



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-87-005

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 ADMINISTRATOR

Dear Dr. Griesemer:

On January 14-17, 1986 the Halogenated Organics Subcommittee of the Science Advisory Board's Environmental Health Committee reviewed fifteen (15) 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, the Subcommittee utilized Drinking Water Criteria Documents as support information for all of the health advisories except for 1,2-dichloroethane, for which the Subcommittee made use of the Agency's Health Assessment Document, supplemented by a Quantitative Toxicological Evaluation for drinking water. Some of the Criteria Documents merit detailed review in the future.

Our comments below are generally divided into general advice, which is relevant to all of the advisories reviewed by the Halogenated Organics 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,

A handwritten signature in black ink, appearing to read "John Doull M.D.", written over a large, stylized flourish.

John Doull, M.D., Ph.D.
Chair, Halogenated Organics Subcommittee

A handwritten signature in black ink, appearing to read "Seymour Abrahamson", written over a large, stylized flourish.

Seymour Abrahamson, Ph.D.
Vice-chair, Halogenated Organics 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 HALOGENATED ORGANICS SUBCOMMITTEE OF THE ENVIRONMENTAL HEALTH COMMITTEE OF EPA'S SCIENCE ADVISORY BOARD REGARDING DRINKING WATER HEALTH ADVISORIES

The Subcommittee recommends that each halogenated organic health advisory provide the CAS number after the chemical name on the first page to facilitate referencing, and that each health advisory provide access information (such as a name and telephone number) for the chemical manager or health advisory manager.

The Subcommittee suggests that the health advisories cite a date through which the literature has been searched comprehensively, and give preference to the use of primary literature citations, whenever they are available. If relatively inaccessible references, such as EPA documents or in-house memoranda, must be used, the health advisory should explain how to obtain them. Citation of abstracts or personal communications should generally be avoided. English translations of any critical foreign language documents used in the health advisory should be made available upon request. Whenever primary reference documents, such as Criteria Documents or International Agency for Research on Cancer publications, are cited, EPA should provide specific page numbers in the reference section. Otherwise, the health advisory as a quick reference will lose value, because a large number of volumes would have to be searched.

The Subcommittee recommends that the Office of Drinking Water provide a consistent and uniform list of physical and chemical properties for each substance. These properties should be presented in a uniform system of units, and should contain factors for converting concentrations between different media. If the literature does not include one or more properties, the health advisory should indicate this absence, rather than omit the property from the list. The Office of Drinking Water should add a glossary of definitions, abbreviations, and acronyms. Situations will occur in which the analytical measurement of the concentration of a substance in water exceeds its solubility when, for example, the water sample contains undissolved substance or when other contaminants enhance solubility. However, it will be worthwhile to compare the levels recommended in each health advisory to the solubility of a substance in pure water since, in some cases, the former exceed the latter.

The description of the occurrence and use of a chemical should include a single primary reference. Whenever available, sections on use and human exposure should be included in the Criteria Documents and health advisories. Occurrence information should be put into perspective with health effects information in the health advisories. Uses listed in the health advisories should be categorized as "past" versus "current," when applicable, but both should be included.

Pharmacokinetic sections should include the half-life of the chemical in humans and/or animals, and the rates of absorption and excretion, where known. This information will be helpful in assessing blood levels which correspond to toxic endpoints. It will also enable the reader to be aware of the persistence of the chemical in the biological system being discussed. Most of the Criteria Documents for halogenated organic chemicals contain this information for some route of administration.

A default assumption of a 20% source contribution of drinking water to total human exposure should not be made: (1) if available exposure estimates indicate that air and/or food are not a major source of exposure, or (2) if the physico-chemical properties of a compound make one or both alternative sources of exposure (food or air) unlikely.

The rationale for the 20% assumption is an estimate of the generic contribution of water to total dose. The assumption of 100% source contribution is appropriate for substances for which exposure occurs mostly through drinking water ingestion, as in the two circumstances above.

The health advisories should indicate that calculations are based on the assumption that the only increase in exposure occurs through drinking water. There may be additional exposure by other routes such as inhalation of vapors from the boiling of water, through showering and by dermal absorption when bathing. Boiling water, except outdoors, should not be recommended for decontamination purposes, since boiling water will transport a halogenated organic material from drinking water into indoor air, where it recirculates, changing the route of administration to inhalation and possibly increasing exposure. Non-water sources of exposure may include food and air. Health advisory recommendations should take into consideration these additional sources of exposure.

The sections about health effects should be reorganized. Human health effects should be presented first, followed by discussion of health effects in animals. Each health advisory should categorize the effects derived from human and animal data in parallel structures. An example is presented below:

(1) Human evidence:

- (a) Acute (brief) exposure or toxicity
- (b) Repeated short-term exposure or toxicity
- (c) Chronic (long-term) exposure or toxicity
- (d) Specific organ system effects and/or mechanism
- (e) Carcinogenicity and mutagenicity
- (f) Reproductive and developmental effects

(2) Animal and other evidence:

- (a) Acute (brief) exposure or toxicity
- (b) Repeated short-term exposure or toxicity
- (c) Chronic (long-term) exposure or toxicity
- (d) Specific organ system effects and/or mechanism
- (e) Carcinogenicity and mutagenicity
- (f) Reproductive and developmental effects

Each of the above categories should include the exposure levels known to cause and not to cause effects. The human evidence category should include experience from the medical, poison control, occupational, and epidemiological literature. In particular, the health advisory should emphasize studies of

groups exposed to contaminated water. Mutagenesis data should be preceded by a statement indicating that positive results may indicate the potential of the chemical to initiate genetic changes that may lead to cancer but may not indicate developmental or reproductive risks.

The Subcommittee recommends that when a health advisory uses data from a particular study for a calculation of the no-observed-adverse-effect-level or lowest-observed-adverse-effect-level, this use should be highlighted as the study is discussed. Otherwise, the user has to flip back and forth in a health advisory and can not easily refer to the data on which the health advisory was based.

Determining a lowest-observed-adverse-effect-level or no-observed-adverse-effect-level from an oral exposure study, especially oral exposure through drinking water, is preferred to a determination using data from other routes of exposure. For some chemicals, oral exposure data may not be available, making it necessary to rely on data derived from other routes of exposure, such as inhalation. When data from an inhalation study are used, factors such as the body weight, tidal volume and respiratory rate of the animal should be considered in the calculation of the total absorbed dose. An uncertainty factor can then be applied to the animal estimate to calculate the health advisory level. Inhalation data also can be used to increase confidence in the calculations derived from drinking water studies. It might be remembered, however, that pharmacokinetic factors, such as differences in absorption rate and first pass effects, may produce predictable differences among different routes of exposure, which in the absence of data on comparable blood levels must be interpreted with caution. Development of a data base comparing the toxicity of halogenated organic chemicals at similar blood levels from studies using different routes of exposure would be desirable; comparisons could be made between various hydrocarbons and between different routes of exposure. Where the appropriate data are not available, EPA should consider these issues as research needs.

In assigning a lowest-observed-adverse-effect-level or a no-observed-adverse-effect-level, EPA should consistently use a dose-related endpoint for a particular effect. Thus, the use of one toxicological endpoint in one health advisory should be consistent within the same advisory as well as between advisories. If a decrease in body weight is used as an endpoint, significant weight loss should not be ignored in other advisories. Similar arguments apply to other endpoints, such as serum enzyme levels, histopathological changes and organ weight changes.

The Subcommittee recommends that the definition of the term "longer-term advisory" include the length of time covered, i.e. month to years. An advisory that recommends a lower level of a substance for a 10-day health advisory than for a longer term (or life-time) exposure level contradicts a principle of toxicology. From the managerial view, once people are exposed to a low level of a substance in drinking water, a higher long-term health advisory value implies that exposed persons will be safer, if they would continue drinking the contaminated water. For most substances, a greater effect is manifest as the duration of an exposure increases. Either interpretation, acute or chronic, could be in error. For certain substances, especially those causing neurotoxic effects, a phenomenon of tolerance can occur. However,

tolerance usually is induced by increasing the dose over time. Even with a substance causing tolerance, safety levels should not be based on the chronically exposed animal, if exposure to this level would cause toxic effects in the previously unexposed person. The problem of health advisory values that are inconsistent with time of exposure may arise when different routes of exposure, different species or different endpoints of toxicity are used for the development of the various health advisories for a substance. In these situations, EPA should explicitly state when the inconsistency arises from the choice of safety (or "uncertainty") factors. The Subcommittee suggests that in these instances the levels derived for longer-term or lifetime health advisories should be used to calculate 10-day and 1-day health advisories.

The Subcommittee believes that the mathematical calculations of health advisory levels are informative, where directly relevant. However, for substances where argument is developed by analogy to another compound, discussion should focus on the strength or weakness of the analogy. Illustrative calculations in these circumstances do not communicate the uncertainty involved in the analogy, and they imply the possession of information that does not actually exist. The health advisory should present alternative analogies and emphasize their comparative strengths and weaknesses.

Statements regarding potential carcinogenic risks should clearly state that the values given represent an estimated plausible upper bound on the possible true risk. For example, a health advisory introduction should state that, for given concentrations of the contaminant, the actual risks are unlikely to exceed the projected excess lifetime cancer risks calculated by EPA. In the section about evaluations of carcinogenic potential, the health advisories should note that the exposure levels provided are unlikely to pose a carcinogenic risk in excess of the stated values. Under "Other criteria, guidance, ..." risks of 10^{-5} , should be changed to "estimated upper limits of 10^{-5} , ...". The intended readers of the health advisories, including operating personnel of water works, probably do not have the technical background to supply the appropriate perspective themselves, which may prove crucial in some decisions.

The Subcommittee requests that the Drinking Water Subcommittee and/or the Environmental Health Committee comment on the revisions of the classification levels of cancer in the Federal Register on pages 46884-46885 as 40 CFR Part 141.142. EPA has moved all group B probable human carcinogens (both group B1 and B2) into a new category 1 of known or probable human carcinogens, which receive equal treatment. Both the International Agency for Research on Cancer categories and EPA's guidelines for carcinogen risk assessment distinguish probable human carcinogens from known human carcinogens. Strict use of the new classification approach might treat a substance as an aqueous carcinogen based on an evaluation of positive inhalation data, with contradictory data for drinking water. Such might be the case with arsenic, for which the Agency has evaluated the literature differently for drinking water.

