are reported as wet weight, except as indicated). Inorganic arsenic concentrations ranged from 0.0042 mg/kg in vanilla ice cream to 0.1 mg/kg in rice and shrimp, and organic arsenic concentrations ranged from undetected in a variety of foods to 0.52 mg/kg in canned shrimp. The percent inorganic arsenic in these foods, calculated here by dividing the average inorganic arsenic for a specific food by the total arsenic for that food,[5] ranged from 1% for marine fishes to 100% for meat (based on samples of pork and pastrami). When data were available for several foods from a food group (*i.e.*, in the case of meat, saltwater fish, and cereals), the average for that food group was also calculated (Table 1).

INTAKE OF INORGANIC ARSENIC

Methods used in estimating dietary intake of inorganic arsenic in United States and Canadian populations are described in the following sections.

United States Diet

Total arsenic intake from a typical diet in the United States was calculated from data compiled by the U.S. Food and Drug Administration (FDA) on food consumption patterns and total arsenic concentrations in foods. Food consumption patterns for United States populations were based on FDA market basket surveys for 1982 through 1990. These surveys provide consumption rates for 11 general food groups that represent the diets of United States populations in three age categories: infants (0 to 6 months), toddlers (6 months to 2 years), and adults (18 years and older) (Borum, 1992; Gunderson, 1995). FDA also reports total arsenic concentrations detected in foods that correspond with the categories evaluated in the consumption surveys (Gunderson, 1995). Foods were prepared for cooking, cooked, digested with nitric, perchloric, and sulfuric acids, and analyzed with hydride generation atomic absorption. In a background document prepared by EPA (Borum, 1992), food consumption data were combined with FDA measurements of total arsenic concentrations in foods to estimate total arsenic intakes of 21.5 μg/day for infants, 27.6 μg/day for toddlers, and 52.6 μg/day for adults.

To derive the inorganic arsenic intake estimates in Table 2, the FDA's total arsenic estimate for each food group presented in Borum (1992) was multiplied by the OME estimates of the percent inorganic arsenic for the corresponding food groups (Table 1). Certain FDA categories did not have an exact counterpart in the OME (1987) study. Specifically, no OME data were avail-

[5] For some samples, less than 100% of the total arsenic was recovered as inorganic arsenic. We calculated inorganic arsenic as a percent of total arsenic, based on the assumption that unrecovered arsenic was either in complex organic forms, or if present as inorganic arsenic, it would not be bioavailable.

TABLE 1. SPECIATED ARSENIC DATA FROM ONTARIO MINISTRY OF THE ENVIRONMENT[a]

Food Category	(N)	Arsenic Concentration			% Inorganic Arsenic[b]
		Total	Inorganic	Organic	
Milk and Dairy Products (average)					26
Vanilla ice cream (average of replicates)	1	0.016	0.0042	<0.002	26
First replicate			0.0035	<0.001	
Second replicate			0.0049	<0.002	
Meat (average)					100
Pork (cured, average of replicates)	1	0.013	0.018	<0.007	144
First replicate		0.013	–	–	
Second replicate		0.012	–	–	
Pastrami (average of replicates)	1	0.024	0.024	<0.009	99
First replicate		0.023	–	–	
Second replicate		0.024	–	–	
Third replicate		0.026	–	–	
Poultry (average)					41
Chicken (average of replicates)	1	0.022	0.0090	0.012	41
First replicate		0.021	–	–	
Second replicate		0.023	–	–	
Fish (saltwater) (average)		2.55	0.024	2.8	1
Sole	1	4	0.022	4.4	1
Tuna	1	1.1	0.025	1.2	2
Fish (freshwater) (average)					15
Pickerel (average of replicates)	1	0.14	0.022	0.086	15
First replicate		–	0.019	–	
Second replicate		–	0.024	–	

TABLE 1. (cont.)

Food Category	(N)	Arsenic Concentration			% Inorganic
		Total	Inorganic	Organic	Arsenic[b]
Shellfish					16
Shrimp (average of replicates)	1	0.65	0.10	0.52	16
First replicate		–	0.12	–	
Second replicate		–	0.086	–	
Rice (average of replicates)	1	0.24	0.1	0.16	43
First replicate		0.24	0.1	–	
Second replicate		0.23	0.1	–	
Cereals (average for all)					49
"Special K" (average of replicates)	1	0.27	0.070	0.15	26
First replicate		0.3	–	–	
Second replicate		0.23	–	–	
Bread (whole wheat, average of replicates)	1	0.024	0.012	<0.006	50
First replicate		–	0.011	–	
Second replicate		–	0.013	–	
Pastry flour (average of replicates)	1	0.011	0.0076	<0.005	69
First replicate		0.011	–	–	
Second replicate		0.011	–	–	
Fruit					73
Apple juice	1	0.012	0.0088	<0.002	73
Vegetables		–	–	–	NA
Potatoes		–	–	–	NA

TABLE 1. (cont.)

