UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

EPA-SAB-EHC-89-038

September 28, 1989

OFFICE OF
THE ADMINISTRATOR

Honorable William K. Reilly
Administrator
U.S. Environmental Protection Agency
401 M Street, S.W.
Washington, D.C. 20460

Subject: Science Advisory Board's review of the ARSENIC issues relating to the Phase II proposed regulations from the Office of Drinking Water

Dear Mr. Reilly:

The Drinking Water Subcommittee of the Science Advisory Board's Environmental Health Committee has completed its review of the arsenic related issues identified in the Phase II proposed regulations from the Office of Drinking Water at its meeting in Cincinnati, Ohio, June 2-3, 1988.

The major recommendations of the Subcommittee are limited to a few specific areas concerning the health effects of arsenic and include the following: (1) that the evidence for the essentiality of arsenic is suggestive but should be excluded in characterizing health risks or in the development of a drinking water standard; (2) that the current state of scientific knowledge cannot resolve the important question of whether or not hyperkeratosis is a precursor of skin cancer and, thus, in establishing the MCL should consider hyperkeratosis and skin cancer as independent effects; (3) that the findings of the Tseng study are adequate to conclude that ingested arsenic can cause cancer in humans; and (4) that at dose levels below 200 to 250 ug As^{3+}/person/day there is a possible detoxification mechanism that may substantially reduce cancer risk from the levels EPA has calculated using linear-quadratic model fit to the Tseng data. We recommend that EPA (1) develop a revised risk assessment based on estimates of the delivered dose of non-detoxified arsenic to target tissues, and (2) consider the potential reduction in cancer risk due to detoxification in establishing an MCL for arsenic.

We appreciate the opportunity to conduct this particular scientific review. We request that the Agency formally respond to the scientific advice provided herein.

Sincerely,

Raymond C. Loehr
Chairman, Executive Committee

Arthur C. Upton

Arthur Upton
Chairman
Environmental Health Committee

Gary P. Carlson

Gary P. Carlson
Chairman
Drinking Water Subcommittee

ARSENIC

The Drinking Water Subcommittee of the Science Advisory Board's Environmental Health Committee met June 2-3, 1988 in Cincinnati, Ohio to review selected issues relating to the scientific background for regulating arsenic in drinking water. The Subcommittee concluded that; the evidence for essentiality is suggestive, that the current state of knowledge cannot resolve whether or not hyperkeratosis is a precoursor of skin cancer and that at dose levels below 200 to 250 up As^{3+}/person/day there is a possible detoxification mechanism that may substantially reduce cancer risk. The Subcommittee recommended that EPA; develop a revised risk assessment based on estimates of the delivered dose of non-detoxified arsenic to target tissues, and consider the potential reduction in cancer risk due to detoxification in establishing a maximum contaminant level for arsenic.

SUBJECT: SCIENCE ADVISORY BOARD'S REVIEW OF THE ISSUES RELATING TO ARSENIC CONTAINED IN THE PHASE II PROPOSED REGULATIONS FROM THE OFFICE OF DRINKING WATER

SCIENCE ADVISORY BOARD COMMITTEE: DRINKING WATER SUBCOMMITTEE OF THE ENVIRONMENTAL HEALTH COMMITTEE

DATE OF REVIEW: JUNE 2-3, 1988

PLACE OF REVIEW: EPA LABORATORY, CINCINNATI, OHIO

A. Nutritional essentiality of arsenic

Whether arsenic is an essential nutrient for humans has been a topic of extensive scientific investigation; and for the present, the issue remains unresolved. Admittedly numerous studies in laboratory and domestic animals have suggested the essentiality of arsenic in some of those species; however, the evidence is not sufficiently persuasive to conclude unequivocally that arsenic is essential for normal health, growth, or reproduction. The body of evidence exploring such a role for arsenic in humans is much more sparse and far less convincing than for animals. Consequently, the Subcommittee concludes that arsenic cannot now be accorded the role of essential trace element for humans. Hence, for EPA's evaluation of health risks from small quantities of arsenic in tap water, attributing a prominent role to the essentiality of arsenic in human nutrition is unfounded. We recommend that the document be revised to acknowledge the existence of suggestive evidence but exclude the concept of essentiality as a factor in characterizing, or modulating, conclusions about health risk -- and, further, as a factor in establishing drinking water standards.

