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OFFICE OF
THE ADMINISTRATOR

Dr. Richard A. Griesemer
Chair, Environmental Health Committee
Science Advisory Board [A-101]
U.S. Environmental Protection Agency
401 M Street, SW
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Dear Dr. Griesemer:

On January 9-10, 1986 the Metals Subcommittee of the Environmental Health Committee reviewed nine (9) draft health advisories for drinking water in public session. The draft health advisories were prepared by the Office of Drinking Water. The health advisories are not regulatory documents but are intended to provide consistent, brief reference information, particularly for technical personnel responsible for the operation of water works or for state and local public health officials. During the review of the health advisories, the Subcommittee utilized Drinking Water Criteria Documents for these substances as support documents. The Subcommittee recommends that the Criteria Document for Mercury undergo further detailed scientific review, because this is the first attempt to set forth the Agency's evaluation of ionic mercury, and some scientific issues will be controversial.

Our comments below are divided into general advice, which is relevant to all of the advisories reviewed by the Subcommittee, followed by advice specific to each of the substances reviewed. Based on the general review, the Subcommittee recommends that the Office of Drinking Water undertake an updating of three guidance documents (issue papers) for use of inhalation data, pharmacokinetics and multiple exposures (mixtures). Although the guidance may be conceptually sound for organic substances, some information in the documents seems inappropriate to the toxicology of metals. Because of the extensive nature of our comments, a Table of Contents and some supporting appendices are included. We appreciate the opportunity to become involved with this program and stand ready to provide further advice, as requested.

Sincerely,

Bernard Weiss

Bernard Weiss, Ph.D.
Chair, Metals Subcommittee

Ronald Wyzga

Ronald Wyzga, Sc.D.
Vice-chair, Metals Subcommittee

EPA NOTICE

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I. GENERAL COMMENTS OF THE METALS SUBCOMMITTEE OF THE ENVIRONMENTAL HEALTH COMMITTEE OF EPA'S SCIENCE ADVISORY BOARD REGARDING DRINKING WATER HEALTH ADVISORIES

A. THE RELATIONSHIP BETWEEN AUDIENCE AND CONTENT NEEDS CLARIFICATION.

The format and content of the health advisories are inconsistent with the audience for which they are intended. Often the descriptions of studies bear only a remote relationship to the aims of the health advisories. Lethal doses in animals, or details of pathological surveys in rodents after high doses, for example, are not usually necessary to convey the basis for the "risk reference dose." A related problem with the health advisories is the presentation of the information. Typically, a few papers are tersely abstracted, with little attempt to integrate their contents. The nickel health advisory, for example, lists nine studies under the heading, "longer-term exposure." Two pages later, under the heading "longer-term health advisory," it states that no suitable studies were identified to derive the longer-term health advisory. Not only were the nine studies not pertinent, but they were described as if in an annotated bibliography, lacking any attempt to integrate their findings. The health advisories should be made crisper and clearer and feature only those data upon which the various calculations rely.

B. THE HEALTH ADVISORIES HAVE DIFFERENT UNCERTAINTIES.

Various health advisories have different degrees of uncertainty associated with them. The uncertainty results from one or more of the following:

- No adequate data exist which can be used to derive a health advisory. The health advisory for arsenic, for example, is based upon subjective opinions about the best experimental data to use.

- A health advisory is calculated from animal data, and it is unclear how to extrapolate to humans. See, for example, the chromium health advisory.

- Health effects data exist for another route of exposure, and it is unclear how and whether to extrapolate for exposure via another media. For example, chromium (VI) is a reasonably well-established carcinogen associated with respiratory cancers, yet the health advisory for chromium states that there is inadequate evidence to determine whether or not oral exposure to chromium can lead to cancer. In such situations, it is unclear whether and how inhalation effects data can be used for health advisories. A different example occurs in the derivation of the lifetime health advisory for mercury. Effects following subcutaneous injection were used to estimate effects from drinking water exposure.

- Exposure durations are different for the health advisory and for the study used to derive the advisory. For example, a 24-week study was used to derive the 10-day health advisory for cadmium.

- There is thought to be some difference in the toxicity of alternative species of a metal, but species-specific health advisories are not estimated. Arsenic is an example here, where the trivalent species is believed to be most toxic, but insufficient data exist to derive species-specific health advisories.

• Different sensitivities were likely applied to alternative studies in measuring health effects. For example, the ten-day health advisory for chromium is based upon an increased incidence of "slight roughness of coat." Other endpoints appear to reflect more severe response.

• There may be conflicting information between two or more studies. For example, the lifetime health advisory for mercury would differ by several hundred fold if an alternative study were used to calculate it. Conflicting studies may have different scientific merit. For example, one study may not have a control group and another may have an incorrect statistical analysis. There is considerable uncertainty in exactly how one should weigh the different merits of these studies.

• A health advisory may be highly dependent on the design of the experiment used to estimate the advisory. For example, the lifetime health advisory for cyanide is based upon a study undertaken at two dose levels. No effects were found at either level, hence, the higher level is assumed to be the no-observed-effect-level. If alternative dose levels were chosen for this experiment, it is likely that both the no-observed-effect-level and the health advisory would differ from the current values.

• The experimental design will also influence the power or ability of an experiment to detect a statistically significant health response from increased exposure to a toxic substance.

• Doses in certain experiments were administered in media other than water. If absorption varies by media, this will produce uncertainty for developing advisories. For example, the lifetime health advisory for nickel is based upon a study of nickel administered through milk.

• The health risk depends on other sources of the metal, and these will vary.

• Interactions may occur between the substance of concern in the drinking water and other substances.

• A lack of understanding of the underlying biological mechanism can impede the interpretation of experimental results.

• The toxicologically critical organ and the critical effect are useful concepts that need to be differentiated, or an uncertainty will be created. The critical organ is the main target of a particular toxicant. The critical effect is the earliest adverse effect to appear. For cadmium, the kidney is the critical organ, whereas many toxicologists believe that beta-2-microglobulinemia is the critical effect. The health advisories should recognize this distinction explicitly and address each accordingly.

To adjust for uncertainty, the health advisories usually reflect assumptions designed to err on the side of safety, and they utilize safety factors in order to be protective of public health. The use of (and rationale for) bias in the interpretation of assumptions and safety factors needs to be clearly explained in the health advisories, in order for them to meet their stated purpose of providing useful information in the field. Without some indication of the bias, operating personnel cannot distinguish between a

decrease in the margin of safety and the imminent possibility of mortality or morbidity in the consuming population. It would be useful, moreover, to provide some indication of the uncertainty associated with a health advisory. The simplest way to do this would be to indicate explicitly the nature of the uncertainties. These could be taken, for example, from the above list. Alternatively, the Agency could develop and incorporate a system to express the levels of confidence associated with the health advisory. Such a system has recently been incorporated into EPA's risk assessment guidelines for mixtures.

C. BIOPROCESSING OF THE METALS NEEDS A CLEARER PRESENTATION.

The Subcommittee noted some inconsistencies in the pharmacokinetics sections between different health advisories for metals and inorganic substances. The content and depth of the discussions varied considerably. In some advisories, extensive animal data were presented without adequate interpretation (e.g., absorption of chromium), and in other places general interpretive statements were presented without data (e.g., absorption of barium). Also, there appeared to be inconsistencies in the definition of the various components of the bioprocessing of metals (absorption, distribution, metabolism and excretion). Examples of this include the following:

- Binding of chromium to iron-binding proteins is discussed in the section on distribution, whereas binding of cadmium to metallothionein is discussed in the section on metabolism.

- Retention of cadmium is discussed in the section on absorption rather than in the section on excretion.

- Renal processing of chromium is discussed in the section on distribution rather than in the section on excretion.

- Transport of chromium is discussed in the section on metabolism rather than the section on distribution.

- Retention of lead is discussed in the section on metabolism.

- The transfer of lead across the placenta is discussed in the section on metabolism rather than in the section on distribution.

- The transfer of nickel across the placenta is discussed in the section on metabolism rather than in the section on distribution.

