UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D C 20460

January 16, 1987

SAB-EHC-87-020

OFFICE OF THE ADMINISTRATOR

Honorable Lee M. Thomas
Administrator
U.S. Environmental Protection Agency
401 M Street, SW
Washington, DC 20460

Dear Mr. Thomas:

The Enviromental Health Committee of the Science Advisory Board has completed its review of a draft Drinking Water Criteria Document for Monochlorobenzene at the request of the Office of Drinking Water. The review was chiefly carried out by the Halogenated Organics Subcommittee, whose report is attached.

Based on the lack of a statistically significant increase in the incidence of tumors in female mice, male mice and female rats, and on the basis of the perception of a diminished biologic significance of reported malignant neoplastic nodules of the liver in the highest dose-treated male rats, the Subcommittee evaluated the animal evidence for carcinogenicity of chlorobenzene to be "inadequate" under EPA's new guidelines. This evidence would place chlorobenzene into the overall weight-of-the-evidence category "D" (not classified).

We request a formal Agency response to our advice.

Sincerely,

Richard Greisemer

Richard A. Greisemer, D.V.M., Ph.D.
Chair, Environmental Health Committee

Norton Nelson

Norton Nelson, Ph.D.
Chair, Executive Committee

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

December 16, 1986

OFFICE OF
THE ADMINISTRATOR

Richard A. Griesemer, D.V.M., Ph.D.
Chair, Environmental Health Committee
Science Advisory Board
U.S. Environmental Protection Agency
401 M Street, SW
Washington, DC 20460

Dear Dr. Griesemer:

On July 23-24, 1986, the Halogenated Organics Subcommittee reviewed a draft Drinking Water Criteria Document for Monochlorobenzene in Kansas City, KS. The Science Advisory Board previously reviewed a draft drinking water health advisory for chlorobenzene. Because of inconsistencies in the health advisory levels for different times of exposure that were noted in the health advisory review, the Office of Drinking Water requested a more detailed evaluation based on the more extensive description in the draft Criteria Document.

The attached Subcommittee report provides advice on resolving the inconsistencies in monochlorobenzene health advisory levels. The draft Criteria Document contained most of the information necessary to discuss this matter, and it should be adequate for Agency use as a support document for drinking water regulatory decisions after the changes indicated in the attached report are incorporated.

We also wish to commend the scientific staff for their excellent cooperation and their clear presentation of the scientific issues. We appreciate the opportunity to comment on this public health issue.

Sincerely,

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

Seymour Abrahamson

Seymour Abrahamson, Ph.D.
Vice-Chair, Halogenated Organics Subcommittee

TECHNICAL COMMENTS OF THE HALOGENATED ORGANICS SUBCOMMITTEE ON EPA's DRAFT DRINKING WATER CRITERIA DOCUMENT FOR MONOCHLOROBENZENE

On July 23-24, 1986, the Halogenated Organics Subcommittee reviewed a draft Drinking Water Criteria Document for Monochlorobenzene in Kansas City, KS. The draft document provided most of the relevant scientific data about this substance and reached reasonable conclusions about the data, except as noted below. When revisions are incorporated, the document should be scientifically adequate for the Agency's needs in developing drinking water regulations for this compound.

Biotransformation

The Subcommittee disagrees with the metabolic pathways illustrated in the draft document and suggests that biotransformation of monochlorobenzene occurs as illustrated in the attached chart developed by the Subcommittee (See Appendix I). This version is based on the references cited in Chapter IV of the draft document.

Mechanisms of Toxicity

The section on the mechanisms of toxicity needs revision. The Agency assumes that the mechanism of hepatotoxicity is similiar to that of bromobenzene, but the work of Dalich and Larson indicates that the mechanism of toxicity of chlorobenzene differs from that of bromobenzene.[1] The mechanism of toxicity of chlorobenzene is not known.

Information that is presently included in the mechanism section on the induction of cytochrome P-450 and porphyria should be moved to the animal health effects section. Tables VII-4 of VII-7 should be also moved and simplified to include only the chlorobenzene data.

Calculation of Health Advisory Values

The Subcommittee recommends that the criteria document not use the inhalation study of Hayes and co-workers to derive a ten-day health advisory for chlorobenzene; interpretation of inhalation data for oral exposure often is problematic. Uncertainties will exist in accounting for dose, absorption, metabolism, distribution and retention that may lead to avoidable inconsistencies in the health advisory, as demonstrated by the draft document for chlorobenzene. The problem of converting inhalation data from one species using respiratory parameters of another species has been discussed in the Subcommittee's previous comments on health advisories. Whenever possible, health advisories should be based on oral exposure data. In the absence of suitable short-term studies, the health advisories for different time periods should increase or remain unchanged with decreasing length of exposure.