Health advisories include standards derived by other groups, such as the Occupational Safety and Health Administration, National Institute of Occupational Safety and Health, American Conference of Government Industrial Hygienists, World Health Organization and National Academy of Sciences.

References to these standards will be of greater value to readers if each health advisory supplies the assumptions made and/or constants used in the derivation of quoted standards. A statement could be made for each standard concerning the endpoint(s) on which the standard was based, the estimated risk and the date the standard was issued. Conversion of such standards to dimensions equivalent to those of drinking water exposures would facilitate comparison. However, some members of the Environmental Health Committee caution that such comparisons can mislead the reader if not properly explained. The Subcommittee also recommends that the health advisories cite Science Advisory Board reviews and the EPA reports where the substance in question was previously reviewed. Otherwise, state and local public health officials will not be aware of the context in which the Board's comments are made.

EPA needs a source document for polychlorinated biphenyls. The Subcommittee has provided a detailed scientific review of the Drinking Water Criteria Document for Polychlorinated biphenyls to the Office of Drinking Water, which included thirty detailed comments and thirteen minor comments. The final draft of this document is dated March, 1985. The data and papers which are included, and some of the interpretations, are highly inadequate. Some of the issues, which have not been thoroughly discussed or even acknowledged, include the following:

- Recent papers indicate that Yusho poisoning is primarily related to the toxic polychlorinated dibenzofurans and not the polychlorinated dioxins in contaminated rice oil. Thus, a discussion of the human health effects of polychlorinated biphenyls should not use "Yusho" as an example. Industrial exposure data more accurately reflect human health effects.
- The discussion of chemical analysis of polychlorinated biphenyls and the complexity of polychlorinated biphenyl mixtures is out of date, and any revised document should recognize important new advances in this field.
- A multitude of important papers on structure-activity relationships for polychlorinated biphenyls have been published but are not cited in the comment. For polychlorinated biphenyls, this is a critical issue which must be thoroughly discussed.
- The mechanism of action of polychlorinated biphenyls has been extensively reviewed but is not covered adequately in the Criteria Document. [See, for example, CRC Crit. Rev. Tox 13: 319 (1985), Environ. Health. Perspect. 60: 47 (1985) or Environ. Health. Perspect. 61: 21 (1985)]. These sections of the Criteria Document are out of date and need revision.

In view of the above comments, as well as those made beginning on page 26, the Subcommittee strongly recommends that the Drinking Water Criteria Document for Polychlorinated biphenyls be extensively revised and updated. The revised document could serve as an Agency-wide source document.

II. SPECIFIC COMMENTS OF THE HALOGENATED ORGANICS SUBCOMMITTEE ON SEVENTEEN DRAFT DRINKING WATER HEALTH ADVISORIES

A. CARBON TETRACHLORIDE HEALTH ADVISORY

The health advisory for carbon tetrachloride is not a legally enforceable federal standard. However, any EPA guideline that quantifies risks will be used as policy by Federal, state and local officials, as well as the public, including the affected industries. In a very practical way, they also become the reference points in litigation proceedings. It is, therefore, desirable that the EPA initially examine a complete data base in preparing the carbon tetrachloride health advisory, although the health advisory does not need to cite the complete literature. The criterion applied is whether the health advisory cites the literature that is crucial to the calculations. Evaluation, interpretation and ultimate utilization of data must be done in an objective way, if the health advisory is to have credibility. The Criteria Document should provide much of the evidence for such a process. However, critical data are excluded in the case of the carbon tetrachloride health advisory.

The support document for the health advisory is the final draft Criteria Document prepared by Life Systems, Inc., which is dated January, 1985. This document represents a condensed version of the more comprehensive, and supposedly multimedia, Health Assessment Document, which was published by EPA in September of 1984. As the Subcommittee understands it, the Health Assessment Document contains data from the health effects literature up to March 1983, and was based in part on the Criteria Document, which appeared in draft. One would assume that the Criteria Document would be more up-to-date, but it contains about one-half as many references as does the Health Assessment Document. It should be pointed out that since March 1983, there have been over one thousand citations in the toxicologic literature related to carbon tetrachloride. Several of these new articles are pertinent to the health advisory and should be incorporated. Where appropriate, references to recent key studies are provided in these comments.

EPA recently issued a final rule for a Recommended Maximum Contaminant Level for carbon tetrachloride at the level of zero based on a B2 carcinogenicity classification with evidence from three animal species by the oral route. The same rulemaking reports that carbon tetrachloride has been detected in drinking water supplies in concentrations ranging from 0.5 to 30 parts per billion (ppb). The Agency's cancer risk estimate (parts per billion) corresponding to an upper bound of 10^{-5} risk) given in the rulemaking is 0 - 2.7 cases. The Office of Drinking Water should note the upper bound nature of the risk estimate. EPA also proposed a Maximum Contaminant Level for carbon tetrachloride (Federal Register, pp. 46902-46933, November 14, 1985) at 0.005 ppm. This rulemaking also proposes 5 ppb as the practical quantitative level of detection of carbon tetrachloride in water. The above numerical estimates of carbon tetrachloride risk or numerical contaminant levels need to be acknowledged, accounted for, and explained in the drinking water health advisory, if the advisory is to be useful for state and local public health officials.

The above comments serve to indicate that the Criteria Document is incomplete. The resulting drinking water health advisory, therefore, is not based on all of the readily available data and merits revision. The Subcommittee recommends either a further scientific review of the Criteria Document, or (better) an updating of the Health Assessment Document, perhaps by a memorandum (or "quantitative toxicological evaluation") and use of the combined Health Assessment Document and memorandum as the reference (or source) document to support the drinking water health advisory.

In the section on "general information and properties," the synonyms section should omit "carbon tetrachloride," and add "methane tetrachloride" and "perchloromethane". Under "properties," the odor threshold may not be known, but the odor is sweetish, aromatic, and moderately strong. The odor of carbon tetrachloride is characteristic. Under "occurrence," after the first two paragraphs the remainder of this section runs together and should be revised to state how carbon tetrachloride gets to air, to water, etc. How much is found in an environmental sink, how long does it stay, and what are the major concerns? There are no references provided in this section of the drinking water health advisory. The Criteria Document has no section on occurrence. This section needs a few key citations to support the statements, judgements, assumptions and uncertainties in this section.

The pharmacokinetics section illustrates the desirability of providing succinct, meaningful summaries. The paragraph provided could be replaced with one which states that, based mostly on animal studies, carbon tetrachloride has been shown to absorb readily through the respiratory tract, the gastrointestinal tract, and the skin. The subsections about distribution, metabolism, and excretion should be revised to provide the basis of the information cited, if the health advisory is to be useful for health professionals.

In the health effects section, the following additional references, which are not covered in the drinking water health advisory and/or Criteria Document for chloroform, should be reviewed and utilized in the overall toxicological evaluation:

- (a) Amacher, D.E. and Zelljadt, I., "The morphological transformation of Syrian hamster embryo cells by chemicals reportedly nonmutagenic to *Salmonella typhimurium*," Carcinogenesis (Lond.) 4: 291-296 (1983).
- (b) Gans, J.H. and Korson, R., "Liver nuclear DNA synthesis in mice following carbon tetrachloride administration or partial hepatectomy," Proc. Soc. Exp. Bio. Med. 175: 237-42 (1984).
- (c) Mirsalis, J.C.; Tysn, C.K.; Loh, E.N.; Spek, D.K. and Spalding, J.W., "Induction of hepatic cell proliferation and unscheduled DNA synthesis in mouse hepatocytes following in vivo treatment," Carcinogenesis 6: 1521-4 (1985).

Shank, C. and Barrows, L.R., "Toxicological effects on carcinogenesis," in Toxicological Risk Assessment, Vol. I of Biological and Statistical Criteria, D.B. Clayson, D. Krewski, and I. Munro, eds., CRC Press, (1985), p. 93.

Sina, J.F.; Bean, C.L.; Dysart, G.R.; Taylor, V.I. and Bradley, M.O., "Evaluation of the alkaline elution/rat hepatocyte assay as a predictor of carcinogenic/mutagenic potential," Mutat. Res. 113: 357-91 (1983).

Uemitsu, N.; Minobe, Y. and Nakayoshi, H., "Concentration-time-response relationship under conditions of single inhalation of carbon tetrachloride," Toxicology and Applied Pharmacology 77: 260-266 (1985).

VanStee, E.W.; Boorman, G.A.; Moorman, M.P. and Sloane, R.A., "Time-varying concentration profile as a determinant of the inhalation toxicity of carbon tetrachloride," J. Tox. Environ. Health 10: 785-795 (1982).

Wilcosky, C.; Checkoway, H.; Marchall, E.G. and Tyroler, H.A., "Cancer mortality and solvent exposures in the rubber industry," Am. Ind. Hyg. Assoc. J. 45: 809-811 (1984).

The human exposure section of the Criteria Document was unavailable for review and comment.

The entire section on "quantification of toxicological effects" rests upon data derived from an EPA sponsored study performed by J.V. Bruckner and co-workers. The paper was recently published in Fundamental and Applied Toxicology 6: 16-34 (1986). It was only accepted for publication in May 1985, but EPA has used it in risk assessments for carbon tetrachloride for more than a year. A copy of this paper was obtained and reviewed by one member of the Subcommittee. This paper presents primarily clinical chemistry data for rats that were dosed for nine days or twelve weeks. Many methodology problems were immediately evident. Only male rats were used. Dosing was discontinuous (i.e., for 9 days: 5 on, 2 off, 4 on); for 12 weeks: 5 on, 2 off, for duration). Animals were not fasted; dosing was conducted at night (initial part of active cycle) because the authors determined that this period is when non-fasted rats are most sensitive to carbon tetrachloride hepatotoxicity. No signs of toxicity or body weight data were provided. Carbon tetrachloride was administered by gavage in corn oil. The Science Advisory Board previously has noted the controversy about the significance for environmental standards of data obtained using corn oil as vehicle. No chemical analyses were provided for carbon tetrachloride, corn oil, or feed. The results were based exclusively on liver enzyme and pathology data.