Inconsistencies such as those cited above confuse the reader, making it difficult to abstract information from the documents and reducing confidence in the documents. It would be helpful if a uniform set of definitions of each of these processes was adopted, and if information concerning each process was categorized in the document accordingly. Also, statements in the documents should be interpretive and should focus on the bioprocessing of metals in humans. If this involves extrapolation from laboratory animal data, the extrapolation should be indicated.

The Subcommittee proposes the following suggestions for the content of the various subsections of the pharmacokinetics sections of the health advisories:

• "Absorption" refers to the processes by which metals enter the internal environment of the body. In this section all routes of absorption that are relevant to human exposure should be indicated, including inhalation of volatile materials from drinking water sources and so forth. Factors that influence the magnitude of gastrointestinal absorption should be indicated. A quantitative estimate of the percent absorption from the gastrointestinal tract in humans (or a range of values) should be provided. The source of the data from which the estimate was made should be indicated (e.g. human data, laboratory animal experiments or conjecture).

• The "distribution" section should describe where the metal is located in the human body. If human data is not available, the location may be inferred through data from laboratory animals or from analogy to similar substances. If possible, a quantitative description should be provided of the distribution of the body burden. This description should indicate the largest depots for the metal and the target tissues. Factors that influence the distribution should be indicated (e.g., speciation, route of absorption or other substances). Transfer of metals across the placenta to the fetus should be discussed in this section. Mechanisms of entry of the metal into target tissues (e.g. membrane transport), if discussed at all, should be reviewed in this section.

• The "metabolism" section should describe the chemical conversions of the metal that are relevant to the absorption, distribution, excretion, detoxification and activation of the metal. This includes oxidation or reduction reactions, binding to intracellular or extracellular proteins, and chelation or complex formation with inorganic components of bone. The significance of metabolism to the overall distribution and elimination of the metal and to the toxicity of the metal should be discussed.

• Under "excretion," a description of the elimination kinetics (e.g., biological half-life) should be presented in each health advisory. The routes of excretion should be identified, and the relative contributions of each of the routes should be discussed. In discussing the fecal excretion of metals, it is important to distinguish the excretion of ingested and nonabsorbed metal from the excretion of absorbed metal. Mechanisms of excretion (e.g., renal tubular transport), if discussed at all, should be reviewed in this section.

D. BIOLOGICAL EFFECTS VARY WITH SPECIATION OF METALS.

In general, metals exist in a number of physical and chemical species. Changes in oxidation state and the formation of organo-metallic compounds (where the metal is covalently bound to at least one carbon atom) are forms of speciation that may have a profound influence on the toxicity of the metal. Speciation should be considered in most of the sub-sections of the health advisory.

In the "occurrence" sections, the global cycle of the metal frequently involves interconversion to more soluble or more volatile species of the metal. The methylation of inorganic mercury in freshwater and oceanic sediments is a key step to the bioaccumulation of mercury in aquatic food chains. The redox potential in water supplies may influence the species in drinking water. The oxidation of trivalent to pentavalent arsenic occurs in well oxygenated water supplies.

In the pharmacokinetics sections, essentially the same principles as above will explain the importance of species in the uptake, distribution, metabolism and excretion of metals. Trivalent chromium crosses cell membranes much more slowly than hexavalent chromium. The methylated forms of metals usually are absorbed better than the inorganic species. Methylmercury must first be demethylated before excretion can take place.

Metallic cations can form a wide variety of complexes with ligands in cells and biological fluids. The induction of and binding to metallothionein by cadmium explains the long-term accumulation of the metals in the kidney. The formation of a glutathione complex in the liver is a key step in the biliary excretion of mercury. The failure to secrete biliary glutathione explains the lack of fecal excretion of mercury in suckling animals.

In the health effects sections, speciation will influence the occurence of health effects both by affecting the pharmacokinetics of the metal or by changing the chemical reactivity and cellular toxicity of the metal. Trivalent arsenic binds to neighboring sulphydryl groups inhibiting sulphydryl containing enzymes and co-factors, such as lipoic acid. Pentavalent arsenic, in the form of anionic arsenates, follows the same metabolic pathway as phosphates, causing uncoupling of high energy phosphate synthesis. Organic metallic compounds such as methylmercury, tetramethyl lead and tetramethyltin produce much more serious effects on the brain than their inorganic counterparts. Carcinogenic properties are well-established for nickel subsulfide but not for soluble nickel compounds.

In the quantification of toxicological effects sections, speciation becomes an important consideration in assessing the importance of different routes of intake to total exposure to the metal and to decisions on using toxicological data from experiments with different routes of exposure. Inhalation studies indicating the carcinogenic effects of nickel subsulfide in lung tissues are probably not relevant to dietary uptake of nickel that will be present in food as a different chemical species. On the other hand, studies on inhaled cadmium compounds may be relevant to dietary intake, if kidney effects are the endpoint for both routes. The same species of cadmium (inorganic divalent cadmium) is involved in renal uptake. The relative contribution of air, water and food to total lead uptake can be directly compared as inorganic lead is the common species. This is not the case with mercury. Mercury vapor is the predominant species in air, methylmercury in food and inorganic divalent mercury in drinking water. Mercury vapor in air and inorganic mercury in food may be compared, if kidney damage is the endpoint. None of these species are comparable if nerve damage is the health effect of concern.

E. MULTIPLE SOURCES OF EXPOSURE INFLUENCE THE HEALTH ADVISORIES.

For most metals, the normal route of intake involves several sources whose relative contributions differ. Often, food constitutes the predominant source and this should obviously be taken into consideration when calculating the health advisory, and it has been practiced in the present set of health advisories. However, it is not clear how the values for source contributions (X% food, 100-X% water) were derived, and this should be stated for the individual metal. In most cases, the source contribution factor may just be a crude speculation, but even such conjectures usually have some basis.

A more serious concern arises when a major contribution and route of exposure is via inhalation. This is of particular importance (a) when the target organ is the respiratory tract and the chemical accumulates in or affects the lung after it is absorbed from the gastrointestinal tract; or (b) when there is a well-defined target organ which is different from the lung where the chemical accumulates once it is absorbed into the blood circulation from either lung or gastrointestinal tract.

Case (a) might be a more hypothetical one, but for case (b) several examples can be given. Lead from automobile exhaust accumulates in the central nervous system; mercury vapor released from dental fillings accumulates as divalent mercuric ion in the kidney; and cadmium inhaled by cigarette smoking accumulates in the kidney. In those cases, where the contribution from inhalation can approach a significant or even major portion of the daily intake, inhalation data must be taken into account and the health advisory must be adjusted accordingly. This has to be evaluated for each chemical individually and is exemplified further in the specific comments for cadmium in this report.

The percentage of the population affected by additional inhalational intake should be considered in a health advisory. For example, if only a small percentage (less than 2%) of the population is exposed occupationally by inhalation to a chemical, such that a major portion of the body burden of the chemical is derived from this occupational activity, should this be reflected in the health advisory? (Examples are workers exposed to manganese dust, mercury vapor or cadmium aerosols in the workplace.) From a scientific point-of-view, both occupational and environmental standards should consider total exposure, unless the applied safety factor in the calculation of the health advisory convincingly covers the additional intake by occupational exposure (or the occupational standard covers environmental exposure). This should then be stated.

If the percentage of people with inhalational exposure is significant, this additional intake will affect the calcualtions in a health advisory. One example, the impact on the cadmium health advisory of smokers in the U.S. population, is described in the specific comments section. In summmary, cigarette smoking alone can contribute as much or more than the daily recommended dose that EPA estimates for non-smokers. Perhaps the applied safety factor of 10 in the present health advisory is high enough to protect smokers also. Nevertheless, a discussion about these relationships should be included in the health advisory.

In any event, multiple exposure sources have to be taken into account once it becomes obvious from knowledge of the pharmacokinetics of a chemical

that lung absorption can significantly contribute to a target site dose. Local authorities should be alerted to the fact that occupational exposure can significantly add to the body burden. Possibly, a "secondary" health advisory can be established for those situations taking into account occupational exposure. With this knowledge and information, local authorities will be able to decide where to set their drinking water standard.