B. Hyperkeratosis

In some epidemiologic studies arsenic exposures were associated with skin lesions including cancer and hyperkeratosis. Unknown at present is whether hyperkeratosis elicited by inorganic arsenic is a lesion independent of the initiation of skin tumors or a step necessary in tumor formation. The distinction is important in assessing the risks from arsenic exposures in the following way: If hyperkeratosis were independent of skin cancer in the same individuals, there might continue to be a suitable justification for assuming that the dose-response curve for cancer would have no true threshold, and the data would be extrapolated toward zero dose/zero effect. On the other hand, if hyperkeratosis -- a lesion for which a threshold is not only plausible but also known -- were an obligatory intermediate to skin tumor formation, then the threshold for the first becomes the threshold for the second, leading to an extrapolation of the dose-response curve to a point below which there would be no likelihood of cancer incidence. The Subcommittee concludes that the issue cannot be

resolved with our current state of knowledge; hence, we recommend that EPA follow its traditional interpretative procedure of assuming that the two effects are independent of one another. Research to resolve this matter is viewed by the Subcommittee as particularly important and timely, and the Subcommittee encourages EPA to conduct appropriate studies aimed at resolving this matter.

Hyperkeratosis was selected by EPA as the basis on which to select a no-observed-adverse-effect level (NOAEL) based on findings of Valentine (1979), Southwick (1983), and Harrington (1978). The NOAELs derived from those investigations ranged from 3 to 10 ug As per kg body weight per day. Using these NOAELs, EPA applied an uncertainty factor of 5 (rather than the more traditional 10) to derive a drinking water equivalent level (DWEL). While EPA's rationale for the selection and application of an uncertainty factor of 5 is based on a reasonable proposition that the NOAEL was derived from a considerably sensitive group of humans, the Subcommittee favors the use of the larger uncertainty factor of 10, because the size of the cohort (250 individuals) from which the NOAEL was derived is sufficiently small to contribute additional uncertainty.

C. Applicability of Tseng epidemiologic study for estimating cancer risks for the U.S population

Of the many epidemiologic studies that explored associations between ingested arsenic and the increased incidence of cancer, that of Tseng et al. was selected by EPA as pivotal to estimate cancer risks in the U.S. population. That conclusion raises two vital questions: Does the study support a strong positive association between ingested arsenic and skin cancer? And, if ingested arsenic caused cancer in humans, can the Taiwanese data extrapolatable to humans in the U.S. (perhaps due to different eating habits)?

The Tseng study of Taiwanese populations credibly relates, in the view of the Subcommittee, arsenic exposures via tap water to the prevalence of skin cancer and reports a positive dose-response relationship that is usable in estimating cancer risks at much lower doses in tap water.

The extent to which one can confidently extrapolate the Taiwanese findings the U.S. population is governed, in part, by the similarities and differences between the two populations. Among the more salient considerations are the relative differences in water consumption, body mass, nutritional status, and background incidence of skin cancer among members of each country. Additional distinctions taken into some account by EPA are sources of arsenic other than tap water and the presence of organic and physical (i.e., UV light) carcinogens and co-carcinogens (viz., ergot alkaloids) in tap water.

There exists an apparent discrepancy among epidemiologic findings. The studies in Mexico and Germany support the

associations reported by Tseng et al.; however, the few epidemiological investigations carried out in the U.S. failed to find any such association. The Subcommittee concludes that part of the basis for the absence of association in the U.S. studies is insufficient statistical power, given the magnitude of exposure of the US cohorts.

The findings of Tseng et al. (1977), in the opinion of the Subcommittee, are adequate to conclude that ingested arsenic can cause cancer in humans; however, the many differences between the populations of the two countries render inconclusive a confident determination of cancer risk at the levels ingested in the U.S. The Subcommittee concludes that, faced with such uncertainty, EPA is justified in considering arsenic a possible human carcinogen for the U.S. population. However, the many differences between the populations -- particularly nutritional status of those exposed -- should be viewed as overestimating cancer risk from relatively high doses of ingested arsenic; that is, the Taiwanese are to be considered as much more vulnerable to the cancer-causing property of ingested arsenic than are residents of the U.S. On the other hand, the presence of Blackfoot disease in the Taiwan study group could result in an underestimate of cancer risk due to earlier mortality.

