[OPTS-41023; FRL-3109-7]

Nineteenth Report of the Interagency Testing Committee to the Administrator; Receipt and Request for Comments Regarding Priority List of Chemicals

AGENCY: Environmental Protection Agency (EPA).

ACTION: Notice.

SUMMARY: The Interagency Testing Committee (ITC), established under section 4(e) of the Toxic Substances Control Act (TSCA), transmitted its Nineteenth Report to the Administrator of EPA on October 31, 1986. This report, which revises and updates the Committee's priority list of chemicals, adds four chemicals to the list for priority consideration by EPA in the promulgation of test rules under section 4(a) of the Act. The new chemicals are isopropanol, C.I. Disperse Blue 79, methyl *tert*-butyl ether, and methyl ethyl ketoxime. These chemicals are not designated for response within 12 months. One substance previously recommended with intent to designate, tributyl phosphate (51 FR 18368), is now designated for response within 12 months. The Nineteenth Report is included in this notice. The Agency invites interested persons to submit written comments on the Report, and to attend a Focus Meeting to help narrow and focus the issues raised by the ITC's recommendations. Members of the public are also invited to inform EPA if they wish to be notified of subsequent public meetings on these chemicals. ITC also notes the removal of five chemicals from the priority list because EPA has responded to the ITC's previous recommendations for testing of the chemicals.

DATES: Written comments should be submitted by December 15, 1986. Focus Meetings will be held on December 16 and 17, 1986.

ADDRESSES: Send written submissions to: TSCA Public Information Office (TS-793), Office of Pesticides and Toxic Substances, Environmental Protection Agency, Rm. NE G-004, 401 M St., SW., Washington, DC 20460.

Submissions should bear the document control number (OPTS-41023).

The public record supporting this action, including comments, is available for public inspection in Rm. NE G-004 at the address noted above from 8 a.m. to 4 p.m. Monday through Friday, except legal holidays. Focus Meetings will be held at EPA Headquarters, Rm. 103 NE Mall, 401 M St., SW., Washington, DC. Persons planning to attend the Focus Meetings and/or seeking to be informed of subsequent public meetings on these chemicals, should notify the TSCA Assistance Office at the address listed below. To ensure seating accommodations at the Focus Meetings, persons interested in attending are asked to notify EPA at least one week ahead of the scheduled date.

FOR FURTHER INFORMATION CONTACT: Edward A. Klein, Director, TSCA Assistance Office (TS-799), Office of Toxic Substances, Environmental Protection Agency, 401 M St., SW., Washington, DC. 20460, (202-554-1404).

SUPPLEMENTARY INFORMATION: EPA has received the Report of the TSCA Interagency Testing Committee to the Administrator.

I. Background

TSCA (Pub. L. 94-469, 90 Stat. 2003 *et seq;* 15 U.S.C. 2601 *et seq.*) authorizes the Administrator of EPA to promulgate regulations under section 4(a) requiring testing of chemical substances and mixtures in order to develop data relevant to determining the risks that such chemical substances and mixtures may present to health and the environment.

Section 4(e) of TSCA established an Interagency Testing Committee to make recommendations to the Administrator of EPA of chemical substances and mixtures to be given priority consideration in proposing test rules under section 4(a). Section 4(e) directs the Committee to revise its list of recommendations at least every 6 months as necessary. The ITC may "designate" up to 50 substances and mixtures at any one time for priority consideration by the Agency. For such designations, the Agency must within 12 months either initiate rulemaking or issue in the **Federal Register** its reasons for not doing so. The ITC's Nineteenth Report was received by the Administrator on October 31, 1986, and follows this Notice. The Report adds four substances to the TSCA section 4(e) priority list.