F. HEALTH ADVISORIES SHOULD DESCRIBE THE RELATIVE CONTRIBUTION OF DRINKING WATER TO EXPOSURE.

For each metal, the Subcommittee suggests that a table (or summary statement) be inserted into the health advisory detailing the relative (intake) contributions for humans from different sources, including water. The importance of this table is described in the specific comments for the lead health advisory. An example of a table is given below for lead. EPA also should consider adding an additional column which indicates "percent absorbed." The resulting figure would represent a net contribution which may mean more to the reader than quantity of source. For example, lung absorption for lead is about one hundred percent for the appropriate particle size; for cadmium, it can be close to one hundred percent, whereas gastrointestinal tract absorption is ten to fifteen percent for both metals. Lead absorption is higher in infants, but there is no infant data for cadmium.

Human Lead Exposure*

	2-year-old child		Adult male	
Source	ug/day	Total (%)	ug/day	Total (%)
Air	0.5	1	1.0	2
Food	18.9	40	35.8	59
Dust	21.0	44	4.5	8
Water	6.9	15	18.9	31
Total	47.3	100	60.2	100

* Adapted from support documents for the lead health advisory.

II. SPECIFIC COMMENTS OF THE METALS SUBCOMMITTEE ABOUT THE HEALTH ADVISORIES FOR METALS AND ASSOCIATED SUBSTANCES

A. ARSENIC HEALTH ADVISORY

The health advisory for arsenic reasonably summarizes the pertinent information available in the Criteria Document. Except for carcinogenic effects, much of the available information on the toxicity of arsenic is anecdotal and/or of limited value in calculating a health advisory. Animal experiments were carried out at very high dose levels. Given the uncertainty about how to extrapolate the outcome of these studies to humans at ambient level arsenic concentrations, animal experiments could not be used to calculate the health advisory values.

It was not possible to apply the formula in the section on quantification of toxicological effects, or any other quantitative method, to derive health advisory values. The result is the adoption of a National Academy of Sciences recommendation. Therefore, more detail should be given to indicate the rationale for this National Academy of Sciences recommendation. In any case, there is considerable uncertainty associated with the health advisory, and this should be specifically indicated. Given the statements that data or evidence exist which indicate that some species of arsenic are more toxic than others, the Office of Drinking Water should consider the possibility of a health advisory specific for an ionic species. Using different assumptions, such as the human essentiality of arsenic, alternative estimates could have been calculated.

The health advisory should be placed in perspective. Assuming an adult drinks 2 liters of water a day, the total consumption of arsenic is about 0.1 mg/day at the health advisory concentration. This level of ingestion should be contrasted with the oral intake of arsenic from diet and other sources.

Two different formulae are given for sodium arsenite. The second should be sodium arsenate.

In the health effects section, the health advisory notes that the toxicity of arsenic depends on its chemical form, yet the summary of health effects information does not support this statement, implying that some relevant information is not mentioned. Descriptions of the animal studies include material on As^{+5} that hardly seem worthwhile given the statements that the toxic species is As^{+3}. The studies which support the conclusions about species-specific toxicity in this section should be cited. A slightly expanded summary in the health effects section would result in a better investment of the reader's time.

The Criteria Document raises questions about the Zaldevar study in the longer-term exposure section. For example, it notes that "the decrease in cutaneous lesions seemed to be too rapid following installation of the water-treatment plant". Accordingly, some qualification should be given to this study in the health advisory, noting that the decrease of some symptoms seemed to be too dramatic as arsenic concentrations decreased to 0.08 mg/L.

The health advisory should mention that the study of Tseng and coworkers has been heavily criticized because of the presence of confounding factors in the study population. The Office of Drinking Water also should note the comments of Andelman and Barnett in the article cited in the health advisory. Many of the U.S. studies may have been negative because of the small size of the study populations and their correspondingly low power to detect a significant increase in health effects.

It is ironic that the same advisory value is calculated for short-term and long term exposure given the statement that toxicity is duration-dependent.

The review of carcinogenicity omits human data from Argentina.

B. BARIUM HEALTH ADVISORY

The arguments for determining the uncertainty factors for barium are not convincing. Why was the uncertainty factor dropped from 1000 to 100? How was a factor of 10 derived as a quantitative measure of the effects of the defined diet on hypertension? There is no critical evaluation of the calculated lifetime health advisory (for example, possible sources of error, subpopulations to which the calculated health advisory may not apply, and information that is unavailable but critical to improving the calculation). Should not a factor similar to the one for defined diet be included that quantifies differences in gastrointestinal absorption of barium in young animals?

The document states that there were no signs of toxicity at any barium dose level. This statement is not correct since hypertension was evident in rats given 100 ppm barium in the study of Perry and coworkers. Indeed, the hypertensive effects of barium are used to calculate the lifetime health advisory. Although, in the lifetime health advisory, an increase in blood pressure of 4 to 7 mm (Hg) was not large enough to be considered an adverse effect, elevations of this magnitude traced to lead exposure are considered by EPA to be a significant public health problem. The evaluation of the study by Tardiff and coworkers concludes that no conclusive signs of barium toxicity were observed. This evaluation should be reconsidered since blood pressure was not measured in this study. Perhaps the evaluation should state that there were no additional signs of toxicity at any dose of barium.

It is not clear why the lowest-observed-adverse-effect-level was established as 5.1 mg/kg.day rather than 0.51 mg/kg·day. The study by Perry and coworkers demonstrated significant elevation of blood pressure in rats given 0.51 mg Ba/kg·day for 8 months. In the same study, hypertension was evident in rats given 5.1 mg Ba/kg.day for only 1 month. Thus, the results of this study support a lowest-observed-adverse-effect-level that may be as low as 0.51 Ba mg/kg·day.

EPA reported several other changes in rats given 100 ppm barium that could be considered as evidence of barium-induced toxicity, such as decreased content of adenosine triphosphate and phosphocreatinine in myocardium, decreased rates of cardiac contraction and depressed electrical activity of the myocardium. In the study by Schroeder and Mitchener, increased proteinuria was observed in rats exposed to approximately 0.25 mg Ba/kg·day for 173 days. The acute toxic threshold dose that is cited in the Criteria Document is 2.9 to 71 mg/kg, whereas the health advisory cites a value of 2.9 to 7.1 mg/kg. Which value is correct?

Citations of scientific literature to support certain statements in the document are missing. Literature citations to support statements concerning the solubility of barium compounds in water and the effects of pH on solubility should be provided. Literature citations to support statements concerning the natural abundance of barium compounds, sources of contamination of drinking water and levels of barium in drinking water should be provided.

The information provided in the document ranges from detailed and highly

technical to vague. Similarly, the document will be improved by using consistent units to describe barium concentration.

The sections about pharmacokinetics were difficult for the Subcommittee to understand. It is not clear what is meant by the statement that substitution of barium for strontium and potassium ions is common. The metabolism of barium should be described in greater detail, particularly the incorporation of barium into bone. Statements concerning the similarities between the skeletal metabolism of barium and calcium do not summarize the skeletal metabolism of calcium and provide useful information only to those individuals who are knowledgeable about calcium. While data obtained from studies of laboratory animals by Lengemann suggest that barium absorption in young animals may be significantly greater than in adult animals, information is currently inadequate to determine if this applies to humans. Only the mouse data is analyzed in the distribution section. This section should summarize the human autopsy data and the data on retention of barium in humans that is presented in the Criteria Document.

Information about the relative magnitudes of fecal and urinary excretion could be presented. The role of diet is discussed too tersely and is confusing. No mention is made of the magnitude of excretion of barium in maternal milk. The Criteria Document reports that 10% of an intravenously administered dose of barium is excreted in the milk of lactating cows. If this applies to humans, excretion of absorbed barium in maternal milk could be a more significant excretory route in lactating females than is excretion in urine.