Food Category	(N)	Arsenic Concentration			% Inorganic Arsenic[b]
		Total	Inorganic	Organic	
Tea (average of replicates)	1	0.035	0.0091	0.025	26
First replicate		0.035	0.0091	0.025	
Second replicate		–	<0.02	<0.02	
Cigarettes	1	0.18	0.11	0.03	61

Note: Values expressed as mg/kg wet weight.

– - not analyzed

OME - Ontario Ministry of the Environment

[a] Arsenic concentration data are reproduced from OME (1987). Percent recovery and percent inorganic arsenic were calculated by the present authors.

[b] Estimated from OME data by dividing inorganic arsenic concentration by total arsenic concentrations. Boxed values represent the entire food group, other values represent individual foods.

TABLE 2. DIETARY INTAKE OF ARSENIC IN UNITED STATES AND CANADIAN POPULATIONS

	Children					
	U.S. Diet[a]				Canadian Diet[b]	
	Infant		Toddler		Ages 1-4	
Food Category	Total	Inorganic	Total	Inorganic	Total	Inorganic
Dairy	13.4	3.5	8.5	2.2	1.1	0.3
Meat	0.6	0.6	0.9	0.9	0.9	0.9
Poultry	0.4	0.1	1.1	0.4	0.8	0.3
Fish (saltwater)	0.0	0.0	6.0	0.1	5.7	0.1
Fish (freshwater)	0.0	0.0	0.4	0.1	0.6	0.1
Shellfish	0.0	0.0	0.5	0.1	0.8	0.1
Legumes[c]	1.2	0.6	0.4	0.2	0.2	0.1
Rice[d]	0.3	0.1	1.1	0.5	0.7	0.3
Cereals	1.7	0.8	2.5	1.2	1.8	0.9
Fruit	2.1	1.8	1.9	1.4	1.1	0.8
Vegetables[e]	1.2	0.6	1.2	0.6	0.3	0.1
Potatoes[e]	0.2	0.1	0.5	0.4	0.6	0.4
Tea	NA	NA	NA	NA	0.0	0.0
Other foods[f]	0.3	0.2	2.6	1.3	0.7	0.4
Totals	21.5	8.3	27.6	9.4	15.1	4.8
Totals without dairy[g]	8.1	4.7	19.1	7.1	14.0	4.5

TABLE 2. (cont.)

	Adults					
			Canadian Diet			
	U.S. Diet[a]		Women 20-39		Men 20-39	
Food Category	Total	Inorganic	Total	Inorganic	Total	Inorganic
Dairy	4.7	1.2	0.6	0.2	0.9	0.2
Meat	2.6	2.6	2.1	2.1	3.5	3.5
Poultry	2.1	0.9	1.2	0.5	1.6	0.7
Fish (saltwater)	23.9	0.3	17.5	0.2	33.3	0.5
Fish (freshwater)	1.5	0.2	0.3	0.1	1.0	0.1
Shellfish	1.9	0.3	3.9	0.6	6.2	1.0
Legumes[c]	0.6	0.3	0.2	0.1	0.3	0.2
Rice[d]	1.3	0.5	1.6	0.7	1.9	0.8
Cereals	3.1	1.5	2.4	1.2	3.5	1.7
Fruit	1.7	1.3	0.8	0.6	1.0	0.8
Vegetables[c]	3.3	1.5	0.7	0.3	0.8	0.4
Potatoes[e]	1.2	0.9	0.7	0.5	1.4	1.0
Tea	NA	NA	0.6	0.2	0.6	0.2
Other foods[f]	4.7	2.4	1.8	0.9	3.6	1.8
Totals	52.6	14.0	34.4	8.1	59.6	12.7
Totals without dairy[g]	47.9	12.7	33.8	7.9	58.6	12.5

Footnotes on next page.

TABLE 2. (cont.)

Note: Values expressed as μg/day.

FDA - U.S. Food and Drug Administration

NA - no data available

OME - Ontario Ministry of the Environment

[a] Estimates based on percentages of inorganic arsenic from OME (unless otherwise noted) combined with FDA market basket consumption values for 1982 to 1990 and total arsenic concentrations as reported in Borum (1992). Infants are up to 6 months, toddlers are 6 months to 2 years, and adults are 18 years and older.

[b] Estimates based on percentages of inorganic arsenic from OME (unless otherwise noted) combined with total arsenic concentrations from the Canadian Health Protection Branch and intake from Nutrition Canada as reported in Dabeka et al. (1993). Totals for each food group in Dabeka et al. (1993) were used in these estimates and the overall sum for all foods does not match the overall sum in Dabeka *et al*. (1993).

[c] No legumes or vegetables were measured by OME: 47% inorganic arsenic assumed (average of rice and cereals in OME).

[d] FDA category for "mixture mainly grain" used in estimates for U.S. populations.