II. Written and Oral Comments and Public Meetings

EPA invites interested persons to submit detailed comments on the ITC's new recommendations. The Agency is interested in receiving information concerning additional or ongoing health and safety studies on the subject chemicals as well as information relating to the human and environmental exposure to these chemicals. A notice is published elsewhere in today's **Federal Register** adding the substances recommended in the ITC's Nineteenth Report to the TSCA section 8(d) Health and Safety Data Reporting Rule (40 CFR Part 716). The section 8(d) rule requires the reporting of unpublished health and safety studies on the listed chemicals. These chemicals will also be added to the TSCA section 8(a) Preliminary Assessment Information Rule (40 CFR Part 712) published elsewhere in this issue. The section 8(a) rule requires the reporting of production volume, use, exposure, and release information on the listed chemicals.

Focus Meetings will be held to discuss relevant issues pertaining to these chemicals and to narrow the range of issues/effects which will be the focus of the Agency's subsequent activities in responding to the ITC recommendations. The Focus Meetings will be held on December 16 and 17, 1986 at EPA Headquarters, Rm. 103 NE Mall, 401 M St., SW., Washington, DC. This meeting is intended to supplement and expand upon written comments submitted in response to this notice. The schedule for the Focus Meetings is as follows: December 16, 10 a.m.—isopropanol; 1 p.m.—C.I. Disperse Blue 79. December 17, 10 a.m.—methyl *tert*-butyl ether; 1 p.m.—methyl ethyl ketoxime.

Persons wishing to attend this meeting or subsequent meetings on these chemicals should call the TSCA Assistance Office at the toll free number listed above at least one week in advance.

All written submissions should bear the identifying docket number (OPTS-41023).

III. Status of List

In addition to adding the four recommendations to the priority list, the ITC's Nineteenth Report notes the removal of five chemicals from the list since the last ITC report because EPA has responded to the Committee's prior recommendations for testing of the chemicals. Subsequent to the ITC's preparation of its Eighteenth Report, EPA responded to the ITC's recommendations for six additional chemicals. The five chemicals removed and the dates of publication in the **Federal Register** of EPA's responses to the ITC for these chemicals are: methylcyclopentane, May 15, 1986 (51 FR 17854); tetrabromobisphenol A, May 15, 1986 (51 FR 17872); triethylene glycol monomethyl ether, May 15, 1986 (51 FR 17883); triethylene glycol monobutyl ether, May 15, 1986 (51 FR 17883); triethylene glycol monobutyl ether, May 15, 1986 (51 FR 17883). The report also notes that tributyl phosphate, which was originally recommended with intent to designate (51 FR 18368, May 19, 1986), has now

been designated for response within 12 months by the ITC.

The current list contains three designated substances, two chemicals recommended with intent-to-designate, and four recommended substances.

Authority: 15 U.S.C. 2603.

Dated: November 6, 1986.

J. Merenda,

Director, Existing Chemical Assessment Division.

Nineteenth Report of the TSCA Interagency Testing Committee to the Administrator, Environmental Protection Agency

Summary

Section 4 of the Toxic Substances Control Act of 1976 (TSCA, Public Law 94–469) provides for the testing of chemicals in commerce that may present an unreasonable risk of injury to health or the environment. It also provides for the establishment of a Committee (ITC), composed of representatives from eight designated Federal agencies, to recommend chemical substances and mixtures (chemicals) to which the Administrator of the U.S. Environmental Protection Agency (EPA) should give priority consideration for the promulgation of testing rules.

Section 4(e)(1)(A) of TSCA directs the Committee to recommend to the EPA Administrator chemicals to which the Administrator should give priority consideration for the promulgation of testing rules pursuant to section 4(a). The Committee is required to designate those chemicals, from among its recommendations, to which the Administrator should respond within 12 months by either initiating a rulemaking proceeding under section 4(a) or publishing the Administrator's reason for not initiating such a proceeding. At least every 6 months, the Committee makes those revisions in the TSCA section 4(e) Priority List that it determines to be necessary and transmits them to the EPA Administrator.

As a result of its deliberations, the Committee is revising the TSCA section 4(e) Priority List by the addition of four chemicals, and is noting the removal of five as a result of responses by EPA. The Committee also is designating one chemical that had been recommended with intent-to-designate in the eighteenth report.