C. CADMIUM HEALTH ADVISORY

The data base for cadmium appears to be fairly complete, although information on cadmium intake via smoking is missing. The acceptable daily intake calculations seem to be correct. However, the ten day advisory is based on values from a study of 24 week duration. The calculations for the longer-term health advisory of 18 ug/L value are not given. How is it derived? The basis for the uncertainty factor of ten, rather the more ususal value of one hundred, should be explained. A rationale exists in the narrow, measurable range of cumulative doses that cause renal disease. There is no critical evaluation in the health advisory of possible sources of error, subpopulations to which the calculations may not apply or information that is unavailable but critical for improving the calculation. The dose of cadmium might be expressed per kg body to facilitate comparisons with other data in the text. The basis for using 10 kg or 70 kg for body weight in the calculation of health advisory should be explained. Similarly, the calculation of the longer-term health advisory for a child of 5 ug/L is not explained.

The risk reference dose (RRFD) of 35 ug/d approximately equals the current U.S. daily intake of cadmium from all sources (mostly food). Using conservative assumptions, the Friberg model yields 352 ug/d as the minimum daily dose that would result in an adverse effect (renal tubular dysfunction). No need exists for an additional safety or uncertainty factor because these data arise from the most sensitive human subpopulation. Many scientists believe that a risk reference dose of about 200 ug/d is adequate protection for humans. The World Health Organization and the European Economic Community have set their standards at this level. However, if EPA retains the current risk reference dose, the Agency should communicate it to the U.S. Food and Drug Administration and the Department of Agriculture, as changes in the pattern of food consumption will be required.

The general question of including effects of widely practiced social habits should be addressed. Specifically, the intake of toxicants by cigarette smoking should be considered. For example, the health advisory is based on the assumption that the risk reference dose is 0.5 ug cadmium per kg·day or 35 ug/day for a 70 kg man. The statement that food appears to be the major route of exposure for cadmium should be modified for smokers. Cigarette smokers constitute approximately 30% of the population, and they will take in an additional amount equal to or exceeding the dietary intake. The health advisory assumes that drinking water contributes 25% of total cadmium intake with the remainder derived from food, which gives a lifetime health advisory of 5 ug/L. It is not entirely clear how the contribution from smoking will affect this calculation, but perhaps it will be lower by a factor of two.

The effects of other metals affecting cadmium absorption should be mentioned, particularly zinc. Lung absorption is not described, although it is important and is discussed in the Criteria Document, and absorption calculations will be in error if this contribution is not included. The main reason for the long half-time of cadmium in the body should be described, i.e., retention in the kidney. Statements about the retention of radiolabelled cadmium chloride do not belong in the absorption subsection. In the study by McLellan and coworkers, the retention of orally administered cadmium was used to

estimate the gastrointestinal absorption of cadmium, but the statement in the advisory about this study does not indicate what was learned about absorption from the study. Perhaps the results of the studies of gastrointestinal absorption of cadmium in humans and studies of laboratory animals that are described in the Criteria Document should be summarized. The statement that cadmium does not cross the skin is vague. Can a quantitative expression be used to describe the absorption of cadmium across the skin? Is data available on the absorption of cadmium across skin in humans?

The whole section on health effects should be reorganized to present a clearer summary, with a emphasis on the kidney as a target organ, rather than a loosely linked series of annotated references. The health effects of cadmium occur as a sequence of events, in which beta-2-microglobulinemia is an earlier indicator. The reference to Itai-Itai disease should note that it appeared in elderly, multiparous women. This disease may not be a sole consequence of high levels of cadmium exposure. Instead, cadmium may be an etiological factor. The symptoms described for humans are for oral exposure. Similarly, for animal data, it is not clear whether described effects are for oral exposure or also after other routes of cadmium administration (injection). If the latter is the case, inhalation effects also ought to be included. The epidemiology study by Thun and coworkers should be cited in the subsection about humans. A better explanation should be provided to support the statement that data on cadmium carcinogenicity are not thought relevant to the consumption of cadmium in drinking water. Effects of cadmium on the respiratory system are not discussed or recognized as human health concerns in the health advisory. This may mislead readers who are not knowledgeable about these aspects of cadmium toxicology.

Friberg and coworkers estimated the daily intake of cadmium that would result in the accumulation of 200 ug cadmium/g renal cortical tissue after 50 years of continuous exposure. Roels and coworkers have shown that this level of cadmium occurs in human kidneys that exhibit symptoms of renal impairment. The health advisory should summarize this information.

Testes exhibit toxic effects after parenteral administration of cadmium. The Subcommittee is divided on the importance of this phenomenon. The results do show that testes of the rat are a sensitive organ for cadmium. However, the pathological effects occur only after massive parenteral doses and after necrosis in blood vessels leading to the testes. Thus, these observations do not have public health significance.

Since the Threshold Limit Values established by the American Conference of Governmental Industrial Hygienists are given, the Occupational Safety and Health Administration's workplace exposure limits should also be described, since these are the legally binding limits for cadmium as dust (0.2 mg/m^3) or fume (0.1 mg/m^3).

What is the evidence to support the statement that commercial use of cadmium has not resulted in the contamination of ground and surface waters? Does this mean that all cadmium in ground and surface water (1-10 ug cadmium/L) is derived from natural sources?

D. CHROMIUM HEALTH ADVISORY

Most of the health advisory evaluation of chromium is accurate, complete and in agreement with the Criteria Document. However, the section on health effects does not adequately reflect the body of the evidence presented in the Criteria Document and is open to question on the evaluation of both carcinogenic and non-carcinogenic effects.

Both the Criteria Document and the health advisory make efforts to distinguish between chromium (III) and chromium (VI). This distinction is important as the toxicity of chromium has been attributed primarily to chromium (VI). The main difficulty with this advisory concerns the appraisal of the carcinogenicity of chromium (VI). The health advisory states that there is inadequate evidence to determine whether or not oral exposure to chromium can lead to cancer. While this is true, there is strong evidence that inhalation of chromium (VI) increases the risk of cancer (most notably for the lung), although there is no direct evidence of carcinogenicity from oral exposure. The advisory concludes that the carcinogenicity of inhaled chromium (VI) has no bearing on risk following oral exposure. This statement is not well justified.

The Criteria Document notes that the International Agency for Research on Cancer concluded that chromium falls into its Group 1 category (meaning that sufficient evidence exists to demonstrate that the chemical is carcinogenic in humans). However, this categorization was not included in the advisory. Further, EPA's Health Assessment Document for Chromium reviews this evidence and reaches agreement with the International Agency for Research on Cancer's categorization. Although the categorization results primarily from inhalation data, it seems reasonable to include it in the advisory (with the associated caveats on inhalational versus oral data). There is one animal study on ingestion of chromium by Ivankovic and Preussman, but it involved chromium (III) not chromium (VI).

The Criteria Document does not attempt to reach either a qualitative or quantitative conclusion on the carcinogenic risk from oral exposure through drinking water based on the inhalation data. Nevertheless, it is critical to consider the carcinogenicity of chromium (VI) from oral exposure in light of the inhalation data, the pharmacokinetics, metabolism and mutagenic effects of chromium (VI). A supporting issue paper reviews the use of inhalation data to develop acceptable exposure levels in drinking water and, therefore, a policy basis exists for the Office of Drinking Water to make this extrapolation for the sake of consistency. However, the Metals Subcommittee recommends that the Office of Drinking Water not use this exact method, since this issue paper is in need of revision.

A secondary concern involves the assessment of the noncarcinogenic health effects in humans. In presenting the evidence, the advisory gives strong weight to a report on the effect of drinking water containing 1 mg/L of chromium (VI) in one family of four persons, based on a physical exam. This report is anecodotal and has little scientific value. Neither was a control family studied nor were details given on health effects measured. In contrast, the health advisory notes that chronic inhalation of dust or air containing chromium (VI) may cause respiratory problems. However, these risks seem understated as the Criteria Document describes at least three well designed and

controlled epidemiologic studies which conclude that chronic inhalation of air containing chromium (VI) causes respiratory problems.

Animal studies on non-carcinogenic effects of chromium are listed but not reviewed. Conclusions such as "no adverse health effects were reported," are not particularly helpful. The emphasis on chromium (VI) is appropriate, but this description might precede the pharmacokinetics section.