[1] G. M. DALICH and R. E. LARSON, "Temporal and Dose-Response Features of Monochlorobenzene Heapatotoxicity in Rats," Fundamental and Applied Toxicology 5 (1985), pp. 105-16.

Battelle performed subchronic and chronic (carcinogenicity) bioassays for the National Toxicology Program. Because of the greater detail, the Subcommittee relied on Battelle's publication. At similar doses, reduced body weight gain occurred in the Battelle subchronic study in mice, whereas no change in body weight occurred in the National Toxicology Program carcinogenicity bioassay. In situations where two experiments provide confliciting data, the Subcommittee believes that it is prudent to assume that the longer-term study with larger number of animals provides the more reliable data. However, implicit in this assumption is the belief that the subchronic toxicity study may be flawed. A flawed study should not be used to derive a health advisory.

There are two subchronic studies and one chronic study of chlorobenzene in the rat which appear suitable as a basis for a health advisory, each with the characteristics listed as follow:

STUDY	BATTELLE	KNAPP	NATIONAL TOXICOLOGY PROGRAM
NOAEL	60 mg/kg/day (5 days/week)	50 mg/kg/day (7 days/week)	60 mg/kg/day (5 days/week)

The Subcommittee then calculated the following health advisory values:

STUDY	BATTELLE		KNAPP		NATIONAL TOXICOLOGY PROGRAM	
HEALTH ADVISORY (TIME)	Child	Adult	Child	Adult	Child	Adult[2]
ONE-DAY	4.3mg/L	15.0/mg/L	5.0 mg/L	17.5 mg/L	4.3mg/L	1.5 mg/L
TEN-DAY	4.3 mg/L	15.0 mg/L	5.0 mg/L	17.5 mg/L	4.3 mg/L	1.5 mg/L
LONGER-TERM	4.3 mg/L	15.0 mg/L	5.0 mg/L	17.5 mg/L	4.3 mg/L	1.5 mg/L
LIFE-TIME	--	1.5 mg/L	--	1.8 mg/L	--	1.5 mg/L

[2]Although the life-time health advisory value derived from the National Toxicology Program bioassay yields a higher virtually safe dose for chlorobenzene than do those derived from the subchronic studies, these values express the Subcommittee's view that prudence suggests the use of 1.5 - 1.8 mg/L for the life-time health advisory. If the standard is "safe" for lifetime exposure, then the same level should be safe for exposures of shorter duration. The National Toxicology Program did not monitor certain endpoints of toxicity, such as induction of porphyria, during its bioassay, and the absence of data on this endpoint influenced the Subcommittee's thinking.

Developmental Effects

In the teratogenicity section (pp. V-13), the Subcommittee suggests deleting the first paragraph because a peer reviewed study of rabbits (Phase I and Phase II) is now available. Although the peer reviewed publication and the preliminary report show no statistical difference in the incidence of terata between groups, the severity of defects appears to differ between treated and untreated fetuses. For this reason, the Subcommittee suggests that the severity as well as the total number of defects should be evaluated.

Carcinogenicity

In the carcinogenicity section (V-24 to 31) of the draft document, the Subcommittee identified several problems that merit attention. The draft is based on the National Toxicology Program's gavage bioassay in rodents which was reported in the Health Effects Criteria Document only on the basis of a National Toxicology Program draft. This report has subsequently been published (National Toxicology Program Technical Report Series No. 261).

The bioassay appears to be of relatively good quality. However, the National Toxicology Program Technical Report does not fully describe certain observations that have major bearing on the interpretation of the study. First, the only lesions of statistical significance were classified as neoplastic nodules of the liver. These occurred in high dose-treated male rats. However, nowhere in the National Toxicology Program report is there a description of the number of sections of liver tissue inspected from these rats. As these lesions are focal, microscopic and multiple, a "significant" frequency difference could result from sampling rather than biological occurrence. Second, the report did not specify the criteria for identification and specification of these lesions as "malignant." Recent observations have cast doubt on the idea that some so-called "malignant" nodules of the liver are invariably progressive, metastatic and lethal to the host. Thus, in the absence of a definitive description, some pathologists today might classify these hepatic lesions as preneoplastic or hyperplastic only. These concerns tend to reduce the perception that the nodules found at a statistically significant incidence in male rats at the high dose were indeed malignant. Additional support for this view may be seen in that no hepatocellular carcinomas were diagnosed in untreated controls or chlorobenzene treated male rats in this study.