The Priority List is divided into three parts: Part A contains those recommended chemicals and groups designated for priority consideration and response by the EPA Administrator within 12 months. Part B contains chemicals and groups recommended with intent-to-designate. This category was established by the Committee in its seventeenth report (50 FR 47603; November 19, 1985) to take advantage of rules promulgating automatic reporting requirements for nondesignated ITC recommendations under the section 8(a) Preliminary Assessment rule and the TSCA section 8(d) Health and Safety Data Reporting rule. Information received following recommendation with intent-to-designate may influence the Committee to either designate or not designate the chemical or group of chemicals in a subsequent report to the Administrator. Part C contains chemicals and groups of chemicals that have been recommended for priority consideration by EPW without being designated for response within 12 months. The changes to the Priority List are presented, together with the types of testing recommended, in the following Table 1:

TABLE 1.—ADDITIONS TO THE SECTION 4(e) PRIORITY LIST, NOVEMBER 1986

Chemical/Group	Recommended Studies
A. Designated for Response Within 12 Months	
Tributyl phosphate [1] (CAS No. 126–73–8).	Health Effects: Chronic Toxicity including oncogenic, neurotoxic, renal, reproductive and developmental effects. Chemical Fate: Persistence in anaerobic soils and sediments. Ecological Effects: Chronic effects on aquatic and terrestrial plants; chronic effects on daphnids and/or other aquatic invertebrates; acute and chronic effects on benthic organisms and soil invertebrates, if found persistent under anaerobic conditions.
B. Recommended With Intent-to-Designate	
Isopropanol [2] (CAS No. 67–63–0).	Health Effects: Genotoxicity, including tests for mutagenicity in mammalian systems and clastogenicity; chronic toxicity including oncogenicity.
Methyl *tert*-butyl ether [3] (CAS No. 1634–04–4).	Health Effects: Chronic inhalation toxicity including neurotoxic, hematologic and ocogenic effects. Chemical Fate: Monitoring at representative gasoline terminals and service stations.
C. Recommended Without Being Designated for Response Within 12 Months	
C.I. Disperse Blue 79 [4] (CAS No. 3956–55–6).	Health Effects: Subchronic toxicity; adsorption and chemical disposition. Chemical Fate: Solubility in water; biodegradation under aerobic and anaerobic conditions and the identification of any relatively persistent biodegradation intermediates. Ecological Effects: Acute toxicity to fish, aquatic invertebrates, algae and benthic organisms (including filter feeders); bioconcentration in fish; chronic effects on aquatic and benthic biota, if the acute studies show toxicity at low mg/L concentration or if the dye does bioconcentrate.
Methyl ethyl ketoxime [5] (CAS No. 96–29–7).	Health Effects: Chronic toxicity with special emphasis on hematopoietic and oncogenic effects.

CA Index Names (9CI):

[1] Phosphonic acid, tributyl ester (tributyl phosphate was recommended with intent-to-designate by the Committee in the eighteenth report (51 FR 18368)).

[2] 2-Propanol.

[3] Propane, 2-methoxy-2-methyl-

[4] Acetamide, *N*-[5-[bis[2-(acetyloxy)ethyl]amino]-2-[(2-bromo-4,6-dinitrophenyl)azo]-4-ethoxyphenyl]-

[5] 2-Butanone oxime.