In the section about quantification of toxicological effects, the data of Bruckner may be appropriate for calculating the 1 and 10 day drinking water health advisories, but they should not be used for the longer term health advisory. There are papers, cited in the Health

Assessment Document, by Smyth and coworkers (1936), Adams and coworkers (1952) and Prendergast and coworkers (1967), which are as suitable as the Brucker data for the calculations, since there is some validity in extrapolating from inhalation to oral exposure. (See K. Khanna, "Use of Inhalation Data for Estimating Acceptable Exposure Levels in Drinking Water," draft, September 12, 1985, EPA issue paper).

The section on quantification of toxicological effects presents health advisories for one day (based on a ten kg child), ten days (based on a ten kg-child), and longer term (for both a ten kg child and a seventy kg adult). Health advisories for one-day and ten-days for a 70 kg adult are missing. The Criteria Document includes these calculations, and they should be included in the health advisory.

There is inconsistent use of data in calculating the RRfd, DWEL, and unit risk estimate for carcinogenic potential. The first two are based on Bruckner's data. The latter values derive from four studies which by EPA's own admission, are "less than ideal for risk estimation for continuous daily exposure over a lifetime." EPA has chosen to estimate unit risk by the geometric mean of the estimates from each of the studies (two in mice, one in the rat and one in the hamster). This is a poor estimate because the geometric mean of four poor estimates is still a poor estimate. EPA should make an effort to provide a more accurate evaluation of carcinogenic potential, or it should describe the uncertainty in the estimate in more detail.

The lifetime health advisory, whether revised or not, should be placed into perspective with the levels of carbon tetrachloride expected in water and other environmental media.

In the section about other criteria, guidance and standards, paragraphs 1, 2, 3 and 4, should be combined or discussed in the section on evaluation of carcinogenic potential (section V).

Since apparently suitable data now are available (i.e., those of Bruckner), what do the calculations in paragraph 5 of section V mean? A better explanation needs to be provided.

Since SNARLS have been replaced by RRfd's, why include them? Overloading the drinking water health advisory with numbers is not helpful.

B. CHLOROBENZENE HEALTH ADVISORY

The spectrum of chlorobenzene induced acute and chronic toxic effects is well-documented in animal experiments for different routes of exposure. Limited human data indicate similarities between man and various animal models. There is also some evidence that chlorobenzene causes neoplastic nodules in male rats, leading to its classification as a Group C carcinogen under EPA's proposed carcinogen risk assessment guidelines. The Science Advisory Board reviewed the Criteria Document for Monochlorobenzene in public session on July 23-24, and a detailed written report is in progress.

In the section about quantification of toxicological effects, the advisory notes that numerous correlations exist between the toxicities, such as liver necrosis and porphyria, versus subcellular events, such as enzyme induction, covalent binding and glutathione depletion. However, in the light of conflicting results, the mechanistic meaning of these correlations ought to be viewed with caution.

An appropriate 10-day (and 1-day) health advisory for chlorobenzene was developed based on an inhalation study. This is compatible with a regulatory philosophy of public health prudence, since after inhalation exposure less of the material goes directly to the liver to undergo metabolism. Thus, there is less of a "first pass" effect, and the inhalation data are likely to represent a more toxic route of exposure than oral administration. The selection of the Battelle studies for both the long term health advisory and the life time health advisory appears sound, as does the quantification of carcinogenic effects.

The criteria document is inconsistent with the health advisory in places, and the health advisory makes inconsistent statements regarding the mouse studies.

The Subcommittee questions why data were not used from the 14-day toxicity study sponsored by the National Toxicology Program. If these values are used, and if animal factors (not human factors) are applied to the animal data, then the shorter term health advisories become consistent with the longer term. Further, if the National Toxicology Program data are used, problems with the absorption fraction are resolved. The Subcommittee notes that the National Toxicology Program usually performs histopathology analyses as part of its 14-day studies.

The Office of Drinking Water should clarify why 125 mg was chosen as a no-observed-effect-level, when growth retardation occurred with the male mouse at 60 mg.

Some perspective will be useful in statements about biodegradation, perhaps by comparing chlorobenzene to other substances, such as hexachlorobenzene, which biodegrades about 1,000 times more slowly. A direct statement of the half-life of chlorobenzene would be useful.

C. DICHLOROBENZENES (ORTHO-DICHLOROBENZENE, META-DICHLOROBENZENE AND PARA-DICHLOROBENZENE) HEALTH ADVISORIES

The health effects section notes that a reasonably well developed data base exists for the toxicity of dichlorobenzenes from animal experiments. Data from various groups of investigators suggest that the spectrum of toxic effects is similar with the three isomers in various species. Limited human data also suggest similarities between man and animals in the manifestations from acute or chronic exposure to dichlorobenzenes. State-of-the-art developmental and reproductive toxicity studies did not reveal any adverse effects. National Toxicology Program carcinogenicity studies in two rodent species indicated a lack of tumorigenic effects of o-dichlorobenzene. Dichlorobenzenes are not mutagenic in animal studies and in some other commonly used mutagenicity assays, but they show some mutagenic effects in onion, fungal and yeast systems.

The pharmacokinetics and disposition of the three isomers also are quite similar with the exception that substantial amounts of mercapturic acids are formed from o-dichlorobenzene and m-dichlorobenzene but not from the para-isomer. Both o- and p-dichlorobenzene cause similar toxicities at comparable dosage levels. O-dichlorobenzene depletes glutathione levels, whereas p-dichlorobenzene does not affect glutathione levels. Thus, it is unlikely that glutathione depletion represents a major mechanism of dichlorobenzene toxicity. To the contrary, the data indicate that the mechanism of toxicity of dichlorobenzenes has little, if anything, to do with glutathione depletion or related oxidative stress. Similar problems exist with attributing any role in dichlorobenzene-induced toxicity to reactive intermediates. Considering the high doses required to induce sub-chronic and chronic toxicity, it is more reasonable to assume that nonspecific membrane effects or interference with hormonal homeostasis is involved in the induction of toxicity, as has been shown for some other chlorinated benzenes. Since specific evidence for dichlorobenzenes is lacking for the latter contention, it must be concluded that the mechanism of action of these compounds is unknown.

In the section about quantification of toxicological effects, development of drinking water health advisories for dichlorobenzenes has been conducted according to EPA's issue paper. Selection of the Battelle studies for the recommended 1-day and 10-day health advisory levels and for acceptable daily intake calculations is reasonable because these bioassays are scientifically adequate. Studies of Varshavskaya indicating orders of magnitude lower no-observed-effect-levels for dichlorobenzenes contrast with a larger number of investigations which yield consistent but different results. Because the details of this study are very sketchy, this study should not be used for health advisories. It is also prudent to use oral gavage data rather than inhalation data to derive recommendations for health advisories because chemicals that are readily metabolized may have vastly different toxicities when administered by these

two routes. Furthermore, in the Battelle studies, dichlorobenzenes were administered in corn oil which leads to essentially complete absorption. However, chlorinated benzenes administered in aqueous solutions are absorbed to a much lesser extent. This introduces a further conservative element into the estimation of the no-observed-effect-level.

The solubility noted in the health advisory is in error.

The health advisory should use an absorption fraction of 60% to be consistent with the available information on absorption.

The term "relatively high absorption" could be better stated in quantitative terms.

D. 1,2-DICHLOROETHANE HEALTH ADVISORY

The Science Advisory Board previously reviewed the health effects data for 1,2-dichloroethane in a report of January 4, 1985, which the Halogenated Organics Subcommittee prepared. Since the Health Assessment Document that the Subcommittee reviewed is a multimedia source document to meet Agency-wide needs, the health advisory was based on this information, updated in an appropriate way by a memorandum titled "quantification of toxicological effects." However, the support document distributed to the Subcommittee was the April, 1984, external review draft and not the September, 1985, final report and, as such, did not incorporate EPA's revisions in response to the Subcommittee's review. Certain of the Subcommittee's comments (below) repeat those in its previous report.

Overall, the health advisory generally is in agreement with the Health Assessment Document, which is appropriate data on which to base the advisory.

In the general information and properties section, the health advisory should note which uses of dichloroethane no longer occur. The rest of the uses should be divided into major and minor categories. The reader for whom the health advisory is intended can not be expected to supply this information, and information on obsolete uses may lead water works personnel to implicate sources which no longer exist.

Some physical properties (solubility, boiling point and density) cited in the health advisory are in conflict with those in the Health Assessment Document.

The sources of release of ethylene dichloride need to be clarified further. The data in the document indicate that the major release in air is from dispersive uses, such as lead scavenging, paint coating and adhesives. The health advisory indicates metal cleaning is the major source of release. Comments by the Chemical Manufacturers Association sent to the Subcommittee indicate that ethylene dichloride no longer is used for the above mentioned purposes.

In the section on pharmacokinetics, the qualitative statements about absorption are a representative summary of the information available, but the Subcommittee believes that a correlation between oral dose, inhalation dose and blood levels can be easily built. This will provide a better quantitative basis than the speculation in the health advisory based on physical and chemical properties. The absorption fraction of 30%, which is assumed in the calculations, needs a rationale, if retained in the light of the above comment.

ODW should modify the statements about distribution to indicate the amount of the dose which remains in the biological system at the termination of the distribution study. For example, this section might read as follows: "Within 48 hours after dosing, 96% of the administered radioactivity of a single oral dose of 150 mg/kg was

eliminated from the body in various metabolised forms." Distribution studies in these animals reveal that the liver and kidneys contained the highest concentration of the radioactivity. Reitz and coworkers showed that successively lower concentrations occurred in the forestomach, stomach and spleen.

Most information about "acute poisoning and toxicity" of humans in the health effects section originates from Russian studies. The Subcommittee has doubts about the veracity of these data, and the level of detail is skimpy. EPA should consider omitting these descriptions.

As opposed to the acute effects results for humans from the Russian literature, the Subcommittee suggests that the mutagenicity studies by Rappaport are credible.

The short term exposure data for animals are LD₅₀, not LD₂₀ results.

Negative mutagenic activity of 1,2-dichloroethylene in Salmonella typhimurium was reported by McCann and coworkers in 1975.