The practical outcome of such conclusions, as endorsed by this Subcommittee, is for EPA to consider promulgating a Maximum Contaminant Level Goal of zero based on a cautious policy of public health protection (although as indicated below, some non-zero concentration would likely achieve nearly the same objective). The setting of the MCL should, in our view, be guided by the characterization and utilization of a non-linear dose-response relationship for skin cancer associated with the effective (non-detoxified) dose of inorganic arsenic.

D. Dose-response assessment for ingested arsenic at low doses

There is clear evidence that arsenic ingested at high doses can cause cancer in humans. The risk of skin cancer at doses encountered in U.S. tap water has not been empirically determined. This depends in part on the ability of the human body to efficiently detoxify relatively small doses of ingested arsenic.

Convincing evidence of human metabolism of ingested inorganic arsenic has been presented by the EPA (see Section VIII of the Health Criteria Document). Specifically, conversion by the liver of inorganic arsenic by methylation to monomethylarsenic acid (MMA) and to dimethylarsenic acid (DMA) is the predominant pathway of detoxification in humans. The findings indicate that daily doses of 250 to 1000 ug As^{3+}/person/day or less may be largely detoxified; whereas, at higher doses, the detoxification pathway becomes increasingly saturated, thereby increasing the possibility of macromolecular binding with consequent pathology such as tumor formation. As a result, the slope of the dose-response curve for arsenic-induced

cancer can be expected to be much steeper above intake levels of 250-1000 ug As^{3+}/person/day than at lower levels of intake. The risks of cancer induction at lower levels of intake are then likely to be greatly exaggerated if the relevant pharmacokinetic considerations are not appropriately taken into account. Whether the concentration of As^{3+} reaching target cells is sufficient to pose a significant risk of carcinogenic effects at levels of intake below 250-1000 ug As^{3+}/person/day is problematic. However, because the detoxification at lower doses does not appear to be more than 80 - 90% complete, the possibility of some risk at lower doses cannot be ignored. The Subcommittee concludes that the metabolic evidence for at least partial detoxification is sufficiently persuasive to incorporate it directly into the derivation of an MCL, with appropriate consideration of the known heterogenicity of detoxification in the human population.

E. Arsenic exposure from drinking water and from food

The major source by far of arsenic exposure to the U.S. population is food -- principally beef, chicken, milk products, and fin- and shellfish. Compared to that large background of exposure, the quantity of arsenic contributed from tap water to daily dose is quite low. Moreover, the ability to eliminate or substantially reduce small quantities (i.e., low ppb) is difficult and costly.

The dietary habits of some individuals may result in doses of arsenic that are much higher than the average dose from food products, and both food and water exposures should be considered in assessing arsenic health risks.

F. Apportionment of reference dose across routes of exposure

Currently, EPA sets MCLs for non-carcinogens and for substances classified by EPA as either C, D, or E in a manner that takes explicit account of tolerable levels of exposure from other sources such as food and air. To the extent that reliable data characterizing contributions from other sources are available, EPA incorporates them in the derivation of MCLs. In the absence of such information, EPA arbitrarily assigns 20 percent of the RfD to tap water (10 percent for inorganic substances).

The Subcommittee concludes that EPA's approach appears to be a reasonable management tool -- even for substances classified as C -- because it appears to foster the protection of public health. The Subcommittee cautions, however, that the application of such assumptions may lead in some cases to regulations that are not in the best interest of the public by virtue of being either too restrictive or inadequately protective. Consequently, the Subcommittee, while acknowledging the practical necessity of using default assumptions (e.g., 20% of RfD), strongly encourages the Agency to obtain data that accurately portray human intake from major sources and routes.

U.S. Environmental Protection Agency
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June 2 & 3, 1988 Meeting

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