



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

October 24, 1986

Honorable Lee M. Thomas
Administrator
U. S. Environmental Protection Agency
401 M Street, S. W.
Washington, D. C. 20460

OFFICE OF
THE ADMINISTRATOR

Dear Mr. Thomas:

The Environmental Health Committee of EPA's Science Advisory Board has completed its review, requested by the Office of Drinking Water (ODW), of thirty-seven drinking water health advisories. The Committee accomplished this task by assigning the review to three separate subcommittees: Metals, Halogenated Organics and Drinking Water. The Science Advisory Board has not previously reviewed health advisories, and its participation in this program has been informative.

The Agency's development of health advisories represents an important component of its drinking water program. By seeking to improve their scientific quality, EPA will better serve the needs of state and local officials who have a legitimate need for the advisories.

In order not to delay the ODW's revision of the advisories, the three subcommittees have already provided transcripts of their oral comments and about 110 pages of detailed comments. The final comments are enclosed with this letter as three Subcommittee reports. The major conclusions of the review are as follows:

- The Subcommittees found the health advisories uneven with respect to their scientific quality. The Office of Drinking Water should develop guidance to assure more consistent quality in the future.
- The Office of Drinking Water has made a commendable effort to provide exposure analysis information in the draft health advisories, including the consideration of exposure from drinking water through routes other than oral ingestion, and the utilization of inhalation toxicologic data. The Subcommittees encourage ODW to perform even more of this work.
- The major problem in reviewing the health advisories was to understand the draft documents in relation to their intended audience(s). According to the Office of Drinking Water, there are multiple audiences with different skill and background levels, such as operating personnel of waterworks and public health officials. As

currently written, the health advisories have the appropriate format and content to satisfy the needs of persons with expertise in toxicology, such as health officials, but not operating personnel. Therefore, the Subcommittees advise that the health advisories not provide summary numerical tables, as indicated in the current drafts. Instead, they recommend that each health advisory contain a narrative summary, written in a style that can be understood by lay persons.

- There will be less of a problem with communicating with various audiences if the Office of Drinking Water adopts a three step process to document drinking water contaminants. This process includes developing Criteria Documents to support Agency regulations; preparing health advisories for public health authorities; and writing a narrative summary for operating personnel of waterworks. The major role for the Science Advisory Board within this process will be to review Criteria Documents and selected health advisories.

The Science Advisory Board appreciates the opportunity to review the health advisories. In behalf of the Board, we request that the Agency formally respond to the scientific advice contained in the attached reports.

Sincerely,

Richard Griesemer

Richard Griesemer
Chairman, Environmental Health Committee
Science Advisory Board

Norton Nelson

Norton Nelson
Chairman, Executive Committee

Review of 37 Office of Drinking Water Health Advisories

by the

Environmental Health Committee

of the

Science Advisory Board

- Metals Subcommittee: (SAB-EHC-87-004)
arsenic, barium, cadmium, chromium, cyanide, lead, mercury,
nickel, and nitrate/nitrite
- Halogenated Organics Subcommittee: (SAB-EHC-87-005)
carbon tetrachloride, chlorobenzene, dichlorobenzene,
1,2-dichloroethane, cis and trans 1,2-dichloroethylene,
1,1-dichloroethylene, dichloromethane, dichloropropane,
dioxin epichlorohydrin, hexachlorobenzene, polychlorinated
biphenyls, tetrachloroethylene, 1,1,2-trichloroethylene,
1,1,-trichloroethylene, and vinyl chloride.
- Drinking Water Subcommittee: (SAB-EHC-87-006)
acrylamide, benzene, p-dioxane, ethylbenzene, ethylene glycol,
hexane, legionella, methylethylketone, styrene, toluene,
and xylene

October 1986



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460
September 20, 1986

SAB-EHC-87-006

Dr. Richard A. Griesemer
Chair, Environmental Health Committee
Science Advisory Board [A-101]
U.S. Environmental Protection Agency
401 M Street, SW
Washington, DC 20460

OFFICE OF
THE ADMINISTRATION

Dear Dr. Griesemer:

On January 6-8, 1986 the Drinking Water Subcommittee of the Science Advisory Board's Environmental Health Committee publically reviewed eleven (11) draft health advisories for drinking water. Health advisories are described by the Office of Drinking Water as nonregulatory documents that are used to provide consistent, brief information to state and local health officials and personnel operating water works. During the review, the Subcommittee utilized Drinking Water Criteria Documents as support information for all of the health advisories except for p-dioxane, ethylene glycol, n-hexane and methyl ethyl hexane, for which the Subcommittee received copies of key papers from the scientific literature that support the calculations. The Subcommittee recommends that preparation of Criteria Documents for these four substances receive priority, because collections of key papers are not adequate support for the health advisories. Although the papers have the essential data, the bare facts are neither evaluated from EPA's perspective nor placed in logical context. EPA does not presently have source (or core) documents for these four substances.

The comments are divided into general advice, which is relevant to all of the advisories reviewed by the Drinking Water Subcommittee, followed by scientific advice specific to each of the substances reviewed. Because of the extensive nature of the 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,

Robert Tardiff, Ph.D.
Chair, Drinking Water Subcommittee

Herschel Griffin, M.D.
Vice-chair, Drinking Water Subcommittee

EPA NOTICE

This report has been written as a part of the activities of the Science Advisory Board, a public advisory group providing extramural scientific information and advice to the Administrator and other officials of the Environmental Protection Agency. The Board is structured to provide a balanced expert assessment of scientific matters related to problems facing the Agency. This report has not been reviewed for approval by the Agency, and hence the contents of this report do not necessarily represent the views and policies of the Environmental Protection Agency, nor does mention of trade names or commercial products constitute endorsement or recommendation for use.

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

A. THE OFFICE OF DRINKING WATER (ODW) NEEDS TO CONSIDER HOW HEALTH ADVISORIES WILL BE USED.

Several groups of people will use health advisories, including state and local health officials (physicians, toxicologists, and engineers), water purveyors, and the general public. A physician will need clinical information, such as which biological tests are the most sensitive, both in terms of monitoring exposure and determining any potential health effects. Of particular importance are potential developmental or reproductive effects, increased sensitivity of a specific subpopulation, such as the young, and potential dermal effects which may occur from bathing. Water purveyors will desire concise statements of risk and "bottom line" numerical guidance for specific situations they may encounter. In most situations, they will have to meet the goal of the the lowest concentration, if the water is used for ingestion purposes. The general public will want information in easy to understand language and will want to know if it is "safe." The most useful format for the health advisory will provide at least the minimum, most basic information for all of these groups.

As currently written, the health advisories are aimed primarily at practicing toxicologists because of their fairly complete summaries of scientific data. However, additional information should be provided on dermal and inhalation exposures, since the ingestion route can easily be eliminated for a short time period by substitution of an alternative water supply. Guidance on showering and bathing is essential.

B. THE ONE AND TEN DAY ADVISORIES SHOULD BE RELATED TO EACH OTHER ACCORDING TO A SCIENTIFIC RATIONALE.

The one and ten day advisories are of of limited use for providing guidance for ingestion exposures. Public water supplies do not have milligram per liter concentrations of organic chemicals unless a spill has occurred. In those cases, the water source or the distributed water will not be used for drinking purposes for a short period of time. Moreover, if the contamination has just been found, no one will know how long people have been exposed to it, or how much time will elapse before the contamination is removed. Therefore, the long-term advisory will most often be used.

There are many examples in which the peak short-term concentration value of a substance produces maximal effects (not the total amount). This situation exists for some developmental effects, for example. On that basis, doubts exist about the adequacy of dividing a ten day advisory into its component parts.

For some substances, insufficient data exist to generate a ten day health advisory. There is no evidence in the literature of a repeated dose study having been performed for several days duration. The use of the one day health advisory as a starting point is in itself not wrong. Dividing by ten assumes that either the substance, or its effect, are strictly cumulative, which is the case for only a few substances. The health advisory level is intended to protect against injury, but cumulative injury is not expected.