[e] No potatoes were analyzed by OME: 75% inorganic arsenic assumed based on the average inorganic arsenic detected in yams in Schoof *et al*. (1997).

[f] Other foods were assumed to contain 50% inorganic arsenic, based on the average of all foods analyzed by OME of 46%.

[g] Concentrations of total arsenic in dairy in U.S. populations are uncertain because of a high number of undetected values in dataset. See text.

TABLE 3. COMPARISON OF TOTAL ARSENIC DETECTED IN OME AND DABEKA *et al.* (1993)

Food Category	OME[a] Average	Dabeka et al. (1993)[b] Average	Dabeka et al. (1993)[b] Range	OME/Dabeka *et al.* (1993) Averages
Milk and Dairy Products (average)	--	0.0038	0.004–0.026	--
Vanilla ice cream	0.016	0.005	0.0007–0.010	3.2
Meat (average)	--	0.028	<0.001–0.536	--
Pork (cured)	0.013	0.018	0.0081–0.028	0.7
Pastrami	0.024	0.014	0.0082–0.037	1.7
Poultry (average)	--	0.026	<0.001–0.1	--
Chicken	0.022	0.047	0.018–0.1	0.5
Fish (saltwater) (average)	2.550	3.05	1.85–4.83	0.8
Fish (freshwater) (average)	0.140	0.45	0.077–1.35	0.3
Shellfish	0.650	2.04	1.01–4.2	0.3
Rice (average)	0.235	0.097	0.075–0.365	2.4
Cereals (average)	0.100	0.011	<0.0001–0.142	9.5
Fruit (apple juice)	0.012	0.0060	0.0045–0.0094	2.0
Vegetables	--	0.0053	<0.0001–0.038	--
Potatoes	--	0.098	<0.0001–0.044	--
Tea	0.035	0.0021	0.0004–0.0051	16.7

Note: Values express as mg/kg wet weight.

All values are averages of replicates or averages of foods in the group except apple juice, which is a single value.

-- - data not available

OME - Ontario Ministry of the Environment

[a] See Table 2 for specific products from these food categories analyzed by OME.

[b] Foods were selected from Dabeka *et al.* (1993) that most closely approximated foods analyzed by OME.

able for legumes or vegetables; an estimate of 47% inorganic arsenic was applied to these foods based on the average percentage of inorganic arsenic detected in rice and cereals. Because no OME data were available for potatoes, the estimate of average inorganic arsenic in yams of 76% from Schoof *et al.* (1998) was applied here. The FDA category of "other foods," which included data for oils, beverages (other than those prepared from dairy or fruit products), coffee, and additional foods, was assumed to contain 50% inorganic arsenic based on the average of the OME percentages for all food categories analyzed. These calculations yielded total United States dietary intake estimates for inorganic arsenic of 8.3 μg/day for infants, 9.4 μg/day for toddlers, and 14.0 μg/day for adults (Table 2). Intake estimates that exclude arsenic intake from dairy products are also presented in Table 2 because of uncertainties in the estimates for that food category (see *Discussion* below).

Canadian Diet

Total arsenic intake in the typical Canadian diet was reported by Dabeka *et al.* (1993), who summarized age- and sex-specific consumption rate data for 112 food categories representative of the Canadian diet and corresponding total arsenic concentrations. Consumption data were collected by the Nutrition Canada Survey of the Canadian Department of Health and Welfare. Total arsenic concentrations in food samples from the 112 food categories were collected from six Canadian cities and compiled by the Canadian Total Diet Program. Food samples had been prepared for consumption, homogenized, and then digested in nitric acid prior to measurement of total arsenic by graphite furnace atomic absorption.

The intake of total arsenic averaged over the six Canadian cities ranged from 15.1 μg/day for children ages 1–4 to 59.6 μg/day for adult men ages 20–39. The overall average for the entire population was 38.5 μg/day (Dabeka *et al.*, 1993).

To derive the inorganic arsenic estimates in Table 2, the total arsenic concentrations for the food categories reported in Dabeka *et al.* (1993) were multiplied by our estimates of percent inorganic arsenic in the corresponding groups (Table 1). These calculations yielded estimates of total Canadian dietary intake of inorganic arsenic of 4.8 μg/day for children ages 1–4, 8.1 μg/day for women ages 20–39, 12.7 μg/day for adult men ages 20–39, and 8.3 μg/day for all ages combined.

DISCUSSION

The analyses presented in this paper suggest that inorganic arsenic comprises approximately 20% to 40% of total dietary arsenic intake. Additional research is needed to confirm these estimates. Cereals, rice, and fish, identified as relatively important sources of total arsenic in the diet (Dabeka *et al.*, 1993; Gunderson, 1995), were well characterized in the OME data set and appear to be important sources of inorganic arsenic as well. The estimates for rice and fish are also supported by other studies. Schoof *et al.* (1998) found an

average of 68% inorganic arsenic in speciation analyses of seven rice samples, Norin *et al.* (1985) reported 5% to 22% inorganic arsenic in freshwater fish, and a review by Shiomi (1994) reported inorganic arsenic in saltwater fish ranging from 0% to 3%.

