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OFFICE OF WATER

MEMORANDUM

Subject: Report on Arsenic (As) Work Group Meetings.

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I. Introduction.

C. Chen, H. Gibb, P. White of ORD and W. Marcus (telephone) and C. Abernathy of ODW met on several occassions to discuss the Tseng (1968, 1977) and Southwick et al. (1983) studies, the ORD trip (Irgolic, 1988 report and other relevant As publications and reports in order to try to reach some conclusions on which study to use for calculating an RfD for As. The adverse effects considered by the Work Group for establishing a NOAEL were hyperkeratosis and Blackfoot Disease. Specific comments by individuals will be attributed to those individuals.

It was generally agreed that, although there were a lot of facts, the data were scattered and there were serious data gaps. The paucity of data in many areas prevented the group from reaching definitive conclusions. The discussion centered around the amount of water (direct and indirect) ingested, the amount of food (rice and sweet potatoes) eaten, the levels of As in food, water and soil, uptake of As from the soil by plants and the percent of As as inorganic As in food and water. The analyses presented below will be based on various assumptions which will be specified.

II. Water Consumption.

A. Direct. The value of 3.5 l of water/day was used for the ORD calculations.

1. H. Gibb talked to 3 to 4 people in Blackfoot treatment center and asked them to estimate their water consumption. They estimated that they drank up to three 1.25 l bottles of water per day. Since he had to ask the questions through an interpreter and only a limited number of persons were asked, H. Gibb felt that the data were a little "soft" and could only be used as an approximation, but that they were consistent with the view of the Work Group on water consumption by the Taiwanese.

2. P. White agreed that the information on Taiwanese water consumption was limited. He felt that the Taiwanese laborers could have had higher fluid consumption than the general U. S. population, but noted that; this water consumption applies to the entire population (laborers and nonlaborers) over the whole year, Taiwanese are physically smaller than average Americans, and U.S drinking water consumption tends to be less than 2 l/day. Therefore, he did not feel confident that water consumption was as high as 3.5 l/day and felt that 3.5 l/day might be an appropriate estimate of total water consumption (see below).

3. Chao Chen, W. Marcus and C. Abernathy felt that in a warm to hot climate, laborers could easily drink 3 to 4 l of water/day.

Most of the workgroup felt that the Taiwanese workers could drink 3 to 4 l of water/day and that 3.5 l/day seemed to be a reasonable estimate for direct water consumption.

B. Indirect. Water was used to cook rice and sweet potatoes and this amount was not factored into the original exposure scenario.

1. Rice. C. Abernathy mentioned the fact the J. Du (ODW) had cooked rice and found that it took approximately 200 ml of water to cook 100 g of rice. This value was accepted by the workgroup.

2. Sweet potatoes. They are eaten either as fresh vegetables or are sun-dried for preservation in order to eat them during nongrowing seasons. The dry form of the vegetable would take more water (The rice and sweet potatoes are cooked together - Chao Chen.) to cook than the fresh form. Taking into consideration the dry and the fresh forms, Chao Chen estimated that it would take 50 to 75% as much water to cook the sweet potatoes as it would to cook the rice. Accodingly, if we assume that it would take 63% as much water for the potatoes as the rice, then for 100 g of potatoes, it would take 125 ml of water (200 ml x 63% = 125 ml).

C. As levels in water. In the NOAEL group (approximately 2,500), there is an exposure range of 1 to 17 ug As/liter of drinking water (Tseng, 1977). Chien-Jen Chen of the National Taiwan University of Taipei, Taiwan (telephone call) thought that more of the exposed people were in the low dose range, but had no data. The As Work Group concluded that an accurate scientific estimate would be difficult to make on the basis of the present data.

III. Food Consumption.

A. Total food. From Table 1 in the Irgolic (1988) report (p. 5), rice and sweet potatoes account for 90% (750 g) of the food intake by this population. Accordingly, only these two sources of food will be considered in the food exposure analysis. The relative proportions of rice and sweet potatoes would vary with the economic status of the families. Irgolic (p. 4) states that the poorer families would eat more and, sometimes exclusively, sweet potatoes, while the more prosperous families would eat more rice.