A health advisory level based on the peak concentration of exposure would depend upon the half-life of the compound. If data are available, elimination rate needs to be considered. If the half-life is very short, the factor of ten may be excessive, especially in view of the safety factor already built into the one day health advisory. If the half-life of the chemical is long, or if accumulation is known to occur, the use of a factor of ten could be warranted. However, it would be peculiar to generate a ten day health advisory level lower than the longer term health advisory, adjusting for the fact that the ten day for health advisory is set for a child and the longer term health advisory for an adult.

C. THE ROUTINE ASSUMPTION THAT TWENTY PERCENT OF TOTAL HUMAN EXPOSURE DERIVES FROM DRINKING WATER IS UNWARRANTED.

An explanation is needed to address the default assumption that drinking water contributes a certain fraction of total exposure, where no data are available for a specific substance. The Subcommittee understands that the Office of Drinking Water often has to develop health advisories with inadequate (or absent) information. However, the current default assumption of a twenty percent contribution is particularly inappropriate for children and infants, on whom the one day and ten day advisories are based. The body surface area to body weight ratio is markedly different between infants and adults. Skin thickness (and dermal exposure) also may differ significantly between children and adults.

The automatic use of a twenty percent contribution from drinking water sources appears to be arbitrary. Further confusion results when the assumption of a twenty percent contribution is applied in some cases and not in others. The health advisories provide no explanations for these exceptions or for the default cases. For those cases where data are available regarding the possibility of exposure in the general public, a contribution calculated from these data should be used. The resulting contribution might be either higher or lower than twenty percent.

The Office of Drinking Water needs to consider inhalation and dermal exposures as additional confounding factors. These exposures could result from the use of water for purposes other than drinking, such as showering or cooking. Even for these factors, there are data for many of the compounds reviewed in this set of health advisories. These data include volatility and inhalational toxicity results. In a few cases dermal absorption rates also may be known. For many of these compounds the toxicity via the dermal route is known. In many cases these data are available from material safety data sheets. There may also be data available on the irritant properties of these substances.

D. THE ASSUMPTION OF A TEN KILOGRAM CHILD FOR EXTRAPOLATION TO INFANTS REQUIRES SOME MODIFICATION.

Just as children may respond very differently from adults, infants can be found to react very differently from children. This is particularly important when one considers that pediatric practice is able to sustain and

achieve survival of increasingly younger premature infants. In many instances, these children carry out in the incubator the kinds of developmental events that are more characteristic of in utero life, and they can be markedly more sensitive to exogenous agents than postnatal individuals. The way to solve these latter two problems is simply to add a general warning to alert the unwary reader that a health advisory based on adults or children might not be directly extrapolatable to increasingly younger and immature individuals.

E. BIODEGRADATION INFORMATION NEEDS A GREATER EMPHASIS.

The health advisories, in general, have a paucity of biodegradation information, which might be among the more valuable knowledge for officials of municipalities in dealing with specific contamination situations. Efforts to obtain such information from the literature should be carefully pursued in each instance, and no usable data should be ignored. In some cases, the Subcommittee does not know whether such information exists, or if the health advisory preparation process does not facilitate its acquisition.

F. OCCURRENCE AND TOXICITY DATA SHOULD BE CONSIDERED TOGETHER.

Most chemical substances are utilized in industry for a variety of purposes and are produced in varying amounts. A good example is the case of ethyl benzene, for which there is no Criteria Document and limited data for the health advisory. Ethyl benzene is manufactured in the amount of approximately 3.3 million tons per year. As a screen for deciding when to develop health advisories and/or Criteria Documents, ODW should make some attempt to correlate the occurrence and usage data of a compound with its potential as a hazardous substance. ODW can subsequently assign priority to those chemicals which have high usage or occurrence data. The Subcommittee understands that this is a complex matter. For example, in the case of a synthetic intermediate, there is little chance of public exposure from routine use, but substantial exposures can occur after accidental releases.

G. SOME PHYSIOLOGICAL ENDPOINTS MERIT INCLUSION.

In considering the adverse effects produced by a substance, it is important not to dismiss toxicological effects as simply being physiologic changes.† In the draft health advisories, certain changes were reported that appeared to be physiological responses or adaptations. For example, in the case of xylenes, ultra-structural changes were observed in the liver, but were considered as toxicologically insignificant. In other cases, increases in cytochrome P-450 were considered to be a toxicological endpoint. Toxicologists have debated the significance of such changes for years without developing a scientific consensus. In some cases, increases in the toxicity (activation) of a compound are observed and, in other cases, a decrease in the toxicity (detoxification) occurs. The problem with the current set of health advisories is a lack of consistency. Office of Drinking Water staff should decide how to carry out the evaluation of such physiological changes, and should use this policy consistently in the health advisories.

† V.A. Newill, "Regulatory Decision-Making: The Scientist's Role," J. Wash. Acad. Sci., 64: 31-48, (1974).

H. PHARMACOKINETIC ANALYSIS IS IMPORTANT IN THE HEALTH ADVISORIES.

The Office of Drinking Water should attempt to provide pharmacokinetic data with the most recent references as well as the best references. Although the advisories generally compare animal data to human data and, in particular, where metabolites are thought to be responsible for toxicity, each advisory also should provide a careful assessment of the qualitative and quantitative differences. If different endpoints of toxicity exist in lower animals and humans, metabolic differences must be carefully considered. If the data base is sparse, this deficiency should be stated explicitly, at the beginning of the section in the health advisory.

I. THE ADVISORIES SHOULD NOTE ODOR THRESHOLDS.

Where odor and taste thresholds are lower than recommended levels, a note should be inserted in the health advisory to indicate that water potability or aesthetics may be an important consideration for field consideration, in addition to safety considerations. Each health advisory also should note where a particular substance present in the water is subject to sensory determination (odor, smell, color), or is determined analytically to be present and usually accompanied by other substances of equal or greater toxicity.

J. THE OFFICE OF DRINKING WATER SHOULD DEVELOP GUIDANCE, PERHAPS IN THE FORM OF AN ISSUE PAPER, ABOUT THE SELECTION OF DATA TO SET THE LEVEL OF AN ADVISORY.

Three subjects discussed by the Subcommittee relate to the concept of a hierarchy of data to be used in selecting studies for use in calculating advisory values. These include:

- Inconsistency in how no-observed-adverse-effect-levels were selected for different substances.
- Criteria to select pivotal studies.
- Use of information prepared by other organizations, such as the American Conference of Governmental Industrial Hygienists.

The Subcommittee recommends that a general and flexible hierarchy be formulated and followed consistently through the health advisory program. Specific points raised by the Subcommittee include:

- Advisories should be developed from data of appropriate exposure length and frequency. However, this should not lead one to calculate a "longer-term" or "lifetime" value substantially larger than a one day or ten day value.
- Oral exposure data should take preference over that from other routes, and drinking water studies are preferred over gavage studies. This is particularly true for gavage studies utilizing oil as a vehicle to attain large concentrations, and in particular where the vehicle alters absorption/pharmacokinetics.