The carcinogenicity bioassay data appear not to have been audited, and their validity may be in doubt. Deficiencies in the 1978 National Cancer Institute study were summarized in the comments presented to the Subcommittee by the Chemical Manufacturers' Association.

The Subcommittee argued in the previous Science Advisory Board report on ethylene dichloride that the structure-activity analogy with ethylene dibromide could be misleading in interpreting the metabolism of ethylene dichloride, especially in regard to possible reactive intermediates. However, a structure-activity analogy may be more appropriate in interpreting possible qualitative carcinogenic and mutagenic effects of ethylene dichloride than for metabolism.

In the section about quantification of toxicological effects, the units in the long-term health advisory should be ug/L, not mg/L.

If the Agency bases conclusions about pharmacokinetics on correlations between blood levels versus oral or inhalation doses, then a more reasonable basis will exist to use inhalational bioassay results.

E. DICHLOROETHYLENES [CIS-DICHLOROETHYLENE, TRANS-DICHLOROETHYLENE AND 1,1-DICHLOROETHYLENE (VINYLIDENE CHLORIDE)] HEALTH ADVISORIES

The information in the drinking water health advisories reflects the criteria documents for dichloroethylenes fairly accurately. All three advisories could be written better from the standpoint of more clearly delineating the differences between non-carcinogenic concentrations and that concentration which relates to carcinogenesis. These three health advisories should use wording similar to that found in the trichloroethylene advisory to distinguish acute from chronic toxicity.

In the sections about quantification of toxicological effects, the definitions of adverse effects for the three dichloroethylenes are inconsistent, as illustrated below:

In the one day health advisory for cis-dichloroethylene, an elevated alkaline phosphatase is considered an adverse but not a life-threatening effect. In the trans-dichloroethylene one day health advisory, increased incidence of degeneration of the liver lobule and lipid accumulation by the Kupffer cells of the liver is not considered an adverse effect. In the one day health advisory for 1,1-dichloroethylene, a doubling of liver alkaline phosphatase and an 80% reduction in liver glucose-6-phosphatase is considered an adverse effect.

In the longer term health advisory for 1,1-dichloroethylene, increased cytoplasmic vacuolization of hepatocytes in livers of both sexes is not considered an adverse effect. In the longer term health advisory for cis-dichloroethylene, an increased cytoplasmic vacuolization of hepatocytes is considered an adverse effect. In the longer term health advisory for trans-dichloroethylene, a trend towards increased fatty deposition in the liver was considered an adverse effect.

Vinylidene chloride may not be an appropriate toxicologic analog of the 1,2-dichloroethylenes. The Subcommittee has compared them, as follows:

<u>1,2-Dichloroethylenes</u>	<u>Vinylidene chloride</u>
Oral LD ₅₀ = 1300 mg/kg	Oral LD ₅₀ = 200 mg/kg
No observed effects at >1,000 ppm	Pathology seen at 10 ppm for 6 hours
Liver and kidney not affected	Liver and kidney affected
200 ppm TLV	5 ppm TLV
Not mutagenic in host- mediated <u>Salmonella</u> assay	Mutagenic for <u>Salmonella</u> with metabolic activation

A bioassay in Salmonella is not adequate mutagenicity testing. A computerized data base on this subject, such as that of the Environmental Mutagen Information Center, needs to be consulted.

COMMENTS SPECIFIC TO CIS-1,2-DICHLOROETHYLENE

The cis-dichloroethylene health advisory identified a no-observed -effect-level of 10 mg/kg, when the 5 mg/kg dose actually gave a decreased kidney to body weight ratio. If this decision was based on the absence of decreased kidney to body weight ratio at 10 mg/kg, a more complete description of the judgment is necessary.

In the longer term health advisory, a lowest-observed-adverse-effect -level is given for 100 ppm, rather than a no-observed-effect-level at 50 ppm.

If contaminated water is the main source of cis-1,2-dichloroethylene, why does the health advisory assume that drinking water supplies are only 20% of the exposure in the longer term health advisory?

In the pharmacokinetics section, almost all of the information is based on analogy. Therefore, some language changes seem desirable for the advisory to avoid confusing the reader. For example, the health advisory could state that "cis-dichloroethylene should be absorbed rapidly," or that "cis-dichloroethylene would be expected to be found in liver and kidney," or that "if similar to vinylidene chloride in excretion, then cis-dichloroethylene will be excreted relatively rapidly."

It is important to note in the health effects section that cis-dichloroethylene is well-tolerated as an anesthetic in man and animals, in addition to describing its anesthetic properties.

The subsection about health effects in animals reports that no data are available, but the American Conference of Government and Industrial Hygienists reports that no exposure related changes occurred from a mixture of 60% trans-dichloroethylene and 40% cis-dichloroethylene at 500 or 1000 ppm in rats, rabbits, guinea pigs, or dogs exposed for seven hours daily, five days each week for six months. Parameters studied included growth, mortality, organ and body weights, hematology, clinical chemistry, and gross and microscopic pathology.

In the section about other criteria, guidance and standards, the Threshold Limit Value (TLV) given is 200 ppm (790 ug/m³). The health advisory states that, in view of the finding that the no-observed-effect-level in animals after prolonged inhalation is at least 1000 ppm, and the supporting information by other routes of administration, the TLV of 200 ppm and the short term exposure limit of 250 ppm may be too conservative. The Office of Drinking Water should note that 200 ppm is equivalent to 790 mg/m³, 790 mg/m³ x 10 m³/day = 8,000 mg/day, and 8,000 mg/70 kg = 112 mg/kg/day. This suggests that the lifetime health advisory value, based on analogy to 1,1-diethylene, is too low.

The American Conference of Government Industrial Hygienists reports that liver and kidney injury do not appear to be important endpoints of cis-dichloroethylene exposure.

COMMENTS SPECIFIC TO TRANS-1,2-DICHLOROETHYLENE

The human health effects discussion does not describe the experience of human exposures without adverse effects.

The subsection addressing effects in animals reports that the oral LD₅₀ is 1/6th of intraperitoneal LD₅₀, which might suggest that a metabolite arises after the first pass that is responsible for the acute toxicity. If so, why does the advisory make a prediction of liver and kidney toxicity when no changes in organ weight were seen after 220 mg/kg by gavage for 14 days? Comparison of the inhalation data with the gavage study involves different endpoints, biochemical for the former and organ weight for the latter. If this difference is the basis of the choice of an inhalation study in preference to a gavage study, the health advisory needs to describe the rationale for the choice.

In the section about quantification of toxicological effects, an alternative derivation of the one-day drinking water health advisory based on inhalational data might be compared to the value of 2.7 mg/L in the health advisory, as follows: $200 \text{ ppm} \times 3.97 \text{ mg/m}^3/\text{ppm} \times 0.00438 \text{ m}^3/\text{hr}/\text{rat} \times 1 \text{ rat}/0.190 \text{ kg} \times 8 \text{ hrs} \times 30\% \text{ absorption} \times 10 \text{ kg child/Liter/day} \times 0.01 \text{ (uncertainty factor)} = 43.8 \text{ mg/L}$

Some relevant papers were not cited in the reference section, such as that by Jenkins and coworkers (1976), and some were incomplete, such as those of Olsen and Gehring (1976) or Lehmann and coworkers (1936).

COMMENTS SPECIFIC TO VINYLIDENE CHLORIDE

In the reference section, a recent review of long-term studies in Environmental Health Perspectives and the Agency's Health Assessment Document on Vinylidene Chloride should be cited.

F. DICHLOROMETHANE (METHYLENE CHLORIDE) HEALTH ADVISORY

The support document for the health advisory is a final draft Criteria Document prepared by Life Systems, Inc., which is dated June, 1985. The Criteria Document represents another version of the more comprehensive Health Assessment Document, which was published by EPA in February of 1985, and the Addendum to the Health Assessment Document, which was published in August of 1985. Several articles and other information have appeared subsequently (cited below) that are pertinent to the health advisory, and this material should be incorporated into the health advisory.

EPA has received detailed comments from the Halogenated Solvents Industry Alliance on December 16, 1985 which focus on the carcinogenicity, non-carcinogenic health effects, exposure and risk assessment of dichloromethane (EPA/Docket No. OPTS-62045). At the same time, the Food and Drug Administration proposed in the Federal Register on December 17, 1985, to ban dichloromethane as an ingredient in all cosmetic products, citing studies showing that inhalation of the chemical causes cancer in rats and mice and poses a possible cancer risk to humans. The same notice did not propose a ban on use of dichloromethane in coffee decaffeination. The responses to both the EPA and FDA proposals need to be evaluated and used, as appropriate, in preparing the final versions of the health advisory and Criteria Document.

Some old business needs completing before the Criteria Document and health advisory are finalized. The health advisory merits revision on the basis that the data base is incomplete, as detailed below. The Criteria Document also is deficient and needs further detailed review or perhaps replacement by the Health Assessment Document and its Addendum. Specific comments include:

- In previous reports, the Science Advisory Board has requested that EPA provide sensitivity analyses of the Agency's risk estimates.
- EPA has decided to have an independent review of the Kodak epidemiology studies, which will be important to the Agency's reviews of available human data.
- EPA reviews of DNA-binding data submitted by the European Council of Chemical Manufacturer's Federation should be completed, if the Agency is to clarify the relative toxicity of the different dichloromethane reactive intermediates.

The health advisory and Criteria Document need to be reinterpreted in the light of the Agency's proposed guidelines for risk assessment, which the Science Advisory Board has reviewed, and which are operational within the Agency. Reinterpretation will be particularly important for dichloromethane with respect to benign versus malignant tumors and to weight of the evidence for carcinogenicity.

- The Agency's interpretation of the pharmacokinetics and comparative metabolism of dichloromethane needs additional peer review, particularly in regard to the use of this information in a risk assessment.
- An EPA report of May 1, 1984, authored by Cothorn, Coniglio and Marcus, which assesses carcinogenic risk to populations from dichloromethane via the ingestion, inhalation and dermal routes, is not mentioned in the health advisory or Criteria Document.

In the section on general information and properties, add methylene bichloride under synonyms.