1. Rice. Chao Chen stated that the endemic study area was very poor and that rice consumption would be below the 376 g average (Irgolic, 1988). It was estimated by the workgroup that 200 to 250 g of rice would be consumed/day.

2. Sweet potatoes. It was estimated that this population would consume 500 g of sweet potatoes (Greater than the 360 g average given by Irgolic, 1988.).

IV. Analysis. Variables will first be discussed separately and then combined in the next section to provide different exposure scenarios.

A. Water.

1. Direct. 3.5 l (from a range of 3 to 4 l).

2. Indirect. Cooking water.
   a. Rice. 225 g X 200 ml/100 g = 450 ml.
   b. Sweet potatoes. 500 g X 125 ml/100 g = 625 ml.
   c. Total indirect. 450 ml + 625 ml = 1 liter (appr.)

B. Food.

1. Rice. 225 g/day (Section III.A.1).

2. Sweet potatoes. 500 g/day (Section III.A.2).

C. Arsenic levels.

1. Water. In the 7,500 control population, approximately 5,000 were from the island of Matsu and they were exposed to virtually no As directly from their drinking water. There were approximately 2,500 control subjects in the endemic area who were exposed to 0.001 to 0.017 mg As/l (1 to 17 ug/l) in their drinking water. This 2,500 is the NOAEL population used in this report.

a. P. White thought that it should be limited to men which would bring the exposed population below 2,500, since women might receive lower exposures due to decreased water and food consumption. He and Chao Chen also noted that a relatively small fraction of the population actually had lifetime exposures.

b. H. Gibb thought that an average exposure value of 9 ug/l should be the maximum used for the NOAEL calculations.

c. C. Abernathy and W. Marcus felt that 17 ug/l should be included in the calculations, since it would give a maximum exposure scenario for drinking water.

d. Chao Chen said that he believed that very few of the 2,500 would have been exposed to the 17 ug/l level and for that reason believed that the average value of 9 ug/l or a geometric mean of 4 ug/l should be used. The committee reached agreement on an exposure range of 4 to 9 ug As/l of drinking water, believing it to be the best estimate that could be reached with the availible data set.

To demonstrate the potential scope of As exposure from As in the drinking water will be calculated using 1, 4, 9 and 17 ug/l (See Tables 1, 2 and 3 on p. 12).

2. Food.

a. Rice

1). On p. 5, Irgolic (1988) gives a range of less than 0.07 up to 3.5 ug of As/g of rice (70 to 3,500 ug/kg) for rice grown in soils not contaminated with As-herbicides. However, he does not give any specific data on how this range applies to the rice consumed by the Taiwanese population. Consequently, the workgroup did not use this range in the calculations.

2). Irgolic (1988) states on p. 5 that soils in the endemic area contaminated with As-herbicides are "said" to contain approximately 8 mg As/kg of soil, while uncontaminated soils have "natural" levels of 0.1 to 40 mg As/kg (average of 5 mg As/kg). He also cited a study which reported that hulled rice grown in soil containing 20 mg As/kg (as sodium arsenate) had As levels of 0.11 mg As/kg of rice. He caveated this figure by stating that without knowledge of soil characteristics, it would be impossible to estimate, with confidence, how much As would be taken up from the soil. Since there were no data availible on types of soil or on the forms of As present in the soil, we based our analysis on the assumption that all forms of As in all types of soil would be concentrated by rice at rates similar to the 0.11 mg As/kg of rice in the rice grown in the soil containing 20 mg As/kg. Therefore, the Work Group adopted the following estimates:

a). Natural soil. 5 mg As/kg is 0.25 of 20 mg As/kg
0.25 X 0.11 mg = 30 ug As/kg rice
(rounded from 28 ug)

b). Contaminated soil. 8 mg As/kg is 0.40 of 20.
0.40 X 0.11 mg = 40 ug As/kg rice
(rounded from 44 ug)

3). Li et al. (1979) reported As levels in three types of rice grown in Taiwan. The highest level found was greater than 0.760 ppm (760 ug As/kg rice) with an average range of 0.3 to 0.5 ppm. Chao Chen identified an analysis of rice from the general area and it had a range of 0.05 to 0.33 ppm (rounded average of 0.2 ppm or 200 ug As/kg rice). These authors believed that the use of As-herbicides contributed to the level of As in the rice. Chao Chen felt that since the people in the endemic area were very poor, they would not have used any As-herbicides during the exposure period. In addition, a great deal of the exposure occrurred prior to the advent of pesticides.