- ODW states that the health advisories are based on the most-sensitive-observed-effects. It should characterize and state its views more clearly on the nature and significance of these effects. This decision will often be specific to the material for which the advisory is developed. For example, consideration of toxic effects from substances of similar structure or from studies of different duration may support selection of the "sensitive effect" as toxic.
- After it develops values for health advisories of different durations for a substance, the Office of Drinking Water should review the entire data base to determine the consistency of individual calculations with each other. A prior description of the underlying logic for which such decisions are made will be useful guidance for preparing advisories.
- For some materials, (e.g. benzene, hexane) there are human toxicity and/or exposure data by other than oral routes. These data may be considerable, involving a good estimate of body burden, and may provide additional data for a no-observed-adverse-effect-level or lowest-observed-adverse-effect-level evaluation. The Environmental Health Committee and its Subcommittees have consistently urged the Agency to take advantage of these kinds of "experience checks."
- The American Conference of Governmental Industrial Hygienists has been active for many years in the setting of Threshold Limit Values. Threshold Limit Value is a registered trade mark of American Conference of Governmental Industrial Hygienists (ACGIH). ACGIH frequently reevaluates these values and publishes the scientific basis of each one. They may be considered consensus values based on the best available published data. While there is some hesitancy to use the Threshold Limit Values because the route of exposure is frequently by inhalation, they often are based on human data. It would be interesting to determine how many of the health advisories cite the same references as those given for the Threshold Limit Values. The Office of Drinking Water might initiate a health advisory with this set of references for purposes of efficiency. The Threshold Limit Value documentation also frequently contains other useful pieces of information. For example, they may cite the lowest doses associated with mortality or other signs or symptoms of toxicity. In addition, they may contain information on irritancy and odor threshold.
- Where the Office of Drinking Water hesitates to use the human inhalation data from a Threshold Limit Value or chooses to use animal oral data, it might be useful to compare the two values. However, the Subcommittee is of a divided opinion regarding the desirability of such calculations. A value based on human inhalation data could be calculated by extrapolating from inhalation to oral route. The difference in safety factors for animals versus humans would also have to be considered, and Threshold Limit Values are established for eight hours per day exposure of healthy workers. Threshold Limit Values should be used only for non-route specific target organ effects. For example, it is not appropriate to set a drinking water value for a metal which causes fume fever when inhaled. Beyond this specific caveats, some members of the Subcommittee urge caution in extrapolating from human occupational inhalation standards to environmental standards for the general population

since the workplace standards often are developed from experience at existing occupational exposures. Thus, the Theshold Limit Values often have an empirical, tentative status and are subject to downward revision as more experience accumulates. In such a situation, comparison to an environmental standard mean to provide safety for the general population can be misleading.

K. THE PRESENCE OF CERTAIN COMPOUNDS IN DRINKING WATER CAN INDICATE THE PRESENCE OF OTHER SUBSTANCES FROM A COMMONLY OCCURRING MIXTURE.

Some of the compounds for which health advisories exist are most likely to be found as part of a mixture. Hexane will probably be found as a component of gasoline, and other components, such as benzene, toluene, xylenes, and ethyl benzene, also may be present. In this case, hexane serves as an indicator or sentinel substance. The health advisory for each of the components should mention this possibility and present some guidance as to how the presence of the total mixture should be evaluated. For example, in the health advisory for toluene, a note might be added that when toluene is found, the reader should also examine the monitoring data for the possible presence of other compounds found in gasoline. If found, the reader should review the health advisories for gasoline related substances, such as benzene, followed by a listing of the gasoline related substances for which advisories exist. The Office of Drinking Water should consider the development of a health advisory for gasoline.

L. THE EXPOSURE ANALYSES THAT SUPPORT HEALTH ADVISORY CALCULATIONS MERIT SOME MODIFICATION.

The health advisories only consider ingestion of two liters of water as the route of exposure. Drinking water contamination can also lead to inhalation and dermal exposure. The advisories should consider these two routes of exposure especially when they address high contaminant levels.

Exposure to contaminants in drinking water occurs not only through the two liters of water that ODW assumes a person drinks in one day. Exposure from drinking water also occurs through dermal absorption and through inhalation of volatile compounds. Because the average per capita use of domestic water approximates 120 liters, which is more than the two liters estimated in the health advisory for oral consumption, these other exposure routes are potentially significant on a mass balance basis. Moreover, if drinking water is obtained from contaminated ground water, the indoor air quality in homes above the ground water can be affected.

Human exposure to some of the compounds considered in the health advisories occurs not only through water but through the air, food, soil and dust. When deriving health advisory values, these other routes of exposure must be considered, and the entire Acceptable Daily Intake can not be allocated to drinking water. In most cases, exposure information will not be complete. Even though an estimate of the known exposure may be possible, ODW should make allowances to ensure that the Acceptable Daily Intake is not exceeded. Therefore, the health advisory should include information on whether or not the compound is absorbed through the skin and whether or not it is a skin irritant.

Users need the one and ten day health advisories to make decisions and provide information on whether or not the water is suitable for bathing and showering purposes since the ingestion route can be avoided for limited time periods by issuing a bottled water order. EPA should consider providing some advice on not using a contaminated raw water source when possible, especially if the contamination is the result of a spill and the source is not essential.

If substantial differences exist in the health effects of a substance when exposure occurs through inhalation rather than ingestion, the health advisory should indicate this difference. If the compound contributes to indoor air pollution, this information should be stated explicitly.

If a health advisory number derives from an acute or subacute effect, EPA should consider basing the number only on a child or infant, not an adult. If a study of chronic effects (lifetime study) drives the value of a health advisory, EPA should develop only the value for an adult.

M. ODW SHOULD IMPROVE THE EDITORIAL QUALITY AND CONSISTENCY OF THE DRAFT HEALTH ADVISORIES.

Overall, the Subcommittee found a high level of proofreading and citation errors. The health advisories did not describe the properties of the substances in a consistent manner, and factual matters, such as molecular weights, were misquoted with a high frequency. In addition, the Subcommittee has pointed out many errors in the calculations. The Subcommittee has not provided a comprehensive technical editing for the health advisories. Therefore, it recommends that the Office of Drinking Water provide for a thorough technical editing before it releases the final versions.

The Office of Drinking Water provided constructive comments on the use of health advisories by states and localities. Both the Subcommittee and EPA have concerns about potential misuse of the health advisories. For example, if the terminology regarding developmental effects is not articulated clearly, the health advisories will be counter-productive of embryonic well-being by tending to generate unwarranted elective abortions. The label "teratogen" refers more often to the dose at which exposure occurred in an animal study than to some intrinsic property of the chemical itself. The current practice tends not to emphasize selective effects on the conceptus. The Subcommittee recommends that the Office of Drinking Water use the terminology of "developmental toxicity" instead of "teratology." Teratology is but one of the four signs of developmental effects.

II. COMMENTS OF THE DRINKING WATER SUBCOMMITTEE ON HEALTH ADVISORIES FOR SPECIFIC SUBSTANCES

A. ACRYLAMIDE HEALTH ADVISORY

The Criteria Document is dated October, 1985, but it fails to include some relevant recent data, including key papers published in 1983. The health advisory, which closely reflects the contents of the Criteria Document, also lacks these references. They may not be important for calculating safe exposure levels but, because they relate to some of the more subtle effects and mechanisms of toxicity, they possess implications for the assessment of long-term adverse effects. To update the references, the Subcommittee recommends the use of some standard computerized literature retrieval service. The Subcommittee provided a printout to Office of Drinking Water staff as an example. The health advisory also has a large number of editorial and typographical errors. For example, the chemical structure of acrylamide is in error.

The Criteria Document for Acrylamide is not an integrative, critical review, but largely consists of a series of descriptions of individual studies. For this reason, it misses a significant aspect of the acrylamide literature: the consistent reports that, first, sensory systems are damaged before motor systems and, second, that detection of functional impairment (behavioral, electrophysiological, neurochemical) often precedes histological damage.

Both the Criteria Document and the health advisory do not adequately discuss the question of dose-duration relationships. They assert that evidence of acrylamide neuropathology is manifest after a cumulative dose of 100-150 mg/kg, but this conclusion is warranted only within a narrow range of dose rates. In some experiments, a single dose of 50 mg/kg to rats inhibited nerve terminal sprouting. This work was not reviewed in the health advisory. In contrast, a dose rate of 1 mg/kg·day induced clinical signs of neurotoxicity in monkeys only after 18 months of treatment and a presumed cumulative dose of about 400 mg/kg. Enough data are available in the literature to calculate a relationship between dose rate and toxicity.