In the subsection about occurrence, the Subcommittee notes that the health advisory says that there are no natural sources, whereas the Criteria Document says that possibly there are natural sources. The question of potential natural sources may be important. The production figure in the health advisory appears to be more up to date than that in the Criteria Document. This conflict needs to be resolved. The remaining paragraphs in this subsection are presented as categorical statements of fact with no references cited; neither is any information provided in the Criteria Document. This needs to be corrected so that data are available to support the statements, judgments, assumptions, and uncertainties in this section.

In the section about pharmacokinetics the most recent pharmacokinetics and comparative metabolic data relative to the interpretation of the findings on the animal studies need to be reviewed in detail by the EPA. In response to the October 17, 1985 Advanced Notice of Proposed Rulemaking, EPA has received comments and new experimental data. In addition to the Halogenated Solvents Industry Alliance comments mentioned previously, EPA has received detailed information (including two publications and five preprint manuscripts) from the National Coffee Association. These papers present pharmacokinetic modelling of data from orally administered dichloromethane to rats and mice. (EPA Docket No. OPTS-62045).

In the health effects section, two drinking water studies are mentioned under long-term exposure, but there is no reference to the Dow chronic inhalation studies. This is also true of the Criteria Document. The Office of Drinking Water draft issue paper by K. Khanna ("Use of Inhalation Data for Estimating Acceptable Exposure Levels in Drinking Water," September 12, 1985) explains the validity of extrapolating from inhalation to oral exposure. The Dow studies may, therefore, be useful.

The subsection on teratogenic/reproductive effects should be revised to emphasize that the studies were not dose-response designs and that high doses were tested. Furthermore, EPA has received a copy of a report by Nitschke, Eisenbrandt, and Lomox (1985), which describes negative results in a two-generation inhalation study in Fischer 344 rats.

In the National Coffee Association submission, a detailed review by Broome and Sivak of mutagenicity data on dichloromethane is included. This paper suggests that a genetic rationale for a carcinogen risk assessment of dichloromethane is inappropriate. EPA should examine this paper and evaluate the assertions made.

Reference to the National Toxicology Program chronic oral study should be deleted in the carcinogenicity subsection since the Board of Scientific Counselors has disavowed this study with respect to providing background information on the forthcoming publication of their inhalation study. The pertinent sections in the Criteria Document (pages V-28-V-30 and V-40-V-41) should likewise be deleted.

The carcinogenicity subsection contains a detailed summary of the Hazelton Laboratories chronic drinking water bioassay. However, page six of the health advisory states that EPA (1985) performed an independent assessment of the data from this study and concluded that "the 250 ng/kg/day dose was borderline for carcinogenicity in Fischer 344 rats." No details of that assessment are provided in either the text of the health advisory or the Criteria Document, and there is no 1985 citation given in the References section. The reasons for this conclusion should be presented before the reader can understand the overall interpretation.

In the carcinogenicity subsection, EPA accepts the National Toxicology Program two-year inhalation data to provide evidence of carcinogenicity. The same studies, however, are not mentioned in the advisory for longer-term exposure. Perhaps, the Agency needs to combine the two subsections for longer-term exposure and carcinogenicity into one.

The human exposure section of the Criteria Document was unavailable for review and comment.

The section on quantification of toxicological effects presents health advisories for a 10 kg child exposed for one day or for ten days. Health advisories are missing for 70 kg adults exposed for one day or ten days. These calculations are included in the Criteria Document and should be included in the health advisory. Also missing from both the health advisory and Criteria Document is a calculation of a longer-term exposure health advisory. It is stated that no data were available for the calculation. EPA needs to reexamine the literature and make the calculations.

Concerning the evaluation and calculation of carcinogenic potential, the National Toxicology Program chronic oral study should be deleted from the data base, and this section should be reworked because the study has not been accepted by the National Toxicology Program Board of Scientific Counselors. The lifetime health advisory should be placed into context with levels of dichloromethane in water and other environmental media. Perhaps the Advanced Notice of Proposed Rulemaking will provide this perspective.

G. 1,2-DICHLOROPROPANE HEALTH ADVISORY

The health advisory contains information that is not provided in the Criteria Document. The quality of the Criteria Document needs to be upgraded to contain the missing information.

In the section about general information and properties, the information about occurrence is not found in the Criteria Document.

The Criteria Document contains no information on the extent of absorption. The statement that "90% of the orally administered dose is absorbed" lacks justification.

The metabolism information provided in the advisory is misleading. The study described by Jones and Gibson (1980) indicates that two metabolites represent only 25-35% of the administered dose. Structures and contributions of other potential metabolites were not determined.

The human health effects information provided in the health advisory is not accurate and was presented with no details. For example, one abstract was cited as describing the toxicity of a cleaning substance which contained substances other than dichloropropane.

In the section about quantification of toxicological effects, the ten day health advisory is based mainly on information from two Russian abstracts. Because the experimental design, data and results are questionable, EPA's conclusions based on this information may be in some doubt.

In the reference section (literature citations), National Toxicology Program (1983) information is available in the Criteria Document. However, the information provided on this report may change pending auditing of the experimental data and issuance of final report by National Toxicology Program. Is this final report available?

H. 2,3,7,8-TETRACHLORODIBENZO-p-DIOXIN HEALTH ADVISORY

There is a relatively good correspondence between the data and conclusions presented in both the health advisory and Criteria Document for 2,3,7,8-tetrachlorodibenzo-p-dioxin. However, there is one important consideration which has not been addressed in either document: the problem of human exposure not only to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) but to other polychlorinated dibenzofuran (PCDF) and dibenzo-p-dioxin (PCDD) isomers and congeners. Recent studies by Rappe and coworkers, and others, have demonstrated that a number of highly toxic PCDDs and PCDFs bioaccumulate in human adipose tissue (Chemosphere 14: 933, 1985; Chemosphere 14: 697, 1985) and in most cases, TCDD is a minor component of these toxic mixtures. There are several studies that demonstrate the value of using "tetrachlorodibenzo-p-dioxin equivalents" for describing the potential adverse human and environmental health effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin and related compounds, and this concept should be noted in the health advisory. It is likely that in the future there will be an increase in the number of reports which confirm the presence of other toxic PCDDs and PCDFs in humans, and it would be prudent to recognize this possibility in both documents.

The Uses section should be retitled Uses and Occurrence, and this section should note identification of TCDD in fly ash as a by-product of combustion.

The formula of TCDD should be properly drawn.

The Pharmacokinetics section should include recent studies which have identified 2,3,7,8-tetrachlorodibenzo-p-dioxin and related compounds in human tissues (Chemosphere 14: 697, 1985; Chemosphere 14: 933, 1985).

The metabolism section should note that the metabolite profiles are consistent with an arene oxide intermediate. The covalent interaction of TCDD with cellular macromolecules is minimal. A statement like this would summarize the likely route of oxidative metabolism and also point out that covalent modification of DNA, RNA and protein is not significant.

Although TCDD is a mouse teratogen it is not "teratogenic in all strains of mice tested." A study by Poland and Glover (Mol. Pharmacol. 17: 86, 1980) reported that at a dose level of 30 ug/kg the CBA/J, AKR/J, SWR/J and 129/J strains were resistant to the teratogenic effects of TCDD.

TCDD is fetotoxic and a reproductive toxin in rats, but it is not generally regarded as rat teratogen.

While the Criteria Document is well written and provides supporting evidence for the health advisory, there are a number of sections which merit modification. Detailed comments on some recommended changes have been sent directly to the Office of Drinking Water by individual Subcommittee members.

I. EPICHLOROHYDRIN HEALTH ADVISORY

The ten day drinking water health advisory for a child is 0.14 mg/kg/day (or other equivalent), and the lifetime drinking water health advisory (and/or DWEL) for an adult is 0.15 mg/day. These values appear inconsistent, perhaps due to an error in accounting for body weight, and merit additional comment in the advisory.

Is there a consistent carcinogen risk policy? Is a risk of approximately 2×10^{-5} an acceptable EPA upper limit of risk? While de facto risk may be orders of magnitude lower than the stated value, what is the rationale for this maximum risk value for epichlorohydrin?

Synonyms should be checked with the Criteria Document and the Epichlorohydrin Health Assessment Document Final Report. For example, chloromethyl oxirane is not listed there, but chloromethyl ethylene oxide is.

A vapor pressure of 12 mm at 20°C is given, but a pressure of 10 mm at 16.6°C and 22 mm at 30°C appears in EPA's final report.

In the section on mutagenicity, the Subcommittee suggests that the fourth sentence read as follows: "Epichlorohydrin also induces gene mutations and very likely chromosomal aberrations in mouse cell culture studies (Moore-Brown and Clive, 1979) and chromosome breakage in human lymphocytes in vitro (Keicerova and coworkers, 1976)."

Through in vivo studies, Sram (1976) demonstrated a clear dose-response relationship in mouse bone marrow studies.

A study by Laskin was used to set the DWEL. Tumors occurred after six weeks, and their incidence suggests a dose-response relationship.

A separate section on organoleptic properties would make the health advisory more useful.

J. HEXACHLOROBENZENE HEALTH ADVISORY

In the section about general information and properties, it is worth noting that hexachlorobenzene has an extremely low water solubility of 5 ug/l (not 0.05 mg/l).

Hexachlorobenzene has no natural sources. Use of hexachlorobenzene as a fungicide has been discontinued. Hexachlorobenzene is a contaminant of some pesticides. The low water solubility implies rapid partition to soil following releases to the environment with a half-life of 3-6 years. Hexachlorobenzene bioaccumulates in fish. It has been detected at 0.005 ug/L in two drinking water supplies and in some foods at ppb levels. Diet probably is the major route of exposure.

In the pharmacokinetics section, gastrointestinal absorption of hexachlorobenzene occurs primarily through lymphatic channels, which route is dependent on solvent vehicle. In olive oil, 80% is absorbed; in aqueous solution, less than 20%. This difference is not accounted for in the calculations, so the health advisory will overestimate the internal exposure via drinking water.

Hexachlorobenzene is lipophilic, accumulates in adipose tissues and crosses the placenta.

Hexachlorobenzene undergoes slow metabolism, with the parent compound excreted in feces (more than 90% of dose) and the metabolites in urine.

In the health effects section, it should be noted that exposure of humans in Turkey occurred via consumption of contaminated wheat seed.