TSCA Interagency Testing Committee

Statutory Member Agencies and Their Representatives

Council on Environmental Quality
Harvey Doerksen, Member
Department of Commerce
Patrick D. Cosslett, Member
Environmental Protection Agency
John D. Walker, Member and Vice Chairperson
Laurence S. Rosenstein, Alternate
National Cancer Institute
Richard Adamson, Member
Elizabeth K. Weisburger, Alternate
National Institute of Environmental Health Sciences
James K. Selkirk, Member
National Institute for Occupational Safety and Health
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National Science Foundation
Rodger W. Baier, Member
Jarvis L. Moyers, Alternate
Occupational Safety and Health Administration
Joseph Jarvis, Member [1]
Stephen Mallinger, Alternate

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Food and Drug Administration
Arnold Borsetti
National Library of Medicine
Vera Hudson
National Toxicology Program
Dorothy Canter

Committee Staff

Robert H. Brink, Executive Secretary
Norma Williams, ITC Coordinator

Support Staff

Alan Carpien—Office of the General Counsel, EPA

The Committee acknowledges and is grateful for the assistance and support

[1] Appointed on August 11, 1986.

[2] Appointed on July 11, 1986.

given the ITC by the staff of Dynamac Corporation (technical support contractor) and personnel of the EPA Office of Toxic Substances.

Chapter 1—Introduction

1.1 *Background.* The TSCA Interagency Testing Committee (Committee) was established under section 4(e) of the Toxic Substances Control Act of 1976 (TSCA, Public Law 94–469). The specific mandate of the Committee is to recommend to the Administrator of the U.S. Environmental Protection Agency (EPA) chemical substances and mixtures in commerce that should be given priority consideration for the promulgation of testing rules to determine their potential hazard to human health and/or environment. TSCA specifies that the Committee's recommendations shall be in the form of a Priority List, which is to be published in the **Federal Register.** The Committee is directed by section 4(e)(1)(A) of TSCA to designate those chemicals on the Priority List to which the EPA Administrator should respond within 12 months by either initiating a rulemaking proceeding under section 4(a) or publishing the Administrator's reason for not initiating such a proceeding. There is no statutory time limit for EPA response regarding chemicals that ITC has recommended but not designated for response within 12 months.

At least every 6 months, the Committee makes those revisions in the section 4(e) Priority List that it determines to be necessary and transmits them to the EPA Administrator.

The Committee is composed of representatives from eight statutory member agencies and seven liaison agencies. The specific representatives and their affiliations are named in the front of this report. The Committee's chemical review procedures and priority recommendations are described in previous reports (Refs. 1 through 3).

1.2 *Committee's previous reports.* Eighteen previous reports to the EPA Administrator have been issued by the Committee and published in the FEDERAL REGISTER (Refs. 1 through 3). Ninety-three entries (chemicals and groups of chemicals) were recommended for priority consideration by the EPA Administrator and designated for response within 12 months. In addition, five chemicals and one group of chemicals were recommended without being so designated.

1.3 *Committee's activities during this reporting period.* Between April 1, 1986, and September 30, 1986, the Committee continued to review chemicals from its fourth and fifth scoring exercises, and from nominations by Member Agencies, Liaision Agencies and State Agencies.

The Committee contacted chemical manufacturers and trade associations to request information that would be of value in its deliberations. Most of those contacted provided unpublished information on current production, exposure, uses, and effects of chemicals under study by the Committee.

During this reporting period, the Committee reviewed available information on 26 chemicals and 7 large classes of chemicals. Four chemicals were selected for addition to the section 4(e) Priority List, and five were deferred indefinitely. The remaining chemicals are still under study.

On August 7, 1986, the ITC published an Intent-to-Designate notice (51 FR 28431) that listed hexamethylenediamine and described additional information needed by the ITC to reach a more informed decision on whether or not to designate hexamethylenediamine in a subsequent report to the EPA Administrator. The Committee requested information on biodegradation in aerobic ponds and under both aerobic and anaerobic conditions in disposal wells, in the presence of other waste constituents typical of hexamethylenediamine production. A deadline of October 6, 1986 was provided for receipt of relevant information.