A more critical evaluation of the health advisory calculations would be desirable by, for example, reviewing possible sources of error, subpopulations to which the calculated health advisory may not apply, or information that is unavailable but would be critical for improving the calculation.

E. CYANIDE HEALTH ADVISORY

The health advisory for cyanide suffers from a haphazard literature review. For example, in the excretion section, three statements are presented. One is a summary statement about the major route of elimination, one refers to rats, and one describes an apparent human suicide attempt. A similar lack of critical interpretation appears in the section on longer-term exposure. Two dog studies are reported. In one, no signs of toxicity apparently were found after 3 mg/kg·day administration for thirty days. In the second, histopathological changes (in a site described as "ganglion cells of the CNS" with no other clarification) were found after 0.27 mg/kg·day for 15 months. In the first study, the cyanide was administered in the diet, in the second, as a capsule. Could the different findings be ascribed to the mode of administration? The text fails to discuss the differences.

The health advisory should add synonyms of prussic acid and hydrocyanic acid. The use of cyanides in electroplating and the need to check for cyanides in business closings are of concern but have been omitted. The section on occurrence should start with a definition of free cyanide. Many organic compounds exist, such as nitriles, which contain the cyanide functional group. Few nitriles disassociate to liberate the cyanide ion. Unless the definition of cyanides is limited to the cyanide ion and hydrocyanic acid, statements in the health advisory about pharmacokinetics should be modified.

Is it valid to apply potassium cyanide data to the case of hydrocyanic acid (or cyanide gas) when discussing percent absorption and time to death? The data of Getter and Baine would be better converted to cyanide ion as is done in the Criteria Document. Free cyanides absorb readily, and hydrocyanic acid is absorbed and distributed more rapidly than potassium cyanide. The distribution of cyanide depends upon the time before exposure and death; volatilization of hydocyanic acid from samples should be suspected when the analytical values are low. The wide range in the concentrations found in human organs in cases of fatal poisoning may be affected by these factors. The rapid distribution of cyanide throughout the organs of the body following ingestion or inhalation is an important fact in characterizing its effects. Yamamoto's data seem to indicate a greater tendency of cyanide to distribute to the liver and spleen by ingestion as sodium cyanide than by inhalation as cyanide gas.

The section on distribution needs to distinguish between the distribution of radioactivity and the distribution of cyanide. The accumulation of cyanide within erythrocytes is mainly due to the oxidation of iron in methemoglobin and the formation of cyanomethemoglobin. The section on metabolism should note that cyanocobalamin is a form of vitamin B-12. This nomenclature should be clarified for the non-expert reader. The effectiveness of different sulfur compounds that detoxify cyanide ion by forming thiocyanate is dependent upon the presence of a free sulfur atom adjacent to another sulfur atom in the the molecule as is the case with thiosulfate.

The discussion of human epidemiological studies in the section about health effects has omitted data on electroplaters.

The health advisory should note that animals can tolerate higher doses of cyanide when administered in the diet or in drinking water during longer-term exposures (20-90 days) than when the same dose is given over a much shorter period such as 1 day. The compound used in the study by Howard and Hanzal was hydrocyanic acid. The average concentrations were 76 mg/kg of diet and 190 mg/kg of diet, instead of 100 mg/kg and 300 mg/kg as described in the health advisory.

Why is Cyanide classified as a carcinogen? The health advisory reports that there is inadequate evidence for such a conclusion. Elsewhere, the health advisory states that there are no pertinent data available. This is contradictory.

The rate at which cyanide is absorbed, distributed and detoxified is important in evaluating the health effects of cyanides. For example, in the study by Palmer and Olson (see data below), it is not clear how much of the effect on liver is caused by greater total uptake of cyanide and how much by faster rate of absorption or distribution. This evaluation will affect the choice of data for calculation of the 1-day health advisory.

Compound	No-observed-effect-level	Duration of study
KCN diet	8 mg(CN-)/kg (body weight)·day	21 days
HCN diet	10.4 mg(CN-)/kg (body weight)·day	104 weeks
KCN water	12 mg/kg (body weight)·day	21 days

The Subcommittee could not find a rationale in the health advisory for the extra 5-fold factor in the safety factor. If this value relates to absorption characteristics, it would be better to describe it separately than to combine it with the traditional safety factor.

The Subcommittee has written a prose summary of the cyanide health advisory (See appendix) to illustrate the advantage of narrative for the reader lacking prior training in toxicology in comparison to the summary table of numerical data that the health advisory currently presents.

F. LEAD HEALTH ADVISORY

The recommended lifetime health advisory of 20 ug/day can be supported by present information about lead metabolism and toxicity. The calculations are correct, but the selection of values of a blood lead level of 15 ug/dl and a safety factor of 5 could be challenged. Although past evidence may have seemed inconclusive, the current literature supports an even lower level than 15 ug/dl, as discussed later in this review. The recommended standard represents a reduction in the interim EPA water standard for lead, currently 50 ug/liter. The Subcommittee also agrees that one day and ten day health advisories are not appropriate for lead. The health advisory generally is consistent with the Criteria Document. However, it does not have a clear focus and would not be especially useful to someone not thoroughly familiar with the lead literature.

An overall statement or description is needed on the range of health effects of lead, from the most mild to the most severe, associated with the corresponding blood levels. A summary statement about the significance of these findings should accompany the table.

In discussing absorption, the health advisory does not note the underlying reasons for enhanced absorption by children. This is a peculiar omission because of regulatory efforts to protect the young. The discussion of distribution is devoted solely to lead in blood and does not present information on where else lead may be found, for example, in kidney and bone. In the section on short-term exposure, several statements are made about the blood levels needed to achieve an effect and the possible latency to effects. These estimates are rather arbitrary and subject to change given current research findings. The statement that it takes 35 days for blood levels to reach a certain value is difficult to understand. The Criteria Document quotes evidence that it takes 100 days to attain a steady state level.

Because the health advisory does not describe complete dose-effect relationships, it is difficult to make sense of the biochemical, behavioral, neurophysiological and reproductive effects that are listed. The manner in which the health advisory chooses a single value of 15 ug/dl seems arbitrary. The change in blood pressure at approximately this level is similar in size to the elevation produced by barium, an elevation estimated to account for over 7,000 myocardial infarctions annually. In the health advisory for barium these data were not taken into account to lower the level.

The studies cited to illustrate the sensitivity of the fetus and child to lead need to be updated. The recent EPA-supported meeting in Edinburgh contained several reports indicating significant adverse effects in the offspring of mothers with blood lead values that previously would have been deemed low or modest. Some of these data, moreover, have been published. Research groups at the University of Cincinnati, Children's Hospital in Boston, and elsewhere have obtained data to indicate a direct relationship between maternal blood levels and lower birthweight, minor malformations, and reduced scores on psychological tests that persist for at least two years. Such data make the calculation of a threshold a tenuous proposition. Although impaired heme synthesis in children may occur at blood lead levels exceeding 10 ug/dl, the health significance of this effect is less clear.

For adults, as for children, earlier data suggested few significant effects on peripheral nerve function at blood leads below 40 ug/dl. Recent data support the occurence of such effects, but the case is not as clear, and the statement in the health advisory about nerve dysfunction should be made more provisional.

The proportionality constant between lead intake in the diet and blood lead needs to be reviewed in terms of diet contents such as other minerals. The statement about the World Health Organization European standard for lead of 100 ug/dl in blood should be re-examined to determine if it is cited correctly.

The Subcommittee questions the validity of the statement about the mutagenicity of lead. Because lead causes toxicity prior to mutagenicity does not mean no genotoxicity will result. In EPA's Air Quality Criteria Document, lead is described as decreasing the fidelity of replication, inhibiting RNA synthesis, causing an S-phase specific cell cycle block that indicates lead will interfere with normal synthesis and replication of DNA, and causing induction of DNA repair synthesis. Human carcinogenesis studies also can be cited in support of the genotoxicity of lead.