A more specific description of the human effects in the Turkish episode would be desirable. For example, very high mortality (95%) occurred in children under 1 year of age. The "few" patients quoted in the health advisory actually was 15/161, almost 10%; the greater than 50% actually was 78% hyperpigmentation, 83% scarring. Thyroid enlargement in 60% of the exposed females is not mentioned. In the Criteria Document, thyroid tumors in 60% of females are described. Hexachlorobenzene also causes hypothyroidism in animals (Rozman and coworkers, "Reduced Serum Thyroid Hormone Levels in Hexachlorobenzene Induced Porphyria," Toxicology Letters 30: 71-78 [1986]).

Both the health advisory and the criteria document report significant increases in liver and kidney weights in several species of treated animals. But Table V-1 and the rest of the subchronic toxicity section indicates an effect on kidney weights only in rats. Has the Criteria Document been checked for internal consistency?

Increased mortality plus hepatic and renal lesions occur in rodents. Histopathologic effects occur in monkey ovaries. The most prominent effect is increased porphyrin levels in liver and urine, to which females are more sensitive than males. Hexachlorobenzene causes

accumulation of beta-H-steroids (not para-H-steroids), which induce porphyrin synthesis. Pentachlorophenol, a hexachlorobenzene metabolite (but not hexachlorobenzene itself) inhibits uroporphyrinogen decarboxylases, but only above 10^{-5} M. Hexachlorobenzene also induces cytochromes and hepatic microsomal enzymes.

Hexachlorobenzene occurs in the milk of nursing dams. Reduced fertility, litter size, hepatomegaly and compromised survival of pups occur on exposure. Developmental effects, such as cleft palate, occur in mice but not rats.

Hexachlorobenzene is not mutagenic in *Salmonella* strains with or without metabolic activation, does not induce dominant lethal mutations in rats, but is mutagenic in yeast.

Hexachlorobenzene is carcinogenic in hamsters, rats, and mice. Most often liver tumors occur, with some adrenal, kidney, thyroid, and parathyroid tumors. The study of Lambrecht and coworkers (1983) is only mentioned in this section, although it is the data set used by EPA to estimate carcinogenic potency.

In the section about quantification of toxicological effects, diets with hexachlorobenzene in corn oil probably overestimate internal dose versus equivalent exposure in drinking water. A no-observed-adverse-effect-level of 0.6 mg/kg/day was found for female rats (a transient increase in liver porphyrin levels four weeks after removal of hexachlorobenzene). Higher doses yielded increased porphyrin levels in liver, kidney and spleen; increased liver to body weight ratios, decreased survival, and so forth. Ten-day drinking water health advisories for child and adult are 50 and 175 ug/L, respectively, which are 10 and 35 times higher than hexachlorobenzene solubility in water.

Based on the study by Arnold and coworkers in 1983, in utero exposure followed at 28 days by dietary exposure at parental levels for 130 weeks, the health advisory derives a no-observed-effect-level of 0.32 ppm. Periportal glycogen depletion occurred, only in F1 generation males at 1.6 ppm, so 1.6 ppm also can be observed as a no-observed-effect-level. At 8 ppm and higher exposures, hexachlorobenzene resulted in increased hepatic centrilobular basophilic chromogenesis, pup morbidity, peribiliary lymphocytosis and fibrosis, severe chronic nephrosis in males, adrenal pheochromocytomas in females and parathyroid tumors in males.

One and six-tenths ppm equals 0.08 mg/kg/day on average, which also yields an adult DWEL of 28 ug/L, the same value as the lifetime acceptable daily intake given in the criteria document. This value is more than five times greater than the solubility of hexachlorobenzene in water.

K. POLYCHLORINATED BIPHENYLS HEALTH ADVISORY

The pharmacokinetics discussion should broadly summarize the data on polychlorinated biphenyls. This section focuses primarily on results from a single paper and is not representative of the facts. The draft health advisory for polychlorinated biphenyls also is inconsistent with the Criteria Document. The section on excretion is an example. The health advisory states that no data were available. It would seem that the major elimination pathway through urine could be inferred from the 1975 data of Yoshimura and Yamamoto, which are quoted in the Criteria Document and which show small percentages of polychlorinated biphenyls excreted in the feces. This inference is supported by two other studies cited in the Criteria Document which report that excretion of specific polychlorinated biphenyls occurs increasingly in the feces as the degree of chlorination of the biphenyl portion of the molecule increased (and as metabolism presumably was increasingly inhibited). In addition, several studies that are cited as dealing with polychlorinated biphenyl metabolites found a negative correlation between rapid urinary excretion and degree of chlorination of the mono- through hexa-chloro isomers. Matthews and Anderson also found that excretion half-life appeared to be negatively correlated with increasing chlorination. Other investigators, such as Muehlebach and Bickel, have reported half-life data. Felt and coworkers (1977) reported polychlorinated biphenyl elimination rates in rhesus monkeys, and Chen and coworkers reported similar data for humans. These studies are summarized in the Criteria Document.

The brief discussion of metabolism is incomplete. This section should note the importance of (a) degree of ring chlorination, (b) substituent orientation and (c) the availability of adjacent unsubstituted carbon atoms.

In the section on short-term exposure, depending on what was meant by "asymmetrical skull" and taking into consideration other factors, such as the developmental stage at the time of abortion, such a finding in aborted fetuses may have little toxicological significance.

The discussion of effects of short term exposure to polychlorinated biphenyls on the immune system does not correspond with that found in the Criteria Document. The specific references, findings, timing, doses at which a response was seen, and so forth, differ between the health advisory and the criteria document.

In the analysis of data from Allen and coworkers, although it is true that the menstrual cycles were irregular and serum levels of sex steroids were depressed, the monkeys had "extreme weight loss." Therefore, the hormonal problems may have occurred secondarily to other toxic effects.

The usage of "isomers" and "cogeners" should be corrected. Polychlorinated biphenyls are not mixtures of isomers but mixtures of isomers and congeners.

The health effects section suggests that the short-term human exposure of Yusho poisoning is representative of polychlorinated biphenyl toxicosis. Recent studies indicate that the major etiologic agents in Yusho were polychlorinated dibenzofurans rather than polychlorinated biphenyls.

At least three papers have reported the immunotoxicity of several polychlorinated biphenyl isomers and congeners (Clark et al, Immunopharmacol. 6: 143, 1983, Silkworth et al, Toxicol. Appl. Pharmacol. 65: 109, 1982 and 75: 156, 1984).

The analysis section is out of date. It is possible to analyse polychlorinated biphenyls by congener-specific capillary gas chromatography using all 209 polychlorinated biphenyls as standards. This procedure will eliminate the guessing from future polychlorinated biphenyl analytical methods and ultimately will permit risk assessment to be based on individual compounds that are present.

EPA needs a source document for polychlorinated biphenyls. The Subcommittee has provided detailed scientific comments on the Drinking Water Criteria Document for Polychlorinated Biphenyls to the Office of Drinking Water, which included thirty major comments and thirteen minor comments. The final draft of the Criteria Document gives a date of March, 1985; whereas the document is out-of-date. The data and papers which are included and some of the interpretations are highly inadequate. Some of the issues have not been thoroughly discussed. In view of the comments below, the Subcommittee strongly recommends that the Drinking Water Criteria Document for Polychlorinated Biphenyls be extensively revised and updated. Specific comments include:

- Recent papers indicate that Yusho poisoning is primarily related to the toxic polychlorinated dibenzofurans and not the polychlorinated dioxins in contaminated rice oil. Thus, a discussion of the human health effects of polychlorinated biphenyls should not use "Yusho" as an example. Industrial exposure data more accurately reflect human health effects.
- The discussion of chemical analysis of polychlorinated biphenyls and the complexity of polychlorinated biphenyl mixtures is out of date, and any revised document should recognize important new advances in this field.
- A multitude of important papers on structure-activity relationships for polychlorinated biphenyls have been published but are not cited in the document. For polychlorinated biphenyls, this is a critical issue which must be thoroughly discussed.
- The mechanism of action of polychlorinated biphenyls has been extensively reviewed but is not covered adequately in the Criteria Document. [See, for example, CRC Crit. Rev. Tox. 13: 319 (1985), Environ. Health. Perspect. 60: 47 (1985) or Environ. Health. Perspect. 61: 21 (1985)]. These sections of the Criteria Document are out of date and need revision.

L. TETRACHLOROETHYLENE HEALTH ADVISORY

The health advisory states that the major sources of exposure to perchloroethylene result from contaminated water and to a lesser extent, air. The Agency's Health Assessment Document states the opposite. The idea that a main source exists in comparison to a secondary source may be misleading.

Some health advisory statements are potentially misleading, such as: "the accumulated human inhalation data indicate that there is a minimal effect on motor coordination at 100 ppm". The time frame is omitted. Similarly, the exposure range at which inebriation first appears is 300-475 ppm, and effects appear to vary with the time of prior exposure. This perspective is more informative than simply noting that inebriation is seen. A related problem occasionally occurs when abbreviated statements of fact are made. For example, in describing the distribution of perchloroethylene, the health advisory states "in rats," whereas a better description might be "in rats previously exposed to perchloroethylene by inhalation at 1340 mg/m³ for 6 hrs/day and 4 days, the perchloroethylene concentration on the fifth day is highest in perirenal fat. Exposure to the same perchloroethylene concentration on the sixth day showed that..."

When such terms as SGOT are used as a measure of toxicity, information on the relationship to liver damage should be included. Most readers will not know the significance of increased serum SGOT.

Some other synonyms could be added, such as ethylene tetrachloride, Nema, Tetracap, Tetropil, Perclene, Ankilostin, Didakene.

The properties section should note that perchloroethylene is a colorless liquid. For specific gravity, add a superscript of 15 and a subscript of 4. Also, the document should note that the partition coefficient (water/air) is 1.22 (20°C), that perchloroethylene is nonflammable, and that the odor threshold in water is 50-300 ug/l.

The health advisory should note that perchloroethylene degrades in the presence of sunlight and moisture.

If degradation to trichloroethylene and vinyl chloride is not a usual route, then the conditions, such as laboratory rather than ambient, should be discussed or the reference should be omitted.