The above cited values from natural and contaminated soil and from the Li et al. (1979) study will be used to give a range of possible exposure scenarios.

b. Sweet potatoes.

1). Irgolic (1988) gave a value of 0.008 to 1.25 ug As/g sweet potato in Table 1 (p. 5). This value, however is for "other potatoes grown in untreated soils" (p. 6), since the only report that he could find claimed that sweet potatoes did not contain any As. The Work Group found these comments impossible to interpret since As was found in sweet potatoes in the FDA "market-basket" survey of U. S. food cited by OPP (OPP, 1987).

D. Type (Inorganic or Organic) of As in water and food.

1. Water. Irgolic (1988) states the As in water is predominantly in the inorganic form (p. 7). Accordingly, As in drinking water will be assumed to be 100% inorganic.

2. Food. There are no data on the forms of As in the diet of the Taiwanese. The only information that we could find on the percent of inorganic As in food was in the FDA survey of U. S. food (OPP, 1987). This memo puts the percent inorganic As in rice and sweet potatoes at 35 and 5%, respectively.

Unless there are data to show that As levels in Taiwanese sweet potatoes are high or that there is a different percentage of inorganic As in the Taiwanese sweet potatoes, its contribution to the total body burden of the individual would be low. For example, if sweet potatoes contained 200 ug As/kg, the the inorganic As in the diet would be 5 ug (200 ug As/ kg x 0.5 kg of sweet potatoes eaten/day = 100 ug As/day x 5% (% of inorganic As) = 5 ug inorganic As/day.

E. Calculations.

1. Drinking water summary.

a. Direct - 3.5 l/day
b. Indirect - 1 l/day

c. Total - 4.5 l/day
d. % inorganic As - 100
e. As in water - 1, 4, 9 or 17 ug/l

2. Food summary.

a. Rice summary.

1). Using As soil uptake data (20 mg As/kg of soil yields 0.11 mg As/kg rice).

a). Natural soil. 5 mg As/Kg soil.
0.25 X 0.11 mg As/kg = 30 ug As/kg rice
0.225 kg X 30 ug As/kg = 7 ug As/day
7 ug As/day X 0.35 = 2 ug inorganic As/day.

b). Contaminated Soil. 8 mg As/kg soil
0.40 X 0.11 mg As/kg = 40 ug As/kg rice
0.225 kg X 40 ug As/kg = 10 ug As/day
10 ug As/day X 0.35 = 4 ug inorganic As/day.

2) Using Li et al.(1979) study.

a). Average value of 200 ug As/kg rice
0.225 kg X 200 ug As/kg = 45 ug As/day
45 ug As/day X 0.35 = 16 ug inorganic As/day.

b. Sweet potatoes. Not included in calculations since we have no reliable data for calculation.

c. The above data are compiled in Tables 1, 2 and 3 on p. 12.

V. Internal Cancer Data.

C. Abernathy inquired about the possibility of ORD calculating a cancer potency estimate for internal cancers and was informed that the data of Chien-Jen Chen (Taiwan) is not complete and, at this time, can not be used for calculations. W. Marcus asked for a time estimate for completion of this task and H. Gibb and Chao Chen said that, even if the time and money were alloted, it would not be possible to give an estimate since the database is not complete.

VI. Southwick et al. (1983) study.

There were 145 "exposed" participants (cities of Hinckley and Deseret) and 105 control participants (city of Delta) in this study. The "exposed" populations of Hinckley and Deseret had a median As exposure level of 5 ug/kg/day, while the "control" group from Delta had a median As exposure level of 0.7 ug/kg/day. All participants came from Millard County, Utah and lived a "predominantly Mormon" lifestyle.