The lifetime health advisory for lead is less than levels sometimes found in air, food, and water. In the Criteria Document for lead, the lifetime health advisory is considered in terms of relative source data. This type of discussion might be included in the health advisory to reconcile the recommended level with actual intakes occurring for most Americans today.

For example, the following calculation for an adult ingestion level can be made using the relationship between blood lead levels and water lead levels derived by Pocock and coworkers.

$$\frac{(15 \text{ ug/dl})}{[(1 \text{ ug/dl})/(0.062 \text{ ug/day})](5)} = 48 \text{ ug/day}$$

where:

(a) 15 ug/dl = blood lead level at which no adverse effects are thought to be observed, and

(b) 5 = an uncertainty factor, which should have a rationale.

Using this maximum ingestion level dividing by an estimate of water consumption per day, a maximum level of lead in water is obtained. For example, if the estimate is two liters of water consumed per day by an adult, calculation is as follows:

$$\frac{48 \text{ ug/day}}{2 \text{ l/day}} = 24 \text{ug/l}$$

Data on the relative sources of lead and how they contribute should be considered. The above calculations assume that 100% of an adult's lead exposure comes from drinking water. However, studies of other routes of lead exposure in adults show that air-borne lead, lead in food, and dust ingestion also

contribute. Drinking water contributes about 30% of total intake in adults of about 100 ug/day. Therefore, the calculation should be modified as follows:

$$\frac{(0.30)\ (48\ ug/day)}{2\ l/day} = 7.2\ ug/l$$

For this reason, a summary of the relative source contributions for adults and children will enhance the health advisory.

G. MERCURY HEALTH ADVISORY

The health advisory generally is consistent with the guidance in the Office of Drinking Water issue papers. The acceptable daily intake calculations are arithmetically correct. However, correcting the acceptable daily intake for intake of mercury from sources other than drinking water poses a difficult problem.

The decision to subtract mercury intakes for food and air from the total acceptable daily intake for inorganic mercury assumes that various forms of mercury are toxicologically equivalent.

The data in the health advisory support the conclusions in the context of a number of assumptions. The judgments reflect those in the Criteria Document. The major decision is to accept the experiment by Druet and coworkers as the basis of calculating the acceptable daily intake. The data of Fitzhugh and coworkers also are listed in the health advisory but not used. If they were used, the acceptable daily intake could be 240 times higher than that calculated in the health advisory. Human data on kidney effects from exposure to mercury vapor are not used. This is also true of the Criteria Document. Human data are variable in the case of mercury because humans react to mercury as an antigen, and the data may be difficult to evaluate for purposes of safety levels. However, human data are preferred, and there is a large data base for humans. The health advisory also neglects a rather sizable literature in children relating to Pink Disease (Acrodynia), which, despite its flaws, is still a better basis for quantification than the data from rats.

The assumptions and uncertainties are not clearly described, but it might require considerably more text to do this. The most important assumptions and decisions to be described are as follows:

- The rationale for choosing the data of Druet and coworkers versus those of Fitzhugh and coworkers.
- The assumption that all forms of mercury-mercury vapor in air, methylmercury in food and inorganic compounds in drinking water are toxicologically equivalent.
- The decision not to consider mercury intake from dental amalgams.

The approach to adjusting for other sources of mercury in the health advisory is to subtract the average total air and food intake of all forms of mercury from the total acceptable daily intake calculated for inorganic mercury. This calculation gives the acceptable daily intake for drinking water.

Another approach is to estimate the fraction of daily intake of total mercury contributed by each medium - air, food and drinking water - as estimated for the general "non-exposed" population and then to apportion the acceptable daily intake in the same proportion. For example, if drinking water accounts for 20% of total mercury, the acceptable daily intake for drinking water would be 20% of 11 ug/day of total mercury or approximately 2 ug/day, given a maximum concentration in drinking water of 1 ug/l, which is in agreement with the value derived by the World Health Organization.

A third approach is to consider the three major forms of mercury as toxicologically independent. Thus, the acceptable daily intake for inorganic mercury would be allocated almost entirely to drinking water, giving a maximum concentration in drinking water of 5 ug/l inorganic mercury.

Some data on mercury are missing from the health advisory that might better be included, such as:

- Information on intakes from food, air and water. These data should be described in the section on general information and properties.
- Intake from dental amalgams. This information also is missing from the Criteria Document.
- Concentrations of mercury found in commonly used indicator media, such as blood and urine, for the non-exposed general population. However, this information also is not present in the Criteria Document.

The health advisory is generally consistent with the Criteria Document. The problems of assessment reside mainly in the Criteria Document.

Mercury represents a special problem in its diverse toxic forms and how they differ in different media. In addition, this is the first attempt by any public health organization to evaluate the effects of ionic mercury in the context of total mercury intake. The Subcommittee has recommended that the Criteria Document for mercury undergo additional scientific and editorial review. Detailed comments on the Criteria Document by one Subcommittee member, which also suggest that the Criteria Document requires additional review, have been sent directly to the Office of Drinking Water.

H. NICKEL HEALTH ADVISORY

Some Subcommittee members have reservations about the proposed lifetime health advisory of 150 ug/l for nickel in drinking water (350 ug/l assuming that all nickel exposure occurs through drinking water) which is higher than the nickel concentrations that usually are encountered in public water supplies. However, EPA's Health Assessment Document for Nickel (Draft final; September, 1985) cites the results of the Agency's STORET data base as a range from <5 ug/l to >1,000 ug/l and gives values of 700 ug/l for the Ohio river. Other Subcommittee members think that setting the lifetime health advisory close to the usual drinking water concentrations is overly stringent and will result in frequent enforcement actions with no clear health benefits. These members recommend further EPA research on nickel carcinogenicity, sensitization and uptake in relation to chemical form (species).

The range of nickel concentrations in ambient surface water is not clear. In another study of 2503 water samples from 969 public water supplies in the United States during 1969-1970, nickel concentrations averaged 4.8 ug/l. The nickel concentrations were < 20 ug/l in 99.0% of the water supplies and < 50 ug/l in 99.9%. The highest observed nickel concentration was 75 ug/liter. Similarly, in running tap water from 20 public water supplies in Sweden and 10 European cities, the nickel concentrations ranged from 3 to 7 ug/l and 5 to 8 ug/l, respectively. In running tap water from 41 public water supplies in the environs of Copenhagen, Denmark, nickel concentrations were < 35 ug/l with two exceptions (91 and 120 ug/l). In Ontario, Canada, at the Sudbury site of the world's largest nickel deposits, mines and refineries, higher nickel concentrations have been reported in drinking water. Nickel concentrations in seven samples of running tap water collected in Sudbury during 1971-1972 averaged 200 ug/l (range = 141 to 264 ug/l), while corresponding values for five samples collected in Hartford, Connecticut, were 1.1 ug/l (range = 0.8 to 1.5 ug/l). Differences in ambient exposures to nickel were reflected by differences in the respective urinary excretions of nickel, which averaged 7.9 ug/day (5.9 ug/g creatinine) in 19 hospital workers who resided in Sudbury, compared to 2.5 ug/day (2.3 ug/g creatinine) in 20 hospital workers who resided in Hartford.

There is no current evidence to suggest that a carcinogenic response is induced in humans or laboratory animals by the ingestion of nickel compounds. However, the Criteria Document emphasizes that there are no bioassays for carcinogenesis of nickel by the oral route at concentrations greater than 5 mg/l. Until adequate oral carcinogenesis bioassays of nickel compounds in drinking water have been conducted, the question of nickel carcinogenicity remains open. This is one practical reason for selecting a lifetime health advisory level for nickel in drinking water close to the prevalent nickel concentrations in public water supplies in the U.S.

A second reason to set the health advisory level close to the levels observed in water is that hypersensitivity to nickel occurs in a significant portion of the general population, and clinical evidence suggests that oral ingestion can exacerbate nickel allergy. The Criteria Document summarizes the literature through 1982 on exacerbation of nickel contact allergy following oral intake and describes the occurrence of positive dermal patch test results from nickel in 7 to 11% of adult women and 0.2 to 2% of adult men. Because of the frequency of nickel hypersensitivity in the population, an additional margin of safety

may be appropriate in setting the health advisory level for nickel in drinking water.