1.4 *The TSCA section 4(e) Priority List.* Section 4(e)(1)(B) of TSCA directs the Committee to: ". . . make such revisions in the [priority] list as it determines to be necessary and . . . transmit them to the Administrator together with the Committee's reasons for the revisions." Under this authority, the Committee is revising the Priority List by adding four chemicals: isopropanol, methyl *tert*-butyl ether, C.I. Disperse Blue 79, and methyl ethyl ketoxime. None of these chemicals is designated for response within 12 months but the Committee intends to designate isopropanol and methyl *tert*—butyl ether unless information received following recommendation influences the Committee to withhold designation. In addition, the Committee is designating for response within 12 months one chemical that wes recommended with intent-to-designate in the eighteenth report. The designated chemical is tributyl phosphate. The testing recommended for these chemicals and the rationales for the recommendations are presented in Chapter 2 of this report.

Five chemicals are being removed from the Priority List because the EPA Administrator has responded to the Committee's prior recommendations for testing them. They are listed in the following Table 2 with citations to EPA responses:

TABLE 2—REMOVALS FROM THE TSCA SECTION 4(e) PRIORITY LIST APRIL 1, 1986 THROUGH SEPTEMBER 30, 1986

Chemical/Group	*EPA Responses*	
	Federal Register Citation	*Publication Date*
Methyl cyclopentane	51 FR 17854	May 15, 1986.
Tetrabromobisphenol A	51 FR 17872	May 15, 1986.
Triethylene glycol monomethyl ether.	51 FR 17883	May 15, 1986.
Triethylene glycol monoethyl ether.	51 FR 17883	May 15, 1986.
Triethylene glycol monobutyl ether.	51 FR 17883	May 15, 1986.

Removal of 87 entries was noted in previous reports (Ref. 1 through 3). To date, 92 chemicals and groups of chemicals have been removed from the Priority List.

With the four recommendations and five removals noted in this report, nine entries now appear on the section 4(e) Priority List. The Priority List is divided in the following Table 3 into three parts; namely, A. Chemicals and Groups of Chemicals Designated for Response Within 12 Months, B. Chemicals and Groups of Chemicals Recommended with Intent-to-Designate, and C. Chemicals and Groups of Chemicals Recommended Without Being Designated for Response Within 12 Months. Table 3 follows:

TABLE 3.—THE TSCA SECTION 4(e) PRIORITY LIST, NOVEMBER 1986

A. Chemicals and Groups of Chemicals Recommended and Designated for Response Within 12 Months	
Entry and date of designation:	
1. Cyclohexane	May 1986.
2. 2,6-Di-*tert*-butylphenol	May 1986.
3. Tributyl phosphate	Nov. 1986.
B. Chemicals and Groups of Chemicals Recommended with Intent-to-Designate	
Entry and date of recommendation:	
1. Isopropanol	Nov. 1986.
2. Methyl *tert*-butyl ether	Nov. 1986.
C. Chemicals and Groups of Chemicals Recommended Without Being Designated for Response Within 12 Months:	
1. 3,4-Dichlorobenzotrifluoride	May 1984.
2. Diisodecyl phenyl phosphite	Nov. 1985.
3. C.I. Disperse Blue 79	Nov. 1986.
4. Methyl ethyl ketoxime	Nov. 1986.

References

(1) Sixteenth Report of the TSCA Interagency Testing Committee to the Administrator, Environmental Protection Agency. TSCA Interagency Testing Committee. May 21, 1985, 50 FR 20930–20939.

Includes references to Reports 1 through 15 and annotative list of removals.

(2) Seventeenth Report of the TSCA Interagency Testing Committee to the Administrator, Environmental Protection Agency. TSCA Interagency Testing Committee, November 19, 1985, 50 FR 47603–47612.

(3) Eighteenth Report of the TSCA Interagency Testing Committee to the Administrator, Environmental Protection Agency. TSCA Interagency Testing Committee, May 19, 1986, 51 FR 18368–18375.