The time dependency of acrylamide dose is deceptive. The pharmacokinetic half-life is between 2 to 5 hours, but metabolites last longer, and the toxic behavioral effects are inconsistent with the pharmacokinetics. One to two weeks after a 10 mg/kg dose in the cat, symptoms appear. At 1 mg/kg·day, symptoms appear after 18 months. Extrapolation based on pharmacokinetic analysis is unwarranted. The exposure calculations would be modified slightly by basing them on 1982 data indicating behavioral effects after a single dose of 10 mg/kg to rats. Collateral neurochemical data also yield the same dose level as at least a lowest-observed-adverse-effect-level. The description of absorption should reflect that acrylamide can be absorbed through unbroken skin as well as through mucous membranes and lungs.

The section on synonyms is incomplete. The Subcommittee recommends that the Office of Drinking Water use a standard source, and it has provided the

program with a printout from a standard commercial source. The section on uses also is incomplete. The health advisory could add data on solubilities in chloroform and benzene, since there is no available octanol/water partition coefficient.

In the short-term exposure section, the analysis should reflect that McCollister used female rats, male guinea pigs and rabbits of both sexes. Pryor reported an acute LD₅₀ of 203 mg/kg and subchronic values of (5 days/week/4weeks) LD₅₀ of 32 mg/kg and subchronic (5 days/week/15weeks) LD₅₀ of 17 mg/kg. In the longer-term exposure section, the advisory should provide a reference for the value cited in the first section, and move the second, fourth and sixth sections to the section on short-term exposure to reflect the dosing. McCollister reported additional no-observed-adverse-effect-level data for rats, cats and monkeys that are not reflected in the health advisory. The drinking water equivalent level calculation should be based on 0.0002 mg/kg·day instead of 0.002 mg/kg·day. There is an error in the calculation. The EPA standard given in the Criteria Document is 0.05%, not 0.05 ug/L.

B. BENZENE HEALTH ADVISORY

The benzene health advisory effectively organizes data from diverse sources and places them into perspective. However, the status of the Criteria Document is not clear, and it differs in places with the health advisory. The Criteria Document appears to be a preliminary draft because of the inconsistent styles between each section and because the logic wanders. The two documents also are inconsistent. For example, the Criteria Document does not mention ground water in extent or significance, but the health advisory states that benzene is released to the ground, binds somewhat to the soil, slowly migrates to ground water and remains stable there.

Several synonyms often are confused with benzene, such as benzin or benzol, and they merit inclusion. Where information exists on mixtures containing benzene, the health advisory should use it. For example, the Criteria Document mentions that the simultaneous treatment with both benzene and toluene or piperonyl butoxide increases the excretion of benzene in breath. The odor threshold for benzene is of considerable importance. No mention is made of the metabolites of benzene, which include phenol, catechol and hydroxyquinone.

The preponderant scientific evidence suggests that benzene is metabolized through formation of an epoxide, which contrasts with the inconclusive statement in the health advisory that different metabolic pathways are involved. For risk assessment, it is important to note that 47% of benzene inhaled was absorbed, 30% retained and 16% exhaled unchanged, when exposed to 52-62 ppm for 4 hours, and was the same for both sexes. Benzene absorbed from ingested drinking water or inhaled from drinking water sources will be subject to these pathways. More detailed information on dermal absorption is needed. The Criteria Document also mentions three elimination phases for humans versus the biphasic results described elsewhere. This discrepancy should be resolved.

Neither the study by Dosken nor that by Chang states that the lowest level of benzene to produce platelet effects in workers was 10 ppm, which represents a modelled result. The description of short-term health studies by Wolfe and coworkers should include a description of duration of exposure.

The description of the Occupational Safety and Health Administration standard as 3.2 microgram/L is in error. The standard is 32 milligrams/M³.

C. DIOXANE HEALTH ADVISORY

The health advisory for 1,4-dioxane constitutes a useful document, but some errors merit correction. The range of dioxane concentrations found in drinking water needs to include a perspective on these data based on the hazard information in the health advisory. The Subcommittee suggests that the health advisory point out that 1,4-dioxane is a synthetic organic compound with no known natural sources. Dioxane is mixable with water at all concentrations, and it may be that its mobility in soil is directly proportional to water passage through the soil.

Given the importance of biodegradation and/or spontaneous degradation information, the Subcommittee recommends a further search of the literature. The current review appears out of date. Degradation by chlorination, which will occur in many drinking water supplies, results in products which are more toxic than the parent compound. The fact that the test material may become chlorinated and thereby become markedly more toxic than the parent compound is not a valid basis for not determining a health advisory. The fact of potential chlorination, with or without altered molar toxicity, is relevant, however, to other aspects of an health advisory, i.e., other criteria, guidance and standards. Since this detail is reported in the longer-term health advisory section, many operating personnel may miss it.

The health advisory for dioxane assumes one hundred percent absorption from the gut. The Subcommittee recommends the addition of a discussion about the cutaneous and pulmonary routes as well.

Covalent binding of 1,4-dioxane was higher in the nuclear fraction than in other cell fractions. The Subcommittee suggests adding a perspective on the extent or absence of covalent binding with DNA and its implications.

Metabolism of dioxane is dose-dependent and saturable. The relevant data are cited but not interpreted. The first sentence of the excretion section speaks of "animals," but if reports from species other than the rat exist, they should be reported. The rate, as well as the form of excretion, constitutes important information.

The health advisory cites the 1979 National Institute of Occupational Safety and Health Registry to provide the oral LD₅₀ values in several species. Some of the references of the Registry also report effects at lower doses and, if these were reported, one would have information significantly more useful than isolated LD₅₀ values. The discussion of acute pathology is very limited, and there may be additional published target organ toxicity information available. The description of the work of Fairley and coworkers with rabbits is difficult to understand. It merits not only rewriting but also expansion. Overall, the slopes of dose-response curves should be given, where possible.

The nature of the tumors reported in the study of Kociba and coworkers merits discussion.

Several studies in chickens may be useful in evaluating the developmental aspects of 1,4-dioxane. A mouse study of some utility existst. There are numerous examples of solvents that represent significant hazards to reproduction. Structure activity relationships for reproductive (but not developmental) effects also are possible in some limited instances, such as alkylating agents and some classes of hormones. This information merits a renewed literature search for relevant data.

Several reports of in vitro mutagenicity tests of 1,4-dioxane occur in the literature that are not cited in the health advisory, and the Subcommittee recommends further searching for similar studies.

The relevance of the calculation of no-observed-adverse-effect levels for a substance with carcinogenic potential, such as dioxane, merits discussion in addition to the retrospective predictive ability of the formula presented. The use of body weight is an essential component of such calculations, but they fail to account for the marked differences among individuals based on age alone. The consumers who take in the largest relative volume of liquid are infants. Awareness of this factor could be one of the qualifiers applied to this calculation. The dangers of extending the mg/kg calculation to the newborn or prematurely delivered infant merits mention. How was the safety factor of 100 for "animal data" arrived at? Retrospectively, how proper has it proven?

With respect to the one day advisory, it is difficult to consider how intravenous dose groups of one animal, each with effects seen in the animal treated at the lowest dose, leads to a useful lowest-observed-adverse-effect-level without carefully reviewing supporting data. However, such an extended rationale is not available in the health advisory. The extrapolation needs a discussion (or citation for a supporting explanation) of its range of limitations. The Subcommittee prefers the use of an acute oral toxicity study to an intravenous study, given the scant knowledge of pharmacokinetics of dioxane.

The fact that an acceptable study for calculating a ten-day health advisory was not located does not justify dividing the one-day health advisory by ten. There are instances where it is not the area under the curve that is proportional to response, but instead the peak level attained that exceeds a threshold of response.

The absence of acceptable data to set a short-term standard and the possibility of enhanced toxicity after biodegradation do not constitute valid reasons to set aside the development of a longer-term health advisory. In other advisories, the Office of Drinking Water has developed longer term health advisories for substances with carcinogenic potential, and some consistency is needed. The data of Kociba and coworkers will support the development of both longer term and lifetime health advisories.

The Subcommittee suggests further literature searches on the topics of movement in ground water and other water degradation, biologic half-time and perhaps bioaccumulation potential.