A third reason to set the health advisory level closer to the levels observed in water is the growing evidence that bioavailability of nickel from drinking water may be greater than from foods and beverages. Solomons and coworkers have studied the effects of foods and beverages on gastrointestinal absorption of nickel in five healthy human subjects following an oral dose of 5 mg, administered as nickel sulfate hexahydrate. No significant post-prandial increases of plasma nickel concentration occurred after consumption of nickel added to beans or eggs, whereas prompt and sustained elevations of plasma nickel concentrations occurred when the same quantity of nickel was consumed as an aqueous solution by fasting subjects. Increases in plasma nickel concentration also were suppressed when 5 mg of nickel (as nickel sulfate) was dissolved in milk, coffee, tea, or orange juice. These studies indicate that certain foods and beverages reduce or prevent the absorption of divalent nickel from the alimentary tract. Foulkes and McMullen also have found that divalent nickel ion uptake from the lumen of the perfused rat jejunum is significantly inhibited by divalent zinc ion and by skimmed milk, supporting the view that certain dietary constituents reduce the bioavailability of nickel.

A fourth reason to set the health advisory level close to the levels observed in water arises from the methodological deficiencies of some published studies on reproductive effects of nickel salts, administered to rats in diet or drinking water. The limitations of these studies are discussed in the Criteria Document. A two-generation reproduction and fertility study of nickel chloride administered to rats in drinking water at three dosage levels is underway at the Research Triangle Institute under EPA sponsorship. The results of this study should soon be available. The outcome of this study is likely to influence the value of the lifetime health advisory for nickel in drinking water.

Oral carcinogenesis tests of nickel compounds added to drinking water might influence the level of the life-time advisory, as well as comparisons of the bioavailability and toxicity of nickel salts administered to rodents in drinking water. Until these data are available, EPA's criteria for regulating oral exposures to nickel in drinking water will remain controversial.

The health advisory does not contain an adequate discussion of nickel as an essential element. The statements in the health advisory about carcinogenicity are somewhat disconnected and mostly irrelevant. An interpretive summary would be far better.

I. NITRATE AND NITRITE HEALTH ADVISORY

The nitrate and nitrite health advisory is well-written and essentially complete. The health advisory fairly reflects the contents and conclusions of the Criteria Document. It is appropriate to recognize the infant as the most vulnerable organism.

The main thrust of the health advisory is that nitrate is not toxic per se, but must be converted to nitrite to be toxic. Nitrate reduction to nitrite is proposed to occur in saliva, which is then swallowed. Nitrate and nitrite are absorbed through the gastrointestinal tract. Nitrate is recycled by excretion into saliva, where conversion to nitrite occurs once again. Nitrite reacts predominantly with red cell hemoglobin to form methemoglobin and nitrate.

Nitrate and nitrite also produce profound vasodilation and cardiovascular collapse. The mechanism of vasodiliation is not clear. Formation of S-nitroso vasodilator compounds has been proposed as one mechanism, but is not mentioned in the Criteria Document. An alteration in chloride transport is another mechanism based on the competition of nitrate and nitrite with iodide and other monovalent cations.

The health advisory focuses on methemoglobin formation as the most significant health effect on the basis that infants suffer from methemoglobinemia after drinking nitrate contaminated water, milk or formula. For the purposes of the health advisory, methemoglobinemia in infants is the most appropriate endpoint. The calculated values assume a 10% conversion of nitrate to nitrite in the bucal cavity and 100% absorption of nitrite. The no-observed-adverse-effect--level selected from the studies reported in the Criteria Document is appropriate. The studies selected as the basis for the no-observed-adverse--effect-level are also appropriate. The calculations do not have arithmetic errors.

A major problem exists in the lack of data on the chronic health effects of nitrate. The lifetime multigeneration study of Newbern is controversial due to the intrepretation of the histopathology. The most recent cancer bioassay with Fisher 344 rats also is confusing due to the 100% tumor rate in both control and exposed animals.

No data are now available on the cardiovascular effects of chronic exposure to nitrate. Given the profound vasodilator effects of nitrates (some of which are used clinically) independent of the development of methemoglobinemia, this aspect of the toxicity of nitrate and nitrite deserves further investigation.

A more pressing problem is the question of the carcinogenicity of nitrate. The Subcommittee agrees with the health advisory conclusion that, under the Agency's proposed guidelines for carcinogen risk assessment, the current data fit best into category D (not classifiable). A major health concern, however, arises from the evidence that simultaneous ingestion of nitrite (or nitrate with amines) results in cancers of many organ systems. N-nitroso compounds are presumed to be the ultimate carcinogenic substances. The calculated excess cancer risk from the combined exposure to a nitrosatable compound and nitrite

can be significant. It is not possible to calculate the risk, if any, from nitrate or nitrite alone.

The Office of Drinking Water should devise a plan to develop appropriate experimental data to clarify this problem. Clearly a number of carcinogenic, nitrosatable compounds exist in drinking water or foods which, if ingested with nitrate or nitrite-contaminated drinking water, will result in formation of the carcinogens and excess cancer risk. Lacking better data, the Subcommittee agrees that a better estimate of human cancer risk can not now be provided, but the public is left uncertain if the present health advisory for nitrate provides adequate protection from this incremental risk.

Some of the difficulty arises from the legislative direction regulating drinking water standards. Like other health risk legislation, drinking water legislation is oriented to specific chemicals; e.g. nitrate rather than N-nitroso carcinogens. The Office of Drinking Water should consider and document how the current health advisory provides or does not provide a means of indirectly regulating human exposure to N-nitroso carcinogens.

The health advisory slips into jargon from time to time. The most glaring example is in the introduction, where the third paragraph refers to the "Health Advisory numbers". Clearly, this intended to mean the "Health Advisory values". This health advisory is better integrated than the other advisories for metals and related substances.

U.S. Environmental Protection Agency
Science Advisory Board
Environmental Health Committee
Metals Subcommittee
January 9-10, 1986

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Dr. Marvin Kuschner, Dean, School of Medicine, Health Science Center, Level 4, State University of New York, Stony Brook, New York 11794

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Executive Secretary

Dr. Daniel Byrd, III, Executive Secretary, Science Advisory Board, [A-101F], U.S. Environmental Protection Agency, Washington, D.C. 20460 (202) 382-2552

COMMENTS SUBMITTED TO THE METALS SUBCOMMITTEE

BY THE PUBLIC REGARDING THE SCIENCE ADVISORY BOARD'S

REVIEW OF DRAFT DRINKING WATER HEALTH ADVISORIES

National Audubon Society
National Capital Office
645 Pennsylvania Avenue, S.E.
Washington, D.C. 20003

Contact: Chuck Pace

Date: December 24, 1985

Chemical Manufacturers Assoc.
2501 M Street, N.W.
Washington, D.C. 20037

Contact: Geraldine V. Cox

Date: December 26, 1986

Natural Resources Defense
Council Inc.
122 East 42nd Street
New York, N.Y. 10168

Contact: Robin Whyatt
Wendy Gordan

Date: November 29, 1986

Water Quality Association
1518 K Street, N.W.
Suite 401
Washington, D.C. 20005

Contact: Danna M. Cirolia

Date: November 22, 1985

The New Jersey Dept. of Health
and The New Jersey Dept. of
Environmental Protection

Contact: Bonnie L. Bishop

Date: August, 1985

State of Connecticut
Department of Health Services

Contact: David R. Brown

Date: December 12, 1985

Michigan Pure Water Council

Contact: Martha Johnson

Date: December 12, 1985

POSTMEETING COMMENTS RECEIVED

National Audubon Society
National Capital Office
645 Pennsylvania Avenue, S.E.
Washington, D.C. 20003

Contact: Chuck Pace

Date: January 27, 1986

U.S. Environmental Protection Agency
Science Advisory Board
Environmental Health Committee
Metals Subcommittee

Open Meeting

Under Public Law 92-463, notice is hereby given that a two-day meeting of the Metals Subcommittee of the Environmental Health Committee of the Science Advisory Board will be held on January 9-10, 1986, in Conference Room 451 of the Joseph Henry Building; National Academy of Sciences; 2122 Pennsylvania Avenue, N.W.; Washington, DC. 20037. The meeting will start at 9:00 a.m. on January 9 and adjourn no later than 4:00 p.m. on January 10.