The occurrence of neoplastic nodules of the liver in the concurrent untreated controls (4/50, 8%) was not significantly different ($p > 0.05$) from that in the concurrent vehicle controls (2/50, 4%), but was greater than that in historical male rat untreated controls for recent National Toxicology Program studies (67/3618, 1.9%). Adjustments were not made for possible differences in survival. Does this upward shift in the incidence of lesions support the introduction of an unidentified variable? Is it necessary to support their recognition or occurrence? The draft document does not clarify these issues.

The draft document does not describe the occurrence of a renal tubular cell adenocarcinoma in a single high dose female rat, or of transitional cell papillomas of the urinary bladder in one each of the low and high dose male rats. Although these lesions were not statistically significant, they are of toxicologic concern because of the relative rarity of their occurrence in F344 rats of the appropriate sex. These observations should be mentioned in the Criteria Document.

Based on the lack of a statistically significant increase in the incidence of tumors in female mice, male mice and female rats, and on the basis of the perception of a diminished biologic significance of reported malignant neoplastic nodules of the liver in high dose-treated male rats, the Subcommittee evaluated the animal evidence for carcinogenicity of chlorobenzene to be "inadequate" under EPA's new guidelines. This evidence would place chlorobenzene into the overall weight-of-the-evidence category "D" (not classified).

Human Health Effects

The Halogenated Organics Subcommittee agrees that the last paragraph in the human health effects section ("Special Groups of Risk") did not contribute anything meaningful to this section and that this paragraph should be deleted. The remainder of the section and the table (V 1-1) are adequate. The Subcommittee observes that the acute exposure effects reported were generally consistent with the revised health advisory recommendations. These values indicate a large margin of safety for actual health effects following exposure to chlorobenzene.

Mutagenicity

Monochlorobenzene does not induce either DNA damage or gene mutations in standard mutagenicity tests with procaryotes and eucaryotes; neither do any studies indicate the induction of chromosomal aberrations. One study in a higher plant did indicate mitotic disturbance at a high dose, and a second study in yeast demonstrated an increase in mitotic recombination.

Multiple Chemical Exposures

Monochlorobenzene and related compounds can interact with the cytochrome P_{450} and, therefore, have the potential to alter the metabolism of other chemicals which are metabolized by the cytochrome P_{450}-dependent monooxygenases. At high doses, chlorobenzene decreases the level of microsomal cytochrome P_{450} in rats. (See Tables V 11-6 and V 11-7.) Presumably, this decrease occurs via suicide inactivation of the cytochromes.

Two studies report interactive effects of chlorobenzene and other xenobiotics. However, in both studies the mechanism of the interactive effect was not delineated which makes it difficult to generalize the results. The studies are:

- Halogenated benzenes and organotin compounds together demonstrated synergistic antifungal activity.[3]

[3] W. HINZE, H. KRUGER and D. KLOTZER, "Synergistic Agents for Organostannic Fungicidal Compounds," British Patent No.: 1,177,433. January (1970).

- An additive interactive effect occurred with CCl_4 and chlorobenzene in the elevation of plasma alanine aminotransferase activity in mice.[4]