The authors found a close correlation between the amount of As consumed and the levels of As in urine and hair samples. Although the dermatological abnormalities were higher in the exposed (6.25%) than in the controls (2.86%), the difference between the two populations was not statistically significant.

With respect to neurological findings, the data suggested that there was a slightly increased proportion of people with slower nerve conduction among the exposed population. However, not all of the study participants took part in this section of the study (Controls - 67 and Exposed - 83) and the results were not statistically different. Although this study offers suggestions that As could have affected nerve conduction in the "exposed" group, the data are not conclusive.

Based on the above observations, the exposure level of 5 ug/kg/day could be considered as a NOAEL or LOAEL. However; due to the small population size of the Southwick et al. (1983) study, the uncertainties about the significance of the slightly increased incidence of dermatological abnormalities and of slowing of nerve conduction in the As exposed group, the fact that some participants were on the study for only 5 years and that very few (less than 20) were exposed for 60 or more years, it was concluded by the As Work Group that the Southwick et al. (1983) study should not be used for calculating a RfD.

VII. Uncertainty Factor (UF).

There was a discussion as to what UF should be used with the Tseng (1977) study and ODW and ORD could not reach agreement on this point. Specifically, ORD felt that an UF should be used in calculating a RfD because:

1. Most individuals in the Tseng (1977) and Tseng et al (1968) studies were young and few had As exposures in drinking water approaching lifetime duration. Therefore, the observed absence of skin lesions provides less convincing evidence than would be the case if the entire population had received exposures of lifetime duration. Age-specific

prevalence for hyperkeratosis in the "exposed" of the Tseng studies indicate that the observation of 2,500 "control" individuals (0.001 to 0.017 ppm or 1 to 17 ug As/l in drinking water) would only be one-fourth as effective in detecting skin lesions as would be the case if all the individuals had recieved lifetime duration exposures. Furthermore, due to the As-associated mortality (in particular, blackfoot disease) in the "exposed" Tseng group, the steepness of the age/prevalence relationship for hyperkeratosis may be underestimated. Thus, the above considerations may still overstate the effectiveness of the Tseng study in establishing a NOAEL;

2. The Cebrian et al. (1983) study reported that 7 of 318 "controls" (exposed to 5 ug of As/l of drinking water) had dermatological signs of As exposure. This introduces uncertainty into the Tseng (1977) derived NOAEL of 4 to 9 ug As/l of drinking water as selected by the Work Group;

3. As noted in # 2, the reported findings of adverse effects in the Cebrian et al. (1983) "control" are not concordant with the absence of effects in the Tseng "control" group. This may indicate that the exposure values developed for the Tseng (1977) study are too high. If this is the case, the calculated NOAEL is also an overestimate;

4. Little information exists on the prevalence or incidence of hyperkeratosis in the United States. The fact that a substantial subgroup of the American population may be exposed to drinking water As levels above 50 ug/l does not in itelf provide any reassurance that As-induced lesions are not occurring. Lesions which do occur may not be called to the attention of a physician. Furthermore, reporting of such lesions in the medical literature would likely be sporadic;

5. Comparisons between the UF appropriate for a RfD derived from the Tseng (1977) study with UFs used in previous RfD calculations may be of limited use because;

(a) the reported data from the Tseng studies were not sufficient to construct a dose-response relationship for hyperkeratosis. When data on a compound indicate that a steep dose-response is observed, one may have greater confidence that a study NOAEL is indeed a "safe" level of exposure, and

(b) much of the uncertainty in establishing a NOAEL using the Tseng (1977) study is due to uncertainty in exposure levels. Exposure levels will generally be better known in small experimentally-oriented studies with human subjects.