Additional inorganic arsenic data on other relatively large dietary arsenic sources such as dairy products (*i.e.*, milk with a range of fat content), beef (*i.e.*, hamburger or steak), poultry (*i.e.*, eggs), and potatoes would reduce uncertainties associated with the use of the OME data set. Although fruits and vegetables do not appear to be primary contributors to total dietary arsenic intake, information on the proportion that is inorganic would be useful in conducting human health risk assessments where consumption of homegrown produce is often evaluated. While arsenic intake from home-grown produce is often dismissed as being irrelevant because only nontoxic organic forms are present, these limited data suggest further evaluation is warranted.

Data in Table 2 suggest United States dietary intake of inorganic arsenic is higher than Canadian intake. The most comparable age categories between the two data sets are United States toddlers (6 months to 2 years old), with a daily inorganic arsenic intake of 9.4 μg, and 1–4 year old Canadians, with a daily intake of 4.8 μg. Although the inorganic arsenic intake estimate for United States adults, 14.0 μg/day, was similar to that for Canadian men ages 20–39, 12.7 μg/day, the estimate for United States adults was higher than estimates for Canadian women ages 20–39 (8.1 μg/day). The single largest difference in intake of inorganic arsenic between United States and Canadian populations appears to be from milk and dairy products. United States intake values range from 1.2–3.5 μg/day, while intake in Canadian populations ranges from 0.2–0.3 μg/day (Table 2). This categorical difference appears to be large enough to account for most of the overall difference in intake (Table 2).

The summary of FDA data used in the current estimates (Borum, 1992) did not allow an exact comparison of consumption rates for dairy products in United States and Canadian populations. A summary of United States consumption rates estimated from 1980–1982 FDA data (Gartrell *et al.*, 1986) suggests, however, that differences in intake from dairy products may be related to higher consumption rates of these products in United States populations. Gartrell *et al.* (1986) reported higher average daily consumption rates of dairy products for United States adults (761 g) than were reported by Dabeka *et al.* (1993) for all Canadians (442 g), Canadian women ages 20–39 (291 g), or Canadian men ages 20–39 (425 g). Verification of summary data on consumption rates for dairy products in United States populations would be useful because this food category is an important contributor of dietary arsenic; however, consumption rate differences alone do not appear to be sufficient to explain the differences in the two data sets.

Observed differences in intake of arsenic from dairy products may be due to uncertainties in the total arsenic concentrations derived from the FDA summary used here (Borum, 1992) where total arsenic concentrations were derived from the average of the detected sample, excluding any nondetected

samples from the estimate. Because there were very few total arsenic detections in dairy products, total arsenic averages based solely on detected samples may have resulted in an overestimate of total arsenic concentrations. Data sets for other food groups had a much smaller proportion of nondetected samples and are less likely to be overestimates. Estimates derived by Dabeka *et al.* (1993) used detection limits in calculating averages including nondetected samples and thus, these estimates are also less likely to overestimate concentrations of total arsenic in dairy products. Calculations of inorganic arsenic intake excluding intake from dairy products show much closer agreement between United States and Canadian populations (Table 2).

Application of inorganic arsenic data from the 15 individual food types analyzed by OME to derive estimates of inorganic arsenic intake for all foods provides preliminary estimates that need to be confirmed by additional studies. Variability of total arsenic among foods within a food group (*e.g.*, specific dairy products within the milk and dairy food group) analyzed by Dabeka *et al.* (1993) often spans an order of magnitude, while data from OME are only available for one food each from the dairy, fruit, and poultry categories. In addition, some food groups (*e.g.*, legumes, potatoes, vegetables) were not represented among the food samples analyzed by OME; the use of extrapolated values from other food groups to represent these food groups may under- or overestimate inorganic arsenic exposures.

Very few studies of arsenic forms in food have been performed, and concerns have been raised that the strong acid digestions used in analyses of organic and inorganic arsenic could break down organic arsenic compounds (Mushak and Crocetti, 1995). Nevertheless, virtually all the speciated arsenic recovered in fish was present in organic forms (*i.e.*, the average percent organic arsenic concentration was 99.6% in two marine fish samples and one shrimp sample) (Table 1). This issue is discussed in more detail in Slayton *et al.* (1996) and in Schoof *et al.* (1998).