The health advisory should include the annual production of perchloroethylene.

The section on absorption should note that ninety-eight percent of a single oral dose of 189 mg/kg perchloroethylene administered to rats was excreted in expired air (Daniel, 1963). In mice given a single oral dose of 500 mg/kg ¹⁴C-labeled perchloroethylene, approximately 85% was recovered in expired air with total recovery of 96.8% in 72 hours (Schumann and coworkers, 1980).

The 25% perchloroethylene absorption figure given for humans in the health advisory does not appear in the Criteria Document. The health advisory states that 25% of inhaled perchloroethylene was absorbed during a four-hour exposure at 72 or 144 ppm. Also, the description of exposure as "72 to 144" ppm implies a variable exposure within a range, whereas the actual conditions were either 72 or 144 ppm exposure.

The Subcommittee has general concerns about the assumption of values for absorption fractions without clearly stating when they are based on reference studies and when they constitute arbitrary assumptions. For perchloroethylene, the 50% value contrasts with the values assumed for other substances, like trichloroethylene, for which a 35% value is used. Perhaps a better systematic approach is to base the values on physical solubility measurements.

The statement about three distinct half-times for perchloroethylene exhalation need clarification and amplification.

The health advisory needs a more extensive description of saturation kinetics of perchloroethylene and the implications of saturation kinetics. It also may be useful to cite recent studies about protein binding of metabolites.

The health advisory should note that trichloroethanol is a human metabolite of perchloroethylene because trichloroethanol is thought to be the active metabolite in some of the hypothetical mechanisms proposed for perchloroethylene effects.

The discussion of the "proposed metabolic pathway" is incorrect. This sentence should state that oxidative metabolism is proposed to proceed through an epoxide intermediate, which can lead to the major metabolite, trichloroacetic acid.

The problem with some of the effects data is that the length of exposure was quite variable. In the study of Rowe and coworkers (1952), effects are associated with a single exposure ranging in time from two minutes to two hours. The study of Stewart and coworkers (1961) noted an impaired ability to maintain a normal Romberg test after a 30-minute exposure of volunteers to 190 ppm. Either the second paragraph is misleading or else these studies should be included as short-term effects. The study of Stewart and coworkers (1970) involved exposures of 7 hours per day for 5 days. In 1974 Stewart's group also exposed 19 volunteers to perchloroethylene at 20 to 150 ppm for a 5 week period and noted deleterious effects at 100 ppm but not at 20 ppm. These data provide a basis for a 10-day advisory.

Results of the study of Schwetz and coworkers (1975) were characterized by fetotoxicity, not developmental effects, and these results would be better placed in the health effects section.

The Subcommittee does not have a general consensus about the use of developmental toxicity data in which maternal toxicity is observed. However, current EPA practice is to use effects information at an exposure for which less than 10% maternal mortality is observed. Obtaining maternal mortality at the highest dose in such studies is not considered inappropriate. ODW should consider performing a comprehensive re-evaluation of the literature on the developmental toxicity of perchloroethylene.

The carcinogenicity section should be updated to include the papers by Van Duuren and coworkers (See J. Natl. Cancer Inst. 63: 1433, 1979). Moreover, a recent paper by this group (Cancer Res. 43: 159, 1983) reports the carcinogenicity of chloroalkene oxides and their parent olefins after topical or subcutaneous administration. Perchloroethylene oxide, presumably the metabolically activated perchloroethylene metabolite, did not significantly increase tumor incidence after subcutaneous injection but did produce benign skin tumors in mice at a low frequency.

The route of administration, dose (or doses), purity, and target organs or tissues should be stated in describing the chronic studies for perchloroethylene.

National Cancer Institute chronic bioassay data suggest that perchloroethylene may be acting as a carcinogenic promoter. The Dow Chemical Study by Rampy and coworkers (1978) merits some mention in the drinking water health advisory. Perhaps it was excluded because it was an inhalation study. However, the results in Sprague-Dawley Spartan substrain rats were negative and can be useful in placing limits on the risk estimates.

In calculating the total absorbed dose, the conversion of a 5-day exposure to a 10-day exposure was omitted.

A recommendation to the public of boiling water to remove perchloroethylene seems dubious, unless it is made clear that the water is to be boiled outdoors.

The Subcommittee suggests that the key to interconverting bioassay data for perchloroethylene administered by different routes of administration is to correlate blood levels with exposure (or dose) for different species. Sufficient data is available for perchloroethylene, including humans, to adopt this approach.

M. 1,1,1-TRICHLOROETHANE (METHYL CHLOROFORM) HEALTH ADVISORY

With the exceptions described below, the drinking water health advisory is generally consistent with the information presented in the Criteria Document.

The drinking water health advisory states that the major source of methyl chloroform results from its use as a metal degreaser. Entrance to the environment is from evaporation and dumping of the grease contaminated chemical into landfills, open ground or sewers. Due to the costs of methyl chloroform and changes in environmental standards, most methyl chloroform is recovered and recycled. Although the evaporation problem continues, current disposal practices are probably not contributing to ground water levels at this time. Much of the existing ground water problem is apparently due to past practices. The drinking water health advisory also states that the major source of human exposure is through the water supply and, to a lesser extent, air. There is no clear indication of source predominance for methyl chloroform on a site-by-site basis. According to the Criteria Document, exposure in water predominates over air only at drinking water levels above 84 ug/L, which are levels to which less than 0.1% of the population are exposed.

The 1,1,1-TCE abbreviation might be changed to avoid confusion with trichloroethylene, or else use the synonym "methyl chloroform" as in the present comments.

The discussion of pharmacokinetics lacks data on the elimination rate. Although the Criteria Document does not present a half-life after acute exposure, 44% of an inhaled dose is excreted within one hour, suggesting a short half-life, but these data receive little attention. There is the possibility of accumulation in tissue during chronic exposure, with one study showing trace amounts of methyl chloroform still present one month after chronic exposure.

There is an apparent error in referring to the study of Monster and coworkers (1979), where the health advisory states that very small amounts of methyl chloroform are excreted unchanged by the lungs. Although lung excretion will depend on dose, the lungs are the major route, with the parent compound accounting for almost all of the excretion. Perhaps the health advisory is referring to the metabolic product, trichloroethanol, which accounts for less than 1% of the total dose of methyl chloroform administered.

The study by Hake and coworkers (1960) suggests that about 3% of methyl chloroform is metabolized by rats. Actually this study showed that 98% of the radioactivity was associated with the unchanged compound and 0.5% as $^{14}\text{CO}_2$. About 50% of the remainder was associated with metabolites, while the other 50% was lost to evaporation. Thus, less than 1% was metabolized.

The description of the human data needs expansion. A concentration (68 mg/L) producing death by central nervous system depression is known. The sensitization of the heart to catecholamines and the sudden deaths due to the cardiovascular effects of methyl chloroform are not mentioned. Central nervous system functional impairment has been demonstrated with concentrations of methyl chloroform as low as 250 ppm in air. Upper respiratory irritation and the unpleasant odor also observed at low concentrations are not mentioned.

The study by Vainio and coworkers (1976) should be placed in perspective. The 1.4 g/kg dose that depressed microsomal metabolism is about 25% of the LD₅₀ and well above the dose that induces anesthesia.

A 1983 National Toxicology Program is presented, but the results of the study are not discussed.

The health advisory uses the studies of McNutt and coworkers (1975) to calculate a lifetime advisory of 200 ug/L. The health advisory uses a lowest-observed-adverse-effect-level of 250 ppm for mice and values for humans into the appropriate formula. If, instead, mouse body weight and ventilation rate are taken into consideration, a 10-fold higher advisory will result.

Skin absorption is not considered in detail. There is some skin absorption with methyl chloroform, but it does not appear to be a major contributor to exposure, based on data in the Criteria Document.

There is considerable data available on human toxicity of methyl chloroform, but little of this data is mentioned in the health advisory.

The analysis of mutagenicity results needs further clarification with respect to the actual material tested, presence of contaminants, and so forth. In particular, the analysis should consider the possibility of action on spindle fibers and resulting clastogenic action.

If methyl chloroform is classified under EPA's new guidelines as a category D carcinogen, the health advisory should not refer to a q₁ for carcinogenic potency.

The health advisory should reference and consider two potentially confusing aspects: (1) the 1-day advisory is approximately the same as the advisory for "longer-term" adult exposure, and (2) the solubility of methyl chloroform in water is less than the advisory levels. Further explanation of these apparent inconsistencies is desirable.

N. 1,1,2-TRICHLOROETHYLENE HEALTH ADVISORY

In general, the information in the drinking water health advisory for trichloroethylene accurately reflects the criteria document. The health advisory for trichloroethylene more clearly delineates the differences between non-carcinogenic concentrations and the concentration which relates to carcinogenesis than do other advisories. However, the trichloroethylene health advisory does not use the Criteria Document for trichloroethylene for all the source material. In many cases, the drinking water health advisory material cited is more recent than that cited in the Criteria Document.

In the section about general information and properties, some other synonyms for trichloroethylene could be added, such as ethinyl trichloride; Tri-Clene; Trielene; Trilene; Trichloran; Trichloren; Algylen; Trimar; Triline; Tri; Trethylen; Trethylene; Westrosol; Chlorylen; Gemalgene; Germalgene.

The description of physical properties is not complete, and the Subcommittee suggests adding the following additional information, which may be of value and which was obtained from Patty's Industrial Hygiene and Toxicology (Vol. IIB, 1981).

Vapor Pressure	75 mm Hg (25°C)
Water Solubility	0.1g/100 ml(H ₂ O, 20°C)
Boiling Point	8.7°C (760 mm Hg)
Density	1.456 (25°C)
Physical State	Colorless Liquid
Nonflammable	
Autoignition Temperature	410°C
CAS #	79-01-6.
% in Saturated Air	10.2 (25°C)
Conversion Factors	1 ppm in air = 5.38 mg/m ³ at 25°C, 760 mm Hg 1 mg/L = 185.8 ppm

According to the comments received by the Subcommittee, trichloroethylene is generally recovered from degreasing residues and recycled, while the dumping of trichloroethylene on the ground has been prohibited. Thus, contamination of ground water is likely to be a result of past disposal practices. The health advisory should state whether the Agency agrees with these comments.