ODW felt that an UF of 1 should be used because:

1. The Work Group used hyperkeratosis, which may not be an adverse effect, as a toxicological endpoint;

2. The Tseng (1977) population is of sufficient size to use an UF of 1. In this regard, it is of interest to note that other RfD studies in humans, with cholinesterase inhibition as an endpoint

and validated by the Agency's RfD Work Group, having exposure groups of 5 to 10 humans/dose use an UF of 10;

3. Other studies, with smaller populations and higher doses than than the Tseng (1977) study, conducted in the U. S. and Canada, such as Harrington et al (1978) in Alaska, Hindmarsh et al (1977) in Canada, Goldsmith et al (1972) in California, Morton et al (1977) in Oregon, Vig et al. (1984) in Nevada and Southwick et al. (1983) in Utah indicate that exposure to concentrations of As up to 50 ug/l in the drinking water does not produce hyperkeratosis and/or other forms of As toxicity;

4. The exposure of 100,000 people in the U. S. to As levels of 50 ug/l or higher (U. S. EPA, 1987) is compatible to the above studies cited in # 2;

5. The report of 7 of 318 "controls" in the Cebrian et al (1983) study having dermatological signs (hypo- and hyperpigmentation) of As exposure is impossible to interpret as an indication of adverse effects caused by As since there is no reported "control background level" for these signs in the general Mexican population and hypo- and hyperpigmentation are cosmetic effects; and

6. The Tseng (1977) population is a sensitive subpopulation of humans. The reasons for such a conclusion are justified by the following facts. Inorganic As is detoxified by methylation in humans prior to urinary excretion (Hindmarsh and McCurdy, 1986; Marcus and Rispin, 1988) and animals fed diets deficient in nutrients such as methionine, choline, folic acid and/or vitamin B_{12} have lower methylation rates due to decreased levels of S-adenosylmethionine, a necessary cofactor in transmethylation reactions (Shivapukar and Poirier, 1983). The Taiwanese population consumed inadequate amounts of protein (Irgolic, 1988) and would therefore be not expected to methylate As at the same rates as do humans with an adequate protein intake.

The enzymatic detoxification data suggest that there could be a "practical" threshold for As. This viewpoint is in accord with the preliminary Science Advisory Board report.

VII. Summary.

The As workgroup has concluded that:

1. The Tseng report (1977) is the best available study to use for calculating a RfD,

2. The range of 4 to 9 ug As/liter of drinking water represents the best estimate of As concentrations in the drinking water in most of the 2,500 control group,

3. This 2,500 population is the appropriate group to use as the NOAEL group,

4. Based on the availible data, the rice and sweet potatoes would not make a major contribution to the overall daily As load. Accordingly, the workgroup believes that the RfD should be in the range of 0.4 to 0.8 ug/kg/day if an uncertainty factor is not used (See Table 3), and

5. No agreement on an UF could be reached by the members of the As Work Group.

In the Introduction, the As Work Group noted several areas in which more information and/or research were needed to remove the uncertainties mentioned in this report. Specifically, we see the need for detailed information on: the amounts of water ingested per day, an exposure distribution analysis of the study group to As, actual rice and sweet potato consumption, levels of inorganic/organic As in the rice and sweet potatoes with respect to As in the soil and whether possible contamination by As-containing pesticides could have occurred.

Table 1. Various Inorganic Arsenic Exposure Levels from Different Sources.

	Drinking Water 4.5 l/day at				Rice grown in		
	1 ug/l	4 ug/l	9 ug/l	17 ug/l	Natural Soil	As Soil	Li et al. Study (79)
ug As/day from Source	5	18	41	77	2	4	16

Table 2. Various Daily Inorganic Arsenic Exposure Scenarios for Calculation of a NOAEL.

As from Rice (ug/day)	Arsenic from Drinking Water (ug/day) 5	18	41	77
2	7	20	43	79
4	9	24	45	81
16	21	34	57	93

(of 1)

Table 3. RfD Calculations from Various Exposures using ~~no~~ Uncertainty Factor.

	Total As from Water and Food (ug/day)											
	7	9	20	21	24	34	43	45	57	79	81	93
RfD (ug/kg/day) (Total divided by 55 kg)	0.1	0.2	0.4	0.4	0.4	0.6	0.8	0.8	1.0	1.4	1.5	1.7

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