Although OME analyzed a limited number of individual foods, the availability of replicate samples and the relatively good agreement of replicates strengthens the OME findings. Eleven of the 15 foods analyzed by OME were analyzed in duplicate or triplicate for either total or inorganic arsenic, with percent differences in replicates ranging from 0% to 29% (Table 1). The good agreement between total arsenic concentrations reported by OME and by Dabeka *et al.* (1993) also suggests that the OME data set accurately represents arsenic concentrations. Average total arsenic concentrations measured by OME are generally within a factor of three of average concentrations measured for those foods by Dabeka *et al.* (1993). Total arsenic detected in all but three of the foods analyzed by OME were within the range reported by Dabeka *et al.* (1993) (Table 3).[4]

[4] At the time of preparation of this manuscript, the authors did not have data needed to conduct a similar comparison of total arsenic in specific foods analyzed by FDA.

Risk assessment of ingested arsenic is based on toxicity values derived from a population exposed to arsenic in drinking water. Absorption of arsenic from soil is less complete than the absorption of arsenic from water (Freeman *et al.*, 1995; Groen *et al.*, 1994; Ruby *et al.*, 1996). Arsenic in food may also have limited bioavailability. To accurately estimate exposure to inorganic arsenic in food, it is necessary to determine the absorption of arsenic from dietary sources. Research on the bioavailability of arsenic in food samples would provide data to more accurately assess the importance of dietary arsenic intake.

CONCLUSIONS

The OME data set published here was used by EPA as a basis for estimates of dietary intake of inorganic arsenic used in developing toxicity values for ingested arsenic. While estimates provided here are preliminary, because of limitations in the OME data set and uncertainties in total arsenic in dairy products in the United States, this analysis suggests that dietary intake of inorganic arsenic is higher than previously assumed. Additional research is needed to more fully characterize inorganic arsenic concentrations in food types. Future study is also needed on the variability of total and inorganic arsenic in foods and the bioavailability of dietary inorganic arsenic.

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PERGAMON

Food and Chemical Toxicology 37 (1999) 839–846

Food and Chemical Toxicology

www.elsevier.com/locate/foodchemtox

Research Section

A Market Basket Survey of Inorganic Arsenic in Food

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(Accepted 7 February 1999)

Abstract—Dietary arsenic intake estimates based on surveys of total arsenic concentrations appear to be dominated by intake of the relatively non-toxic, organic arsenic forms found in seafood. Concentrations of inorganic arsenic in food have not been not well characterized. Accurate dietary intake estimates for inorganic arsenic are needed to support studies of arsenic's status as an essential nutrient, and to establish background levels of exposure to inorganic arsenic. In the market basket survey reported here, 40 commodities anticipated to provide at least 90% of dietary inorganic arsenic intake were identified. Four samples of each commodity were collected. Total arsenic was analysed using an NaOH digestion and inductively coupled plasma–mass spectrometry. Separate aliquots were analysed for arsenic species using an HCl digestion and hydride atomic absorption spectroscopy. Consistent with earlier studies, total arsenic concentrations (all concentrations reported as elemental arsenic per tissue wet weight) were highest in the seafoods sampled (ranging from 160 ng/g in freshwater fish to 2360 ng/g in saltwater fish). In contrast, average inorganic arsenic in seafood ranged from less than 1 ng/g to 2 ng/g. The highest inorganic arsenic values were found in raw rice (74 ng/g), followed by flour (11 ng/g), grape juice (9 ng/g) and cooked spinach (6 ng/g). Thus, grains and produce are expected to be significant contributors to dietary inorganic arsenic intake.

Keywords: inorganic arsenic; dietary exposures; arsenic in food.

Abbreviations: DMA = dimethylarsenic acid; MMA = monomethylarsonic acid.

INTRODUCTION

Arsenic has been detected in most foods tested. Although arsenic may be present in foods in a variety of organic compounds as well as in inorganic forms, most studies have reported only total arsenic concentrations. Based on studies in laboratory animals, inorganic arsenic may be a required nutrient for humans; however, the required intakes and the intakes from typical diets are not well characterized (Uthus, 1994a,b; Uthus and Seaborn, 1996). During the last two decades, much progress has been made in understanding the forms and concentrations of arsenic in some foods. The primary focus of prior research has been on arsenic in aquatic organisms, many of which contain total arsenic concentrations two to three orders of magnitude greater than total arsenic concentrations in foods of terrestrial origin (Jelinek and Corneliussen, 1977; Schroeder and Balassa, 1966).

Studies of the arsenic forms found in finfish and shellfish have demonstrated that most arsenic in these foods occurs as methylated arsenic compounds, with only small amounts of inorganic arsenic present (Buchet *et al.*, 1994; Francesconi and Edmonds, 1994; Phillips, 1994; Yost *et al.*, 1998). Inorganic arsenic is not formed after ingestion of these compounds (Buchet *et al.*, 1994, 1996), indicating little or no metabolism in humans to the most toxic forms of arsenic. The complex arsenic compounds that predominate in marine organisms are much less acutely toxic than soluble inorganic arsenic compounds, with arsenobetaine (the predominant compound in finfish) being virtually non-toxic (Shiomi, 1994; Yamauchi and Fowler, 1994). Monomethylarsonic (MMA) and dimethylarsenic (DMA) acids are also less acutely toxic than the

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0278-6915/99/$ - see front matter
PII S0278-6915(99)00073-3

inorganic forms, arsenite (As^{3+}) and arsenate (As^{5+}).