A degree of value judgment and/or guidance is merited in the analysis section. The paragraph offered is not meaningful in guiding the reader to the appropriate technique.

† See Toxicology letters 12: 191-198 (1982).

D. ETHYLBENZENE HEALTH ADVISORY

With the exceptions noted below, the health advisory is consistent with information presented in the Drinking Water Criteria Document for Ethylbenzene. Overall, acceptable daily intake calculations are consistent with guidance provided in the issue papers for such calculations.

The health advisory should include "tobacco smoke constituent" as a source of exposure to ethylbenzene since this source results in the highest exposure amounts in ambient air. Similarly, motor vehicle exhaust may reasonably be expected to result in exposure.

The pharmacokinetics section needs modification. The Criteria Document should include several important references† published in 1984 that provide new information on the metabolism and excretion of ethylbenzene in rats.

The uncertainty in human health effects reported at 100 ppm is not properly presented. The report of Bardodej and Bardodejova states that the total number of volunteers was 18. The authors report that exposure to 100 ppm caused no ill effects. Duration of exposure was not specified in the Criteria Document, but an increase in exposure resulted in reported symptoms of sleepiness, fatigue, headache and mild eye and respiratory irritation. The authors did not report the increase in exposure that caused these symptoms.

This report does not attain the same quality as information considered in establishing and maintaining the present American Conference of Governmental Industrial Hygienists Threshold Limit Value of 100 ppm. Most available information indicates that 100 ppm-8 hour exposure represents a no-adverse-effect-level, not an effect level.

The mutagenicity section needs improvement because the health advisory fails to cite the work of Dean and coworkers* which reports that ethylbenzene is not mutagenic in Salmonella typhimurium, E.coli, S. cerevisiae and in the recessive lethal chromosome assay in Drosophila.

The National Cancer Institute has not yet initiated a bioassay for carcinogenicity of ethylbenzene. Activity is at the design committee stage.

No rationale exists to support the establishment of a ten day health advisory value through the procedure of dividing the one day value by ten, when ethyl benzene (1) appears to have a threshold, and (2) seems to be rapidly metabolized and cleared from the body. A consortium of ethylbenzene producers is currently conducting 28-day inhalation probe studies in mice, rats and rabbits. These studies should provide better data for calculating short-term health advisories.

No data are presented to support the conclusions about treatment of water.

† K. Engstrom, "Urinalysis of Minor Metabolites of Ethylbenzene and m-Xylene," Scan. J. Work. Env. Health 10: 75-81 (1984); K. Engstrom, "The Metabolism of Inhaled Ethylbenzene in Rats," Scan. J. Work. Env. Health 10: 83-87 (1984); K. Engstrom and Coworders, Int. Arch. Occup. Env. Health 54: 355-363 (1984).

* B.J. Dean and Coworkers, "Genetic Toxicology Testing of 41 Industrial Chemicals," Mutation Research 153: 57-77 (1985).

E. ETHYLENE GLYCOL HEALTH ADVISORY

No Drinking Water Criteria Document is available for ethylene glycol. The health advisory derives from a number of key references and, in general, adequately reflects the contents of the journal articles cited. The studies by Mason are correctly transcribed, but it is not clear how thoroughly the pathology portion of the study was conducted, other than the tumor counts. For example, what is meant by selected tissues? How carefully were the kidneys examined?

The only study reported under the section of developmental and reproductive effects is that of Elis and Raskova. However, their report lacks experimental detail.

The study by Blood and coworkers represents a key reference and is used in the calculation of the longer-term health advisory. This study used only three monkeys, and the experimental details in the report are sketchy. Another study which EPA should consider is that of Roberts and Seibold which also studied monkeys at various doses although for shorter periods of time.¹ This study found kidney damage in the absence of calcium oxalate crystals which required a dose of 15 ml/kg or greater for formation.

The study of Laug and coworkers adequately describes the acute effects in a variety of animals, but the study by Reif is questionable. It does not constitute a well controlled study but merely reported observations on one individual. More information on humans is available, including a number of studies in the literature on the toxicity of ethylene glycol. These studies are addressed in reviews and texts.² Also, studies of individual cases have demonstrated a wide range of sensitivity among humans to the toxic effects of ethylene glycol. The paper by Reif may not be adequate to estimate percentages of metabolites. Ethylene glycol elimination is a very dose dependent process which has been documented well in animal studies, such as those by Marshall.³ Dose dependency of elimination works strongly against the use of high doses to make estimates on long term, low level exposures.

EPA should review a number of other multiple dose studies in animals, such as that of Rajagopal and Ramakrishnan,⁴ which also list other

¹ J.A. Roberts and H.R. Seibold, "Ethylene Glycol Toxicity in the Monkey," Toxicology and Applied Pharmacology, 15: 624-631 (1969).

² See, for example, Haddan and Winchester, Clinical Management of Poisoning and Drug Overdose; R.W. Moriarty and R.H. McDonald, "The Spectrum of Ethylene Glycol Poisoning. Clinical Toxicology," 7: 583-596 (1974); C.D. Peterson and Coworkers, "Ethylene Glycol Poisoning: Pharmacokinetics during Therapy with Ethanol and Hemodialysis," New England Journal of Medicine 304: 21-23 (1981).

³ T.C. Marshall, "Dose-dependent Disposition of Ethylene Glycol in the Rat After Intravenous Administration," Journal of Toxicology and Environmental Health 10: 397-409 (1982).

⁴ G. Rajagopal and S. Ramakrishnan, "Effect of Ethylene Glycol Toxicity on Hepatic Carbohydrate Metabolism in Rats," Toxicology and Applied Pharmacology 46: 507-515 (1978).

relevant references. The study by Gessner and coworkers on metabolism and the study of Marshall also are germane.

Another important factor is the literature base used to develop the Threshold Limit Value by the American Conference of Governmental Industrial Hygienists. Although many of the data relate to studies conducted by using the inhalation route, there are a number of good studies referenced.

In summary, the Health Advisory on ethylene glycol represents a reasonable distillation of the references used. However, it suffers from the omission of useful data generated in the last decade and underestimates what is already known about the toxicity of this compound in humans. In addition, recent incidents will generate new data on human exposure by ingestion.

F. n-HEXANE HEALTH ADVISORY

Since no Drinking Water Criteria Document for n-hexane exists, the health advisory is based on a collection of supporting papers. The health advisory omits recent references dealing with metabolism and toxicity, especially with the agents responsible for toxicity. It also lacks some papers dealing with toxicity and mechanisms.

The 1290 mg/kg dose used as the basis of most calculations is difficult to justify. With a substance producing an irreversible toxicity it is necessary to understand the mechanism, the metabolite responsible and the rate at which humans might be expected to produce the metabolite. If this kind of explanation cannot be provided for n-hexane, EPA should explore this issue and provide a rationale for the method through which it calculates the safety levels.

In the study by Heshkowitz and coworkers, the exposures averaged 650 ppm with peaks up to 1,300 ppm, instead of ranging between these two levels. In the study by Krasavage and coworkers, it is not clear that the 1,140 mg/kg dose was administered for 120 days. The paper could be interpreted as indicating that the 1,140 mg/kg dose was given for 90 days. ODW should re-evaluate if the dose of n-hexane in the study by DiVincenzo and coworkers may be 250 mg/kg and not 450 mg/kg.

Nerve conduction velocities may be one of the more sensitive indicators of impairment by n-hexane. The experiments used to calculate the health advisories were not based on these endpoints, nor was this mentioned in the health advisory.

The health advisory mentions furan and valerolactone derivatives as metabolites of n-hexane. In discussing metabolites of methyl n-butyl ketone, DiVincenzo and coworkers indicate that a furan derivative may be formed in the gas chromatograph and may not actually be a metabolite of methyl n-butyl ketone. The same artifact may occur with n-hexane and its cyclic derivatives. The level of 2-hexanol referred to in the excretion section should be 0.5 mg/liter and not 0.05 mg/liter. The hexane used was commercial hexane and not pure n-hexane. The study by Bus and coworkers shows that n-hexane and its metabolites reach the fetus. The reproductive section should state this conclusion.