Chapter 2—Recommendations of the Committee

2.1 *Chemicals recommended for priority consideration by the EPA Administrator.* As provided by section 4(e)(1)(B) of TSCA, the Committee is adding the following chemical substances to the section 4(e) Priority List: isopropanol, methyl *tert*-butyl ether, C.I. Disperse Blue 79, and methyl ethyl ketoxime. The recommendation of these chemicals is being made after considering the factors identified in section 4(e)(1)(A) and other relevant information, as well as the professional judgment of Committee members. In addition, the Committee is designating for response within 12 months one chemical substance that was recommended with intent-to-designate in the eighteenth report. The designated chemical is tributyl phosphate.

2.2 *Chemicals designated for response within 12 months*—2.2.a *Tributyl phosphate.* In the eighteenth report to the Administrator of EPA (51 FR 18368), tributyl phosphate was recommended with intent-to-designate. The rationale for that recommendation appears in the eighteenth report. Information reviewed by the Committee in response to the eighteenth report included any public comments on the Committee's recommendations; production volume, use, exposure and release information reported by manufacturers of tributyl phosphate under the TSCA section 8(a) Preliminary Assessment rule; health and safety studies submitted under the TSCA section 8(d) Health and Safety Data Report rule; and any unpublished and published data available to the Committee. Health effects information included acute toxicity studies and skin and eye irritation studies (Ref. 1, Dow Chemical Co., 1986; Ref. 2, Eastman Kodak Co., 1986; Ref. 3, FMC Corp., 1986; and Ref. 6, Stauffer Chemical Co., 1986), mutagenicity (Ames test) data (Ref. 3, FMC Corp., 1986) and delayed neurotoxicity studies (Ref. 5, Monsanto Co., 1986). Chemical fate information included chemical and physical properties, biological oxygen demand (BOD) data and monitoring reports (Ref. 2, Eastman Kodak Co., 1986; Ref. 3, FMC Corp., 1986; Ref. 4, Glyco, Inc., 1986; and Ref. 5 Monsanto Co., 1986). Ecological effects information included acute toxicity values with aquatic invertebrates and fish (Ref. 5, Monsanto Co., 1986).

After reviewing the information, the Committee concluded that data are still lacking on chronic toxicity, chemical fate and ecological effects. For these reasons and for the reasons previously presented (51 FR 18368) the Committee is now designating tributyl phosphate for response within 12 months and recommending that it be tested for the following:

1. *Health effects.* Chronic toxicity including oncogenic, neurotoxic, renal, reproductive and developmental effects.

2. *Chemical Fate.* Persistence in anaerobic soils and sediments.

3. *Ecological Effects.* Chronic effects on aquatic and terrestrial plants; chronic effects on daphnids and/or other aquatic invertebrates; acute and chronic effects on benthic organisms and soil invertebrates, if found persistent under anaerobic conditions.

References

(1) Dow Chemical Co., Midland, MI. Letter from R.L. Hagerman to Document Control Officer, U.S. EPA. August 15, 1986.

(2) Eastman Kodak Co., Rochester, N.Y. Letter from R. Hays Bell to U.S. EPA. August 11, 1986.

(3) FMC Corp., Philadelphia, PA. Letter from Ann S. Keller to U.S. EPA. August 8, 1986.

(4) Glyco, Inc., Norwalk, CT. Letter from Michael J. Reale to U.S. EPA. August 8, 1986.

(5) Monsanto Co., St. Louis, MO. Letter from J.R. Condray to Document Control Officer, Office of Pesticides and Toxic Substances, U.S. EPA. August 15, 1986.

(6) Stauffer Chemical Co., Westport, CT. Letter from Stauffer Chemical Co. to Document Control Office, Office of Toxic Substances, U.S. EPA. August 12, 1986.

(7) Union Carbide Corp., Danbury, CT. Letter from D.L. Heywood to U.S. EPA. August 11, 1986.

2.3 *Chemicals recommended with intent-to-designate—2.3.a Isopropanol—Summary of recommended studies.* It is recommended that isopropanol be tested for the following:

1. *Health Effects.* Genotoxicity studies, including tests for mutagenicity in mammalian systems and for clastogenicity Chronic toxicity, including oncogenicity.