The forms of arsenic present in foods of terrestrial origin are not well characterized, largely due to their occurrence at ng/g concentrations that are below the detection limits of many analytical methods. In contrast, the methylated arsenic forms in seafood, which occur at μg/g concentrations, have been much more thoroughly studied (Francesconi and Edmonds, 1994). Methylated arsenic compounds are much less prevalent in terrestrial food sources than in seafood. A recent report indicates that between 25 and 100% of total arsenic in terrestrial foods may be inorganic arsenic (Yost *et al.*, 1998).

Accurate estimates of the forms of arsenic in the diet are an important component of evaluations of background arsenic exposures and of possible nutritional status for this microelement. However, most dietary studies have reported only total arsenic concentrations. For example, recent diet studies that included evaluations of total arsenic in foods have been reported for Canada, the United States, and Japan (Dabeka *et al.*, 1993; Gunderson, 1995; Tsuda *et al.*, 1995). These studies used market basket survey techniques in which a large number of foods or food composites were tested, often after cooking, for total arsenic concentrations. Food consumption data were then used to estimate daily arsenic intakes.

Daily intake estimates varied substantially among the three countries, from 38.6 μg total arsenic for young American men to 59.2 μg for a similar age group of Canadian men, with far higher values being reported for Japanese women (160 and 280 μg during two different years) (Dabeka *et al.*, 1993; Gunderson, 1995; Tsuda *et al.*, 1995). In all three countries, total arsenic intake was dominated by arsenic from seafood. Thus, the variations in daily arsenic intake among residents of different countries largely reflect variations in seafood consumption. Seafood accounted for almost 90% of daily arsenic intake in the United States (Gunderson, 1995), approximately 70% in Canada (Dabeka *et al.*, 1993), and 60–70% in Japan (Tsuda *et al.*, 1995). In Japan, an additional factor was consumption of seaweed and rice, which accounted for most of the remaining arsenic intake.

Some indirect estimates of inorganic arsenic intakes can be made from the studies of total arsenic in the diet if seafood sources of arsenic are excluded (based on the assumption that almost all arsenic in seafood is organic, while arsenic in terrestrial foods is mostly inorganic). For example, in young American men, only 4.5 μg of daily arsenic intake was attributable to sources other than seafood (Gunderson, 1995). In young Canadian men, approximately 20 μg arsenic per day was from nonseafood sources (Dabeka *et al.*, 1993).

Direct measurements of inorganic arsenic in diets are scanty. A duplicate diet study of Japanese adults reported an average daily inorganic arsenic intake of 13.7 μg when total arsenic intake was 202 μg (Mohri *et al.*, 1990). A recent study suggests that typical North American diets contain less than 15 μg inorganic arsenic per day, but these estimates are considered preliminary due to the limited number of foods for which inorganic arsenic concentrations were available (Yost *et al.*, 1998). The study reported here provides inorganic arsenic concentrations for a wide variety of foods, selected so that a market basket approach can be used to estimate inorganic arsenic intake from the diet.

MATERIALS AND METHODS

Market basket design and sample collection

Food consumption data from the US Department of Agriculture Continuing Surveys of Food Intakes by Individuals (USDA, 1992, 1993, 1994), surveys of total arsenic in food (Dabeka *et al.*, 1993; FDA, 1997), and estimates of inorganic arsenic concentrations in food (Yost *et al.*, 1998) were used to select 40 commodities that were predicted to account for at least 90% of the dietary inorganic arsenic in the United States. The USDA consumption data were used to determine the foods consumed in the largest quantities. Total arsenic levels in foods from the total diet studies conducted in the United States and Canada were adjusted to reflect predicted inorganic arsenic levels and used to identify foods likely to have the highest inorganic arsenic levels. All foods thus identified (high consumption and/or expected high levels of inorganic arsenic) were included in inorganic arsenic dietary intake analyses for the United States. The estimated intakes for the foods (consumption × inorganic arsenic concentration) were ordered from highest to lowest; the foods that together contributed the top 90% of inorganic arsenic intake were selected for the market basket survey.

A modified market basket survey method was used to collect four samples of each commodity. The food samples were collected during October 1997 from large supermarkets in two towns in Texas, two samples each from Bryan and Tyler (except that the "Tyler" beer samples were collected in Coffee City, Texas). Tap water was also included in the study; samples were collected in a hotel (Tyler samples) and in restaurants (Bryan samples).