The Subcommittee suggests that, given the amount of information available about human industrial exposures and abuse, the advisory could base the calculations directly on the human data. The drinking water issue paper by Khanna, which discusses the conversion of inhalation data into drinking water standards, provides one means of doing so. Also, it would be useful to apply such a technique to the Threshold Limit Value. At a minimum, a calculation based on human data can compare with the current calculation as an "experience check." Information on respiratory uptake and retention of hexane also would be useful, if EPA extrapolates between the oral and inhalation route. Inhalation experiments indicate that continual exposure may be more toxic than intermittent exposure. In addition, Perbellini and coworkers suggest that humans may be more susceptible to n-hexane than experimental animals based on the different

ratios of metabolites among the species. The advisory should address these possibilities as part of the experience check.

EPA should incorporate into the health advisory the issue of the toxicity of mixtures of which n-hexane is a constituent. The paper referred to in the health advisory reports that the hepatotoxicity of chloroform is greatly enhanced when simultaneous exposure to n-hexane occurs. Water supplies are unlikely to be contaminated with only n-hexane, and the health advisory indicates that the major source of hexane in the environment will be gasoline. However, the health advisory does not mention how this should be factored into the use of the values given.

Since other gasoline components will accompany n-hexane contamination most of the time, additional guidance on how the health advisories should be altered for the complex mixture would prove valuable. It may be worthwhile to note that some gasoline components have been associated with carcinogenic effects and that gasoline itself is probably is carcinogenic for humans. Office of Drinking Water staff should consider whether it may be a better strategy to issue a health advisory for gasoline, rather than deal with possible problems in a piecemeal fashion.

For a volatile substance like n-hexane, the greatest need for the one- and ten-day advisories will be to provide guidance as to whether or not the water can be used for bathing and to provide information on the adverse impact on indoor air quality. The exposure scenarios only use ingestion as the route of exposure, which can easily be eliminated by issuing an advisory against the use of the contaminated water source for drinking and cooking purposes, or in the case of the one-day advisory, not using the contaminated raw water source and using stored water. Information on whether or not hexane is absorbed dermally would provide some indication of the potential for exposure while bathing.

The Subcommittee suggests some additional references as a basis to initiate revision of the health advisory:

Baker and Rickert, "Dose-dependent uptake, distribution and elimination of inhaled n-hexane in the Fischer-344 rat," Toxicology and Applied Pharmacology, 61: 414-422 (1981).

T.A. Marks, et al, "Influence of n-hexane on embryo and fetal development in mice," Drug and Chemical Toxicology 3: 393-406 (1980).

Raje, "In vitro toxicity of n-hexane and 2,5-hexanedione using isolated perfused rabbit heart," J. Tox. and Env. Health 11: 879-884 (1983).

Lungarella et al, "Respiratory tract lesions induced in rabbits by short-term exposure to n-hexane," Res. Comm. in Chem. Path. and Pharm. 29: 129-139 (1980).

Kronevi et al., "Histopathology of skin, liver, and kidney after epicutaneous administration of five industrial solvents to guinea pigs," Env. Res. 19: 56-69 (1979).

Jakobson et al., "Uptake via the blood and elimination of 10 organic solvents following epicutaneous exposure of anesthetized guinea pigs," Tox. and App. Pharm. 63: 181-187 (1982).

Howd et al, "Relation between schedules of exposure to hexane and plasma levels of 2,5-hexanedione," Neurobehavioral Tox. and Teratology, 4: 87-91 (1982).

Couri and Milks, "Toxicity and metabolism of the neurotoxic hexacarbons n-hexane, 2-hexanone, and 2,5-hexanedione," Ann. Rev. Pharmacol. Toxicol. 22: 145-166 (1982).

Calvender et al, "A 13-week vapor inhalation study of n-hexane in rate with emphasis on neurotoxic effects," Fund. and App. Tox. 4: 191-201 (1984).

Bravaccio and Ammendola, "H-reflex behavior in glue (n-hexane) neuropathy." Clinical Tox. 18: 1369-1375 (1981).

Graham et al, Tox. Appl. Pharm. 64: 415-422 (1982).

G. LEGIONELLA HEALTH ADVISORY

The Subcommittee questions the classification of potential bacterial pathogens in water as toxic substances on the basis that bacterial cells are complex, dynamic entities, capable of replication. Placing them into the same group as toxic substances may not be appropriate.

The format of the health advisory for Legionella differs from that of the chemical substances, perhaps in recognition of the incongruence. However, EPA should articulate the rationale for the difference, and the Subcommittee recommends that the emphasis of the final health advisory be placed on surveillance of respiratory illness, not drinking water.

Twenty-three recognized species of Legionella exist, twelve of which have been implicated by culture techniques as sources of pneumonia. One species, L. pneumophila, causes approximately 85% of these cases. With only one exception (L. feeleii), L. pneumophila has been implicated as an agent for Pontiac Fever, although no isolates of legionellae have been obtained from patients with Pontiac Fever. Thus, grouping all legionellae as pathogens with equivalent virulence cannot be justified at this time.

Most public health officials would agree that an advisory on legionellae is needed at this time, because of numerous inquiries by the public, especially engineering personnel and health officials given the responsibility of taking appropriate measures to prevent the spread of Legionella from water in their facility. However, the advisory should emphasize that epidemics and sporadic cases should be dealt with on a case-by-case basis. The beginning of the advisory should state the following: (1) The source for the spread of legionellosis or Pontiac Fever should be determined epidemiologically before intervention. It does not make sense to attempt widespread eradication of mostly nonpathogenic organisms, when the pathogenic strain can be traced. (2) Environmental strains implicated as a cause of disease should be matched with patient isolates. (3) Routine monitoring of water for Legionella is not recommended. (4) There is no all encompassing disinfection procedure that can be recommended each time.

Although the health advisory is not legally enforceable, the Subcommittee understands that it will be accepted by some workers as policy for installation and maintenance of plumbing systems. The guidance in the health advisory focuses on how to deal with a problem once it is recognized, rather than how to decide when one has a problem. The Subcommittee recommends the following sequence of investigation as more appropriate:

- Given the impossible task of eradicating legionella, legionellosis appears selective for high risk individuals. The attention of clinical and public health workers should focus initially on surveillance for respiratory illness, especially in high risk patients. If an increase is detected, they should attempt to establish the etiology, not by culturing the water but by culturing the patients and by performing serologic studies. Microbiological analysis of clinical specimens is as rapid as culture of environmental specimens, and preliminary information can be gleaned from acute-phase serological specimens.

- If Legionella is implicated in an outbreak of clinical illness, public health officials should attempt to culture environmental sources. They may undertake temporary measures designed to control environmental legionellae, while using modern molecular techniques to determine if the source has, in fact, been identified correctly. If all the data suggest a clinical problem, and that it is probably associated with a particular environmental source, continuing effort should be directed at that source because past experience suggests that the problem may recur.

- Maintenance of decontamination procedures should occur in a way to minimize danger to individuals and damage to the plumbing systems. A careful program of microbiologic monitoring of the environment and clinical monitoring of human disease represents an integral part of that program because it cannot be assumed that the problem has been controlled indefinitely. A focus on a few problem sites makes much more sense than a dilution of effort by attacking all potable water systems. When dilution of effort occurs, the likely result is that none of the sites is treated optimally.

- The Subcommittee also has several technical corrections to improve the accuracy of the final health advisory, as follows:

- The importance of matching the patient isolate with the environmental isolate from a source implicated by epidemiologic data should be discussed in more detail. Also, grouping and characterization of L. pneumophila strains by isoenzyme profiles may be more definitive than monoclonal subgrouping.†

- The contamination of a water system by new distribution components is not well documented.