The purpose of the meeting will be to discuss draft drinking water Health Advisory documents for the following substances:

Arsenic	Lead
Barium	Mercury
Cadmium	Nickel
Chromium	Nitrate/Nitrite
Cyanide	

The Metals Subcommittee will not receive oral comments on the Health Advisory documents at the meeting. Written comments on any of the specific substances should be delivered within forty (40) days from the date of this notice to Manager, Health Advisory Program; Criteria and Standards Division [WH-550]; U.S. Environmental Protection Agency; 401 M Street, S.W.; Washington, DC; 20460.

EPA's Office of Drinking Water prepared the draft Health Advisory documents. They are neither regulations nor regulatory support. To obtain copies of the draft Health Advisory documents for specific substances please write to the Manager of the Health Advisory Program at the above address.

The meeting will be open to the public. Any member of the public wishing to attend or to obtain further information should contact either Dr. Daniel Byrd, Executive Secretary to the Committee, or Mrs. Brenda Johnson, by telephone at (202)382-2552 or by mail to: Science Advisory Board (A-101F); 401 M Street, S.W.; Washington, DC: 20460, no later than c.o.b. on December 20, 1985.

Terry F. Yosie
Staff Director
Science Advisory Board

October 15, 1985

Date

U.S. ENVIRONMENTAL PROTECTION AGENCY
SCIENCE ADVISORY BOARD
ENVIRONMENTAL HEALTH COMMITTEE
METALS SUBCOMMITTEE

Conference Room 451
Joseph Henry Building
National Academy of Sciences
2122 Pennsylvania Avenue, NW
Washington, DC 20037
January 9-10, 1986

ORDER OF BUSINESS

REVIEWS OF DRAFT DRINKING WATER HEALTH ADVISORIES

Opening Remarks	.....	Dr. Weiss
Administrative Matters	.....	Dr. Byrd
Introduction	.....	Dr. Crisp Dr. Weiss

*Tentative Sequence of Reviews, beginning Thursday, January 9, 1986

Substance (Manager)		Reviewers
Arsenic (Marcus)		Drs. Wyzga and Goyer
Lead (Marcus)	.....	Drs. Goyer and Clarkson
Nickel (Bathija)		Drs. Sunderman and Brookmeyer
Barium (Bailey)	.....	Drs. Diamond and Sunderman
Cadmium (Bailey)		Drs. Mossman and Diamond
Chromium (Bailey)	.....	Drs. Brookmeyer and Mossman

On Friday, January 10, 1986

Mercury (Khanna)		Drs. Clarkson and Wyzga
Cyanide (Bathija)	.....	Drs. Ferrand and Kuschner
Nitrate (Bailey)		Drs. Menzel and Ferrand

At the conclusion of the reviews

*Completion of reviews (previously deferred)	Dr. Weiss
General comments	Dr. Weiss
Nomination of Criteria Documents for further review	Dr. Weiss

Other Subcommittee Business

Concluding remarks	.....	Dr. Weiss Dr. Byrd

ADJOURNMENT

* The sequence in which the Subcommittee reviews Health Advisories for different substances and the time allocated to each review are at the discretion of the Chair.

CYANIDE

DEFINITION

For the purposes of this document cyanide refers to hydrogen cyanide and its water soluble salts, primarily sodium and potassium. Organic compounds called nitriles because they contain a cyano, (-CN), functional group are sometimes referred to as cyanides. These are not included because they do not readily dissociate to form cyanide ion. Cyanide ion has a tendency to combine with certain cations to form complexes. Their contribution to the "free" cyanide measured in water solution depends on their stability and the analytical procedure.

Pure hydrogen cyanide is a colorless liquid with a bitter almond taste which biols near room temperature (25.7° C) and is miscible in all proportions with water. Sodium and potassium salts are colorless, crystalline solids which are quite soluble in water where they are converted to hydrogen cyanide to an extent dependent upon the acidity of the water.

SOURCES OF CYANIDES

Cyanides are used by the chemical industry in the manufacture of pesticides, rodenticides, photographic and metal polishing products and in the preparation of other chemicals such as nitriles and plastics. Wastes from the manufacture or use of cyanide products, for example, from electroplating and case hardening operations are potential sources of cyanide contamination of water supplies.

Cyanide, at the concentrations normally found in drinking water supplies, ordinarily is not an important contributor to the body intake. Therefore, it is not a public health problem in the United States. A survey reported in 1970 of 2595 samples collected from over 800 water supplies found a maximum concentration of 0.008 mg per liter. Nevertheless, the possibility of cyanide in water supplies by accidental or intentional contamination requires that monitoring programs or at least an anlytical capability should be maintained by water suppliers.

There are other contributors to the body burden which should be considered if cyanide is a concern. Unusual diets, smoking habits and occupational exposures can be more important contributors than drinking water. Individuals with a metabolic defect in the enzyme system that converts cyanide to less toxic thiocyanate, with a vitamin B12 deficiency or with defective B12 metabolism or with an iodine deficiency, as well as fetuses in utero of smoking mothers, are at greater risk than the normal population.

There is no available evidence pertaining to the carcinogenicity of cyanides.

ADVERSE HEALTH EFFECTS

Cyanide acts as an asphyxiant by preventing body tissues from using the oxygen transported to them by the blood. Thus, the inhalation, ingestion or absorption through the skin of high concentrations of cyanide can cause serious damage to the tissues of many organs. Hydrogen cyanide is absorbed most rapidly by inhalation.

Studies relating cyanide exposures to adverse health effects indicate that a daily intake of up to 0.021 mg of cyanide per kg of body weight over an extended period will not cause observable adverse effects to the health of children. If all exposure comes from drinking water, then to avoid exceeding the daily dose, the concentration of cyanide in the water supply must not exceed 0.21 mg per liter of water. This value is based upon the assumption of a 10 kg child who drinks an average of 1 liter per day:

$$\frac{0.21 \ \frac{\text{mg } CN^-}{\text{kg (bw) day}} \times 10 \text{ kg (bw)}}{1 \ \frac{\text{liter}}{\text{day}}} = 0.21 \ \frac{\text{mg CN}}{\text{liter}}$$

A 70 kg adult drinking 2 liters per day from this same water supply will receive a considerably smaller daily exposure per kg of body weight.

$$\frac{0.21 \ \frac{\text{mg } CN^-}{\text{liter}} \times 2 \ \frac{\text{liter}}{\text{day}}}{70 \text{ kg (bw)}} = 0.006 \ \frac{\text{mg } CN^-}{\text{kg (bw) day}}$$

REMOVAL OF CYANIDE FROM WATER SUPPLIES

Cyanide ion, CN^-, in water is in equilibrium with hydrocyanic acid (HCN) with the equilibrium concentrations dependent upon the pH of the water:

$$CN^- + H_2O = \begin{matrix} HCN \text{ (gas)} \\ | \\ HCN \text{ (aq)} \end{matrix} + OH^-$$

At pHs less than 7, over 99% will be in the HCN (aqueous) form. Therefore, in an open body of water there will be a tendency to lose cyanide slowly by evaporation as gaseous HCN. Chlorination of the water supply or use of other oxidizing substances for disinfection will convert some cyanide to the less toxic isocyanate form.

ANALYSIS OF WATER FOR CYANIDES

Free CN^- can be measured: by titration with silver ion using a silver sensitive indicator; by colorimetry based upon conversion to cyanide chloride using chloramine followed by formation of a dye, or by cyanide-selective electrode.

Depending on the pretreatment method used in the analysis, anything from free cyanide to total cyanide, including insoluble and complex cyanides, can be determined.

REFERENCES