The food samples were prepared in accordance with Appendix B from *Appendices for the 1990 Revision of the Food and Drug Administration's Total Diet Food List and Diets* (Pennington, 1992), with some exceptions. Rice samples were not cooked (raw rice was tested to facilitate comparisons with arsenic concentrations reported in previous studies). Vegetables were cooked in a

microwave oven, instead of being boiled in water. Commodities collected, a description of the samples, the state or country of origin of the raw commodity (if known), and a brief description of the preparation/cooking methods are presented in Table 1. Each sample was then analysed separately (i.e. no composites were prepared).

Sample analyses

All samples were analysed at Battelle Marine Sciences in Sequim, Washington. Total arsenic was analysed in food commodities after NaOH digestion by inductively coupled plasma–mass spectrometry (ICP–MS). Approximately one in every 10 samples was analysed in triplicate. For the digestion of liquids (milk, juices and water), NaOH was added to 8 g liquid to produce 2 N NaOH solution. This solution was heated for 16 hr at 80°C. For the digestion of solid food, either 1 or 2 g food was digested in 13 ml 2 N NaOH for 16 hr at 80°C. In preparation for ICP–MS analysis, 1 ml digestate was diluted with 9 ml 2% concentrated HNO_3. A model Elan 5000 Perkin-Elmer ICP–MS was operated using the stock cross-flow nebulizer. Several ions were monitored to evaluate polyatomic interference from Ar^{40} Cl^{35}, which has the same mass as arsenic. When interference occurred, the manufacturer's correction factor was used to reduce the interference.

Food samples were digested for analysis of total arsenic using NaOH instead of HNO_3, which had been used in a previous study of arsenic in rice and yams (Schoof *et al.*, 1998). The NaOH digestion was expected to be more effective than HNO_3 in dissolving food with high fat content. A comparison between these two types of digestions on five different rice samples resulted in a relative percent difference of 10% between the mean concentrations. Total arsenic results for oyster tissue digested with NaOH or HNO_3 agreed within 5%. Analysis of standard reference bovine liver (certified 0.055 μg/g As) digested with NaOH resulted in 0.071 μg/g and digested with HNO_3 resulted in 0.062 μg/g. These results indicate that both digestion methods are comparable and accurate.

Arsenic speciation was determined in food samples digested with HCl. Between 0.5 and 2 g of food was digested with 13 ml 2 N HCl at 80°C for 16 hr. The digestates were stored at 4°C before analysis by EPA Method 1632, (US EPA, 1996). A 2-ml aliquot of the digestate was analysed for As^{3+} by arsine generation at pH 6 with the reducing agent sodium borohydride. The hydride was collected on a cryogenic column before quantification by atomic absorption (AA) using a quartz tube with an air–hydrogen flame positioned in the light path.

The HCl digestion is effective in dissolving the arsenic compounds in food without changing the oxidative states of As^{3+} and As^{5+} (Beauchemin *et al.*, 1988; Schoof *et al.*, 1998). Also, MMA and DMA are not decomposed during the digestion. Recovery of matrix spikes of As^{3+}, As^{5+}, MMA and DMA added to 21 different foods indicates that the digestion process does not alter the speciation of these four compounds. Mean spike recoveries for the four arsenic species were 92% for As^{3+}, 86% for As^{5+}, 89% for MMA and 98% for DMA. Because there are few published data on arsenic speciation in food, comparisons with other digestion methods are limited. The Canadian National Research Council reported the certified reference material DORM-1 (dogfish muscle) contained 0.47 ± 0.02 μg/g DMA (Beauchemin *et al.*, 1988). Our results for seven replicates of DORM-1, analysed with different batches of food, had a mean and standard deviation of 0.56 ± 0.07 μg/g. The concentrations of arsenic species were stable for over 1 month in the digestates of certified reference materials stored at 4°C.

The quantification of total inorganic arsenic, MMA and DMA was conducted similarly to that of As^{3+}, except that arsines were generated at pH 1. The three arsines (arsine, methylarsine and dimethylarsine) were collected on the cold column, then quantified by AA when the column was heated. The different column retention times of the arsines allows quantification of inorganic arsenic, MMA and DMA. The concentration of As^{5+} is determined by the difference between inorganic arsenic and As^{3+}. Every fourth sample was analysed in triplicate.

The data were blank-corrected by subtracting the mean of the procedural blanks. The mean blank concentrations are shown in Table 2. The method detection limits were determined from the variance in triplicate analyses of food samples containing low but detectable arsenic. The standard deviation was multiplied by the Student's *t*-value for 95% confidence level. The method detection limits are shown in Table 2.

If no arsenic was detected (after blank correcting), one-half the value of the method detection limit was given with a "*U*" flag. One-half the detection limit was used in subsequent calculations. Mean values have a "*U*" qualifier if all values used to calculate the mean were "*U*" qualified. When the concentration of arsenic in food (after blank correcting) was detected above the blank concentration but below the method detection limit, the value was "*J*" flagged. The same rule as was used for the "*U*" flagged values was also applied in assigning "*J*" qualifiers to mean values.