Trichloroethylene is degraded in the presence of light and moisture.

The section about pharmacokinetics should note that after excretion in human urine, Soucek and Vlachova (1959) reported the ratio of trichloroethylene metabolites to be 1:5:12 (monochloroacetic acid: trichloroacetic acid: trichloroethanol). More recent studies with humans are reported in the Criteria Document, although results are similar. Based on total trichloro compounds in the urine of factory

workers, the biological half-life of trichloroethylene was calculated to be approximately 41 hours (Ikeda and Imamura, 1973). Trichloroethylene does not bioaccumulate.

Acute exposure to trichloroethylene is associated with liver damage and cardiac irregularities. After longer exposures, the most common complaints of exposed workers involve central nervous system disturbances.

Inhaled trichloroethylene (500 ppm) depressed myocardial activity in dogs (Aviado and coworkers, 1976).

The health advisory should note that Tucker and coworkers (1982) found that pale, spotty and granular livers developed in all groups of male and female mice exposed for six months to trichloroethylene in drinking water at 100, 1,000, 2,500 and 5,000 mg/L.

The health advisory does not describe developmental effects bioassays in which no positive results were found, or summarize any of the information about reproductive effects. For example, Zenick and coworkers (1984) found no trichloroethylene-related effects on the sperm of male rats after oral administration, and Manson and coworkers (1984) found no fertility and pregnancy effects in female rats. Reproductive effects were not found in four epidemiology studies.

The health advisory omits reference to a 1980 National Cancer Institute bioassay. Doses of trichloroethylene should be listed for all carcinogenicity studies.

The study by Kimmerle and Eben (1973) does provide a reasonable basis for the calculation of a DWEL, but it should be noted that increased liver weight was found after 14 weeks exposure (5 days/wk) to 55 ppm by inhalation, which indicates a toxic response in the liver. The advisory might report the number of animals per group, effects on body weight, and any other endpoints that were reported by Kimmerle and Eben.

The RRFD value reflects a calculational error.

The Subcommittee recommends that Agency staff carefully review the available chronic bioassay data for possible pathological changes, such as organ weight changes, that could be used to calculate effects levels.

O. VINYL CHLORIDE HEALTH ADVISORY

The health advisory and the Criteria Document contradict each other about population exposures. The health advisory states that little or no exposure is expected from food, whereas the Criteria Document states that the principal source of vinyl chloride exposure for most Americans is probably from polyvinyl chloride food containers, which contribute approximately 1 ppb to the diet.

The difference in ¹⁴C-vinyl chloride distribution between the study by Bolt and coworkers (1976) compared to those of Watanabe and coworkers (1976a,b) is not a time difference in distribution but a difference in the time of ¹⁴C assay after administration of the labeled compound (72 hours post-administration compared to immediately). The Bolt article is also misquoted.

The information about the model of Withey and Collins (1976) relates to absorption instead of excretion.

In the section about human health effects, the actual exposure conditions of 40-900 ppm in air should be cited, rather than describe them as "high." These values might be compared to the U.S. Occupation Safety and Health Administration standard of 1 ppm.

The description of carcinogenic effects should be placed in the section on human health effects, should refer to Tabershaw and Gaffey (Journal of Occupational Medicine, 1979) and should begin with note on the work of Creech and Johnson (Journal of Occupational Medicine, 1974). It may be worthwhile to point out the high risk and specificity of association with a rare tumor.

Although the studies by Infante on birth defects have been in dispute, they should be mentioned. Dominant lethal studies have been negative, as reported by Purchase and coworkers (Lancet, 28: 410, 1975).

The health advisory describes the data of Torkelson and coworkers (1960) as a 7 hour daily exposure, but the Criteria Document describes the same study as a 2 hour daily exposure. If the latter value is correct, a difference of 3.5 is introduced into the calculation of the 10-day advisory. A 10-day advisory also could be calculated from the inhalation study of Torkelson and coworkers (1961), using the calculation of Withers and Collins (1976), as follows:

$$100\text{ppm} \times \frac{7}{24} \times \frac{5}{7} \times \frac{20\text{mg/L}}{2 \text{ ppm}} \times \frac{40\text{ml/day/rat}}{250 \text{ gram/rat}} = 33 \text{ mg/kg/day}$$

The data of Feron (1981) and Til (1983) are misdescribed. Feron found no angiosarcomas at 1.7 mg/kg/day and at 5 mg/kg/day found a significant excess of angiosarcomas in male rats and a significant excess of hepatocellular cancers in female rats. Til found no significant excess of hepatocellular cancer at 1.7 mg/kg/day in female rats, but did in males. Til also found a nonsignificant increase in the incidence of angiosarcoma at 1.7 mg/kg/day for either sex of rat.

The data of both studies can be summarized, as follows:

<u>Male Effects</u>	<u>Data of Til (1983)</u>				
Dose	0	0	0.017	0.17	1.7
Basophilic Foci	5	16	12	15	23
Neoplastic Nodule	0	0	0	0	3
Hepatocellular Cancer	0	0	0	0	3
Angiosarcoma	0	0	0	0	1

<u>Male Effects</u>	<u>Data of Feron (1981)</u>					
Dose	0	1.7	5	14.1
Basophilic Foci	8	18	21	22
Neoplastic Nodule	0	1	7	23
Hepatocellular Cancer	0	1	2	8
Angiosarcoma	0	0	6	27

<u>Female Effects</u>	<u>Data of Til (1983)</u>				
Dose	0	0	0.017	0.17	1.7
Basophilic Foci	19	7	17	31	32
Neoplastic Nodule	0	0	1	1	10
Hepatocellular Cancer	1	0	0	1	3
Angiosarcoma	0	0	0	0	2

<u>Female Effects</u>	<u>Data of Feron (1981)</u>					
Dose	0	1.7	5	14.1
Basophilic Foci	2	33	17	28
Neoplastic Nodule	0	26	39	44
Hepatocellular Cancer	0	4	19	29
Angiosarcoma	0	0	2	9

U.S. Environmental Protection Agency
Science Advisory Board
Environmental Health Committee
Halogenated Organics Subcommittee
January 14-17, 1986

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Dr. Tom Starr, CIIT, P.O. Box 12137, Research Triangle Park, NC 27709

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 HALOGENATED ORGANICS SUBCOMMITTEE
BY MEMBERS OF THE PUBLIC REGARDING THE 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.
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Washington, D.C. 20005

Contact: Danna M. Cirolia

Date: November 22, 1985

Halogenated Solvents Industry
Alliance
1330 Connecticut Ave. N.W.
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Washington, D.C. 20036

Contact: Paul A. Cammer

Date: December 9, 1986

Diamond Shamrock Corporation
World Headquarters
717 North Harwood Street
Dallas, Texas 75201

Contact: Ross E. Jones

Date: December 2, 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

Date: August, 1984

State of Connecticut
Department of Health Services

Contact: David R. Brown

Date: December 12, 1985

Michigan Pure Water Council

Contact: Martha Johnson

December 12, 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

Chemical Manufacturers Association
2501 M Street, NW
Washington, DC 20037

Contact: Ann M. Mason

Date: April 30, 1986

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

Open Meeting

Under Public Law 92-463, notice is hereby given that a four-day meeting of the Halogenated Organics Subcommittee of the Environmental Health Committee of the Science Advisory Board will be held on January 14-17, 1986, in Conference Room 3906-3908 at Waterside Mall; U.S. Environmental Protection Agency; 401 M Street, S.W.; Washington, DC; 20460. The meeting will start at 9:00 a.m. on January 14 and adjourn no later than 4:00 p.m. on January 17.

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

Carbon tetrachloride	Dioxin
Chlorobenzene	Epichlorohydrin
Dichlorobenzenes	Hexachlorobenzene
1,2-Dichloroethane	Polychlorinated biphenyls
1,2-Dichloroethylenes	Tetrachloroethylene
1,1-Dichloroethylene	1,1,1-Trichloroethane
Dichloromethane	Trichloroethylene
Dichloropropane	Vinyl chloride

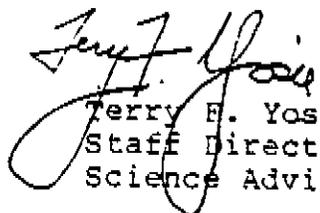
The Halogenated Organics Subcommittee will not receive oral comments on the Health Advisory documents at the meeting. Written comments on any of the specific substances should be delivered within forty (40) days from the date of this notice to Manager, Health Advisory Program; Criteria and Standards 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.

October 15, 1985

Date


Terry E. Yosie
Staff Director
Science Advisory Board

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

Conference Room 3906-3908
Waterside Mall
401 M Street, SW
Washington, DC 20460
January 14-17, 1986

ORDER OF BUSINESS

REVIEWS OF DRAFT DRINKING WATER HEALTH ADVISORIES

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

*Tentative Sequence of Reviews, beginning Tuesday, January 14, 1986

<u>Substance (Manager)</u>	<u>Reviewers</u>
Carbon tetrachloride (Anderson)	Drs. Keller and Ahmed
Trichloroethylene (Khanna)	Drs. Radike and Hornbrook
Dichloromethane (Khanna)	Drs. Keller and Hood
Dichloroethylenes (Crisp)	Drs. Hornbrook and Lamm
Methylchloroform (Patel)	Drs. McMillan and Keller
Dichloropropane (Patel)	Drs. Ahmed and McMillan
Polychlorobiphenyls (Khanna)	Drs. Hood and Safe
Tetrachloroethylene (Khanna)	Drs. Radike and Safe
1,2-Dichloroethane (Khanna)	Drs. Ahmed and Abrahamson
Dioxin [TCDD] (Anderson)	Drs. Safe and Hood
Vinyl chloride (Anderson)	Drs. Lamm and Radike
Chlorobenzene (Anderson)	Drs. Rozman and Abrahamson
Epichlorohydrin (Anderson)	Drs. Abrahamson and Starr
Dichlorobenzenes (Anderson)	Drs. Rozman and Starr
Hexachlorobenzene (Anderson)	Drs. Starr and Rozman

At the conclusion of the reviews

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

Other Subcommittee Business

Concluding remarks	Dr. Doull Dr. Byrd
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ADJOURNMENT

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