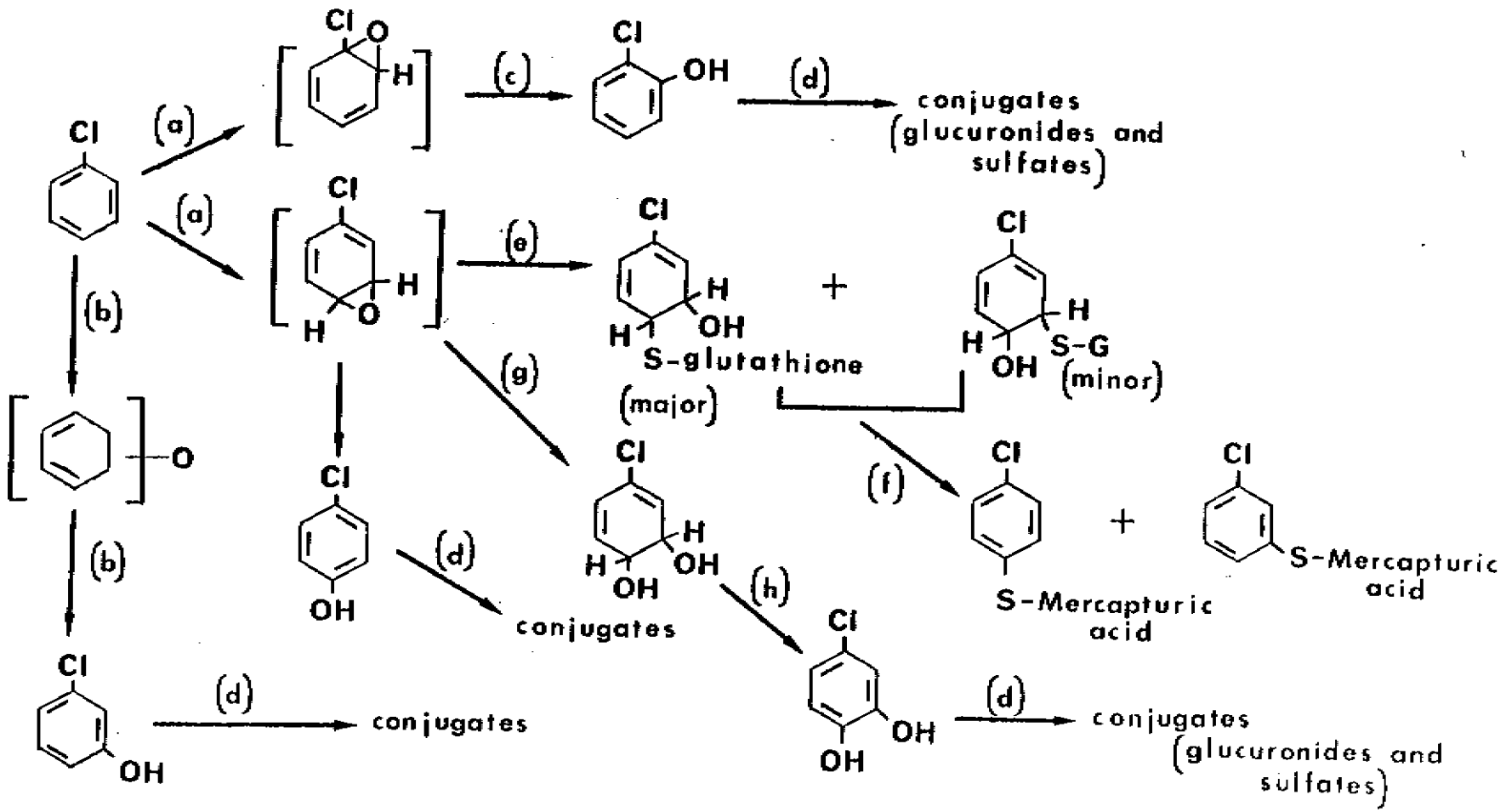
Editorial Quality

The Subcommittee suggests that this document needs editing for typographical errors, clarity in some sections, and accuracy of the parameters in tables. There are a number of obvious errors. The Subcommittee suggests that the Office of Drinking Water implement an internal process for editorial review of documents for typographical and grammatical errors, as well as for clarity and scientific accuracy. When a final draft is prepared, staff should verify all data for agreement with the cited literature. For example, in Table VII-1 (page VII-3) the doses for chlorinated benzenes are reported as "1 mmol/kg" and "1 mmolM/kg."

Use as a Source Document

The Halogenated Organics Subcommittee recommends that the Chlorobenzene Health Effects Criteria Document for Drinking Water serve as the major source document for monochlorobenzene for all other EPA Offices. The Subcommittee has provided an extensive review of the document which encompasses all of the chlorobenzene animal studies performed to date as well as existing human data.

[4] D. W. SHELTON and L. J. WEBER, "Quantification of the Effects of Mixtures of Hepatotoxic Agents: Evaluation of a Theoretical Model in Mice." Proc. West. Phamacol. Soc. 23 (1980), pp. 275-276.



(a) mixed function oxidases (MFO), NADPH, O_2; (b) unknown mechanism; (c) spontaneous rearrangement; (d) glucuronosyl transferases/UDPGA and sulfotransferases/PAPS; (e) glutathione transferases/GSH; β dehydration, peptidase, acetyltransferase yields mercapturic acid; (g) expoxide hydrolase/H_2O; (h) dehydrogenase ($-H_2$)

NOTE: Additional oxidation of phenols and catechols and dioxygenase ring cleavage can also occur.

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

July 23 & 24, 1986
Kansas City, KS

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Executive Secretary

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