RESULTS

Table 3 shows mean concentrations of total and inorganic arsenic for 40 commodities and tap water. The data from the two towns from which food samples were collected did not differ significantly.

Table 1. Commodities tested: description and preparation method

Food	Sample description (origin)[1]	Preparation method
Fats, oils, sweets		
Sugar (beet)	Granulated sugar (unknown)	As is
Sugar (cane)	Granulated sugar (unknown)	As is
Corn syrup	Light corn syrup (unknown)	As is
Butter	Unsalted sweet cream butter (1 Illinois, 2 Minnesota, 1 Ohio)	As is
Soybean oil	Soybean/vegetable oil (unknown)	As is
Salt	Iodized salt (unknown)	As is
Beer	Bottled beer (2 Texas, 2 Missouri)	As is
Milk, yogurt, cheese		
Milk, skim	Vitamin A & D skim milk (1 Ohio, 1 Texas, 2 Utah)	As is
Milk, whole	Vitamin D whole milk (1 Ohio, 1 Texas, 2 Utah)	As is
Meat, poultry, fish, eggs, nuts		
Beef	Top sirloin steak (1 Texas, 3 unknown)	Baked 30 min at 350°F
Chicken	Split chicken breasts with rib (1 Georgia, 1 Texas, 2 unknown)	Baked (with skin) until done at 350°F
Pork	Pork loin chops (2 Minnesota, 1 Ohio, 1 Texas)	Baked 30 min at 350°F
Eggs	Large, grade A eggs (2 Texas, 2 unknown)	Peeled, boiled 3 min
Saltwater finfish	Orange roughy fillet [1], cod fillet [2], halibut steak [1] (unknown)	Baked 15–25 min at 350°–400°F
Tuna	Chunk light tuna packed in water (unknown)	Drained
Freshwater finfish	Catfish fillet [3], rainbow trout [1] (1 Texas, 2 unknown, 1 Idaho)	Baked (bones removed) until done
Shrimp	Shrimp (1 Gulf of Mexico, 1 Mexico, 2 unknown)	microwaved (shelled)
Peanut butter	Creamy peanut butter (unknown)	As is
Vegetables		
Beans (green)	Cut/frozen green beans (1 Wisconsin, 1 Minnesota, 1 unknown, 1 Tennessee)	Microwaved 6–12 min (no water added)
Carrots	Bagged/loose carrots (2 Colorado, 1 California, 1 unknown)	Peeled, microwaved 4–8 min (ends removed)
Corn (kernel)	Cut/frozen whole kernel corn (1 Ohio, 2 Wisconsin, 1 unknown)	Microwaved 6–7 min (no water added)
Cucumber	Cucumber (unknown)	Peeled (ends removed)
Lettuce	Iceberg head lettuce/salad (4 California)	Washed (individual leaves), drained
Onions	Yellow/white onions(2 Colorado, 2 unknown)	Peeled (first layer removed)
Peas	Frozen peas (1 Minnesota, 2 Wisconsin, 1 unknown)	Microwaved 4–6 min (no water added)
Potatoes	Russet/Idaho/long potatoes (1 California, 1 Idaho, 1 Washington, 1 unknown)	Peeled, some chopped, microwaved 10 min or until tender
Spinach	Frozen chopped/cut leaf spinach (2 Georgia, 1 Wisconsin, 1 unknown)	Microwaved 4–6 min
Tomato	Roma/vine-ripened tomatoes (3 California, 1 Mexico)	Washed (skin left on)
Fruit		
Apple, raw	Red delicious/Jonathon/McIntosh apples (2 Washington, 1 Michigan, 1 Missouri)	Washed, peeled, cored (skin left on)
Apple, juice	Apple juice (1 US, 1 Washington, 1 Hungary, 1 unknown)	As is (single strength)
Banana	Banana (4 Guatemala)	Peeled
Grapes	Red/green Thompson seedless grapes (3 California, 1 Nicaragua)	Washed in cool water, stems removed
Grape juice	Grape juice (2 US, 2 unknown)	As is (single strength)
Orange	Navel/Valencia oranges (1 New Mexico, 2 Texas, 1 Australia)	Peeled, excess white membrane and seeds removed
Orange juice	Frozen concentrated orange juice (4 US/Brazil mixture)	As is (concentrated)
Peaches	Peaches from mixed fruit/frozen peaches (unknown)	As is
Watermelon	Cut watermelon/seedless/fresh watermelon (1 New Mexico, 1 Mexico, 2 unknown)	Rind and most seeds removed
Bread, cereal, rice, pasta		
Corn (meal)	Enriched/stone-ground/all-purpose/de-germinated corn meal (2 unknown, 2 Texas)	As is
Flour (wheat)	Graham/whole wheat flour (unknown- US)	As is
Rice	Long grain enriched rice (1 unknown, 3 Texas)	As is (uncooked)
Water		
Tap water	Local taps/drink dispenser	As is (ran tap for 2 min)