- Since legionellae can reside in cold water pipes, disinfection of a plumbing system by heat treatment alone is not as effective as the combination of heat treatment and chlorination. Chlorination without heat treatment has been effective in several cases. Growth of legionellae may theoretically be enhanced on the cold water side of a hot-cold water mixing valve in a heat-treated plumbing system.

- Since the overall cost of using heat for disinfection is greater when considering all of the costs such as personnel time to monitor heat treatment, cost of the heating, costs for precautionary measures taken against scalding, and the cost of periodic treatments, this factor should be discussed when comparing the advantages and disadvantages of chlorination versus heating.

- The health advisory should state that ozone, ultraviolet, and ethylene oxide methods for disinfection of legionellae have not proven effective in field tests. The advisory should note the difficulties of controlling manual batch chlorination and the availability of devices that continually monitor and adjust chlorine levels.

- Information on the specific types of gaskets and fittings that support the colonization of legionellae is not well documented. More research is needed to confirm published reports, and make recommendations on acceptable materials.

† R.K.Selander and Coworkers, "Genetic Structure of Populations of Legionella pneumophila," J. Bacteriol. 163: 1021-1037 (1985).

H. METHYL ETHYL KETONE HEALTH ADVISORY

The Office of Drinking Water has not prepared a Criteria Document for methyl ethyl ketone. Instead, it included key references for calculating the health advisory values. Although the data base for methyl ethyl ketone is meager, it appears adequate for the purpose of calculating these values. The evaluation of the literature is reasonable, and the values correct, except that the lack of a ten day advisory is inconsistent with the use of subchronic data.

Similar to the situation with n-hexane, the mixtures problem needs to be addressed especially since methyl ethyl ketone enhances the neurotoxicity of n-hexane. That combination is suspected as responsible for the outbreak of neuropathies among substance abusers in West Berlin who, until the addition of methyl ethyl ketone, seemed to suffer relatively mild toxicity.

Although the advisory makes statements concerning the dermal absorption and the quantitative nature of certain metabolites, the Subcommittee is not aware of adequate studies dealing with distribution and metabolism. The lack of adequate studies merits greater emphasis and should precede the paragraphs on absorption and metabolism.

I. STYRENE HEALTH ADVISORY

The health advisory has addressed the major scientific issues in the Criteria Document on Styrene. Except as noted below and in the general comments sections, it has appropriately summarized and drawn sound conclusions.

The styrene health advisory notes that experiments in humans support the use of no-observed-effect-levels based on central nervous system effects. The one-day exposure level, however, derives from a study that relied on hepatotoxic endpoints. It also seems inconsistent that the longer term acceptable daily intake is equivalent to the 10-day health advisory for a child and quite close to the one-day health advisory. The health advisory should offer some explicit cautions.

In the section on distribution, the radioactivity detected was styrene or its metabolites. The health advisory should also specify where in the molecule the ¹⁴C label was located.

In the section on transplacental transfer, the measurement of transferred styrene was made on cord blood. This does not imply a one-way transfer but rather a selective concentration on the fetal side of the placenta. This could be the result of an equilibrium in a two-way transfer situation.

ODW should expand the section on metabolism to include a more extensive treatment of styrene oxide, which is a highly reactive chemical, a carcinogen and a mutagen. It would be valuable to know what percentage of styrene gets metabolized to styrene oxide and how this might vary from organ to organ. The effect of dose on metabolism should also be described. Many studies on mercapturic acid formation have not been included.

In the developmental and reproductive effects section, the advisory should comment that the doses studied were 300 mg/kg·day or less, and that these were comparatively low doses. Effects are possible at higher doses. Perhaps it would suffice to add a parenthetical statement at the end of the paragraph noting comments on the comparatively low doses. The dose of styrene oxide should be specified and noted as a source of concern. In the Finnish study the control incidence was 8% and the exposed 15%. The control incidence is the unusual finding, since in many comparable studies, it is 15%.

Considerably more evidence about the mutagenicity of styrene oxide exists than is described in the health advisory. It would be valuable to add information about mutagenicity in other systems including mammalian cells. Activity as measured with a number of other endpoints, which are not necessarily mutagenic but related, might also be noted, such as sister chromatid exchanges, chromosomal abnormalities, and so forth.

The data regarding the carcinogenicity of styrene is complicated and deserves somewhat more discussion in this section. The statement about excessive mortality suggests that the study by Ponmarkov and Tomatis was done poorly. Instead, there were many early deaths related to treatment

in this study, and among the animals dying early there were an excess of lung tumors including a disproportionate share of malignant tumors. More discussion of these issues is warranted. The advisory should also include some information about the carcinogenicity of styrene oxide, since it is a major metabolite and an active chemical which could relate to the possible carcinogenicity of styrene.

In the one-day Health Advisory, the data cited is from the article by Das and coworkers, not Srivastava and coworkers. Some explanation is also needed to justify using the study by Das in preference to that of Agarwal, which showed effects on dopamine receptors at 200 mg/kg/day.

ODW should extend the paragraph on the assessment of carcinogenic activity to provide a clearer explanation of why it chose this study and selected lung tumors for the evaluation. Because of the complexity of the data in this study, it is important for ODW to provide a more explicit description of how it used the data and factored early deaths with tumors into the estimate.

The last section concerns the possible biodegradation of styrene by oxidation. Since styrene oxide is a possible oxidation product and an active chemical, it should be considered here. Will styrene oxide be formed by this process? If so, what is the stability of styrene oxide in water, particularly at the range of pH of water coming from treatment plants. It is most important that the efforts to reduce the concentration of detectable styrene not be achieved by the generation of a different, but more active and more hazardous byproduct.

As noted in the discussion of n-hexane, styrene is a component of gasoline and some discussion of its presence as part of a mixture should be included.

A large number of typographical and editorial errors occur in the health advisory. For example, the melting point for styrene is -30.6°C , while the value of 145°C is the boiling point. The density listed is incorrect. The statement about pulmonary absorption should be reworded to avoid the impression that the lungs were removed to measure retentions as might happen in studies of animals.

J. TOLUENE HEALTH ADVISORY

The toluene health advisory has a high level of typographical and editorial errors. For example, it incorrectly states the molecular formula. The reference dose calculation appears to have a hundred-fold error (stated as 28.8 mg/kg·day but calculated as 0.288 mg/kg·day). The health advisory states an LD₅₀ for toluene that is ten-fold higher than that described in the Criteria Document.

The health advisory should refer to synonyms of methacide and methylbenzol.

The Office of Drinking Water should refer to the Agency's Health Assessment Document for Toluene for information on uses. The Criteria Document lacks any information on this subject, and the three uses cited in the health advisory, while correct, omit other significant uses. Similarly, the Criteria Document lacks information on occurrence, while the health advisory does not cite the sources of information on occurrence.

In the section on pharmacokinetics, the health advisory has correctly referred to information from the 1974 paper of Nomiyama and Nomiyama, but a number of inconsistencies occur with the Criteria Document, which misquotes the data from this source.

The health advisory and the Criteria Document differ with respect to sources of toluene exposure. The health advisory refers to intentional abuse plus laboratory and occupational settings as the usual sources of exposure, whereas the Criteria Document cites drinking water, food, ambient air occupational settings and consumers products as sources of exposure to toluene.

The health advisory should briefly describe what is known about the mechanism of toxicity. The Subcommittee recommends that the health advisory provide a clearer statement of the human health effects of toluene. The health advisory refers to effects on the liver at 200 to 800 ppm, whereas the Criteria Document cites hematological effects associated with benzene contamination of toluene.

The data base is not up-to-date and should be compared against a standard reference data base.

K. XYLENES HEALTH ADVISORY (ORTHO-XYLENE, META-XYLENE AND PARA-XYLENE)

The health advisory for xylenes generally follows the Criteria Document for these compounds. The studies selected for establishing the known effects and for the calculations appear appropriate. For the health advisory on xylenes, the allowable exposures are based primarily on gross toxicity rather than the primary central nervous system effects. This may be necessary for the calculations, but the reader should be warned. The Subcommittee understands the difficulty created by the lack of oral administration data in the published literature.

While the health advisory correctly cites the amounts of xylene found in water, it does not recognize that other studies have occasionally found higher concentrations. An additional problem stems from the fact that values in the health advisory for the physical characteristics of the xylenes do not agree with those in the Criteria Document, notably the solubilities and the octanol/water partition coefficients. This appears to result from the use in the health advisory of an older version of the reference for these values (Verschueren).

A greater emphasis in the health advisory on metabolic profile studies actually conducted in humans would be more appropriate. These include work by Ogata, Riihiachi and Sedivec and Flek. The health advisory cites the latter in a different context. The health advisory may have used older references that are not adequately updated, but the Criteria Document has more recent data.

The health advisory may underestimate the possibility of effects on the liver. The studies by Tetrai and Ungvary cited in the Criteria Document suggest that this may be a sensitive target organ. The studies of Morley support this view, albeit in humans high levels of exposure were encountered. The epidemiological studies are equivocal. In this regard, EPA should consider the numerous studies on the capacity of these agents to induce drug metabolism.

The advisory acknowledges the study of Bowers and coworkers but dismisses it from consideration as the basis for the calculation. However, if material were lost by evaporation in this study, it would tend to underestimate the toxicity of the xylenes, not overestimate it. Furthermore, the lack of examination of other tissues is a moot point since positive effects were observed in the liver. The Criteria Document is not much help on this point since it tends to argue somewhat teleologically that the ultrastructural changes observed were adaptive in nature. However, one could also argue that the significance of these changes observed by electron but not by light microscopy is unknown.

The section on teratology is overly brief considering the number of available studies. The Criteria Document tends to emphasize that pregnant women may represent a sensitive population, but the health advisory does not address this issue fully. This lack of concern may be justified in view of the recent review of the complete literature commissioned by EPA, which reviewed the various studies from the perspective of dose and concluded that xylenes may be embryotoxic and maternally toxic but only at high doses.*

The study by Jenkins is hard to reconcile with that of Carpenter. In the Jenkins study, rats died at 3,358 mg/M³, so it is difficult for the Subcommittee to accept Carpenter's no-observed-effect-levels of 2,000 and 3,500 mg/M³.

The lack of a ten day health advisory conflicts with the position in the Criteria Document. Both the health advisory and the Criteria Document make the calculations using the same formula and data from the same study. Both documents arrive at the same values. However, the Criteria Document describes this calculation as a ten-day advisory, whereas the health advisory uses it as a long-term (not lifetime) advisory, which a water works official might use as a temporary ten-day advisory.

The calculations assume that 20% of human exposure to xylene arises from drinking water. This assumption is not supported by the data presented in the Criteria Document that demonstrates that only a very small amount (0.1 to 3.9 ug/kg/day) would be expected from air with essentially no intake from food. Thus, the inclusion of this factor is highly questionable.

The calculations of values for advisories should use the minute volume for the species from which the effect level is derived. Staff can then extrapolate the effect level for this species to humans.

Xylene is a component of gasoline and should be evaluated as part of this mixture, as discussed above in the comments on n-hexane.

* R.D. HOOD and M.S. OTTLEY, "Developmental Effects Associated with Exposure to Xylene: A Review," Drug and Chemical Toxicology. 8: 281-297 (1985).

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COMMENTS SUBMITTED TO THE DRINKING WATER SUBCOMMITTEE
BY THE PUBLIC REGARDING THE SCIENCE ADVISORY BOARD'S
REVIEW OF DRAFT DRINKING WATER HEALTH ADVISORIES

National Audubon Society

Contact: Chuck Pace

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

Date: December 24, 1985

Chemical Manufacturers Assoc.

Contact: Geraldine V. Cox

2501 M Street, N.W.
Washington, D.C. 20037

Date: December 26, 1986

Natural Resources Defense
Council Inc.

Contact: Robin Whyatt
Wendy Gordan

122 East 42nd Street
New York, N.Y. 10168

Date: November 29, 1986

Water Quality Association

Contact: Danna M. Cirolia

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

Date: November 22, 1985

Diamond Shamrock Corporation

Contact: Ross E. Jones

World Headquarters
717 North Harwood Street
Dallas, Texas 75201

Date: December 2, 1985

American Cyanamid Company
One Cyanamid Plaza
Wayne, New Jersey 07470

Contact: Linda Dulak

Date: November 27, 1985

The Society of the Plastics
Industry, Inc.
1025 Connecticut Ave.
Washington, D.C. 20036

Contact: Hugh Toner

Date: December 16, 1985

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

Contact Bonnie L. Bishop

August, 1984

State of Connecticut
Department of Health Services

Contact: David R. Brown

Date: December 12, 1985

Michigan Pure Water Council
Educational, Non-Profit
Non-Political thru Investigation,
Research

Contact: Martha Johnson

December 12, 1985

Synthetic Organic Chemical
Manufacturers Assn.
1330 Connecticut Avenue
Washington, D. C. 20036

Contact: Alan W. Rautio

November 27, 1985

Ethylbenzene Producers' Association
1330 Connecticut Avenue
Washington, D. C. 20036

Contact: Eric A. Clark

November 27, 1985

Synthetic Organic Chemical
Manufacturers Association
1330 Connecticut Avenue
Washington, D. C. 20036

Contact: Alan W. Rautio

December 18, 1985

POST MEETING COMMENTS RECEIVED

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

Contact: Chuck Pace

Date: January 27, 1986

Hazco
5301 Lee Highway
Arlington, Virginia 22207

Contact: Redmond Clark

Date: March 14, 1986

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

Contact: Ann M. Mason

Date: April 30, 1986

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

Open Meeting

Under Public Law 92-463, notice is hereby given that a three-day meeting of the Drinking Water Subcommittee of the Environmental Health Committee of the Science Advisory Board will be held on January 6-8, 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 6 and adjourn no later than 4:00 p.m. on January 8.

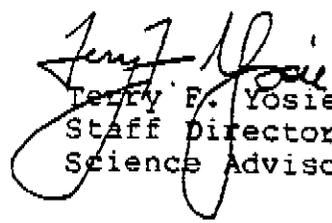
The purpose of the meeting will be to discuss draft drinking water Health Advisory documents for the following substances:

Acrylamide	<u>Legionella</u>
Benzene	Methylethylketone
p-Dioxane	Styrene
Ethylbenzene	Toluene
Ethylene glycol	Xylene
Hexane	

The Drinking Water 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
DRINKING WATER SUBCOMMITTEE

Conference Room 451
Joseph Henry Building
National Academy of Sciences
2122 Pennsylvania Avenue, NW
Washington, DC 20037
January 6-8, 1986

ORDER OF BUSINESS

REVIEWS OF DRAFT DRINKING WATER HEALTH ADVISORIES

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

*Tentative Sequence of Reviews, beginning Monday, January 6, 1986

<u>Substance (Manager)</u>		<u>Reviewers</u>
p-Dioxane (Khanna)		Drs. Johnson and Ray
Ethylbenzene (Khanna)	Drs. Andrews and Ray
Ethylene glycol (Khanna)		Drs. Ray and Johnson
Toluene (Khanna)	Drs. Griffin and Dajirmanjian
Benzene (Marcus)		Drs. Brubaker and Kim
Styrene (Marcus)	Drs. Kaufman and Andrews
Xylene (Patel)		Drs. Carlson and Griffin
Methylethylketone (Patel)	Drs. Tephly and Brubaker

On Tuesday, January 7, 1986

Legionella (Berger)	Drs. Barbaree and Winn
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On Wednesday, January 8, 1986

Acrylamide (Crisp)		Drs. Dajirmanjian and Weiss
Hexane (Patel)	Drs. Kim and Tephly

At the conclusion of the reviews

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

Other Subcommittee Business

Concluding remarks	Dr. Tardiff Dr. Byrd
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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.