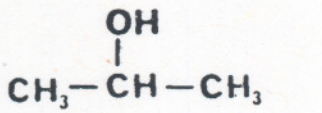
Physical and Chemical Information

CAS Number: 67–63–0

Synonyms: 2–propanol (9 CI); dimethylcarbinol; isopropyl alcohol

Acronym: IPA

Structural Formula:



Empirical Formula: C_3H_8O

Molecular Weight: 60.11

Melting Point: −87.8°C (Ref. 29, Mellan, 1977)

Boiling Point: 82.3°C (Ref. 29, Mellan, 1977)

Vapor Pressure: 33.0 mmHg at 20°C (Ref. 29, Mellan, 1977), 44.0 mmHg at 25°C (Ref. 7, Browning, 1965), 105.6 mmHg at 40°C (Ref. 18, Hatch, 1961)

Solubility in Water: Miscible with water, insoluble in salt solutions (Ref. 56, Windholz, 1983)

Solubility in Organic Solvents: Miscible with ethanol, ether, and chloroform (Ref. 56, Windholz, 1983)

Specific Gravity: 0.79 at 20/20°C (Ref. 29, Mellan, 1977)

Log Octanol/Water Partition Coefficient: (log P): 0.2 (estimated; Ref. 27, Leo et al., 1971)

Description of Chemical: colorless liquid

Rationale for Recommendations

I. *Exposure information*—A. *Production/use/disposal/environmental release.* The annual production capacities of four domestic producers of isopropanol as of January 1, 1985, totaled 2.5 billion pounds (Ref. 46, SRI, 1985). The 1985 U.S. production of isopropanol was reported to be 1.12 billion pounds, giving it the ranking of 50 among the top 50 chemicals for that year (Ref. 9, C&EN, 1986). The 1984 U.S. production of isopropanol was reported to be 1.39 billion pounds (Ref. 54, USITC, 1985), up from the 1983 production of 1.21 billion pounds (Ref. 53, USITC, 1984) but down from the 1980 production of 1.21 billion pounds (Ref. 52, USITC, 1981).

Imports of isopropanol in 1985 totaled 136.2 million pounds (Ref. 49, USDOC, 1986a). Exports in 1985 accounted for 178.4 million pounds (Ref. 50, USDOC, 1986b).

Most isopropanol produced in the United States is manufactured by the indirect hydration process. In this two-step process, propylene reacts first with sulfuric acid; the products are then hydrolyzed to isopropanol and sulfuric acid (Ref. 45, SRI, 1980).

Isopropanol has a large number of uses. The percentage breakdown of isopropanol demand for 1984 was estimated to be the following: production of acetone (24 percent), coatings and related solvents (15 percent), other solvents (11 percent),

pharmaceuticals (11 percent), household and personal products (11 percent), chemical process solvents (9 percent), chemical intermediates (7 percent), and gasoline additives (4 percent). Exports account for the other 8 percent (Ref. 12, CMR, 1984).

It has been estimated that 50 percent of commercial isopropanol is ultimately released to the environment. An additional 1.5 percent is estimated to be lost during production (Dorigan et al., 1976, cited in Ref. 51, USEPA, 1979).

B. *Evidence for human and environmental exposure.* The National Occupational Hazard Survey (NOHS), conducted by the National Institute for Occupational Safety and Health (NIOSH) from 1972 to 1974, estimated that 5,483,862 workers in 357,173 plants were potentially exposed to isopropanol in the workplace (Ref. 32, NIOSH, 1976a). These estimates were derived from observations of the manufacture and use of the compound, of trade name products known to contain the compound, and of generic products suspected to contain the compound (19, 40, and 42 percent of the total estimate, respectively).

NIOSH conducted a second workplace survey, the National Occupational Exposure Survey (NOES), from 1980 to 1983 (Ref. 34, NIOSH, 1984). Preliminary data from NOES indicated that 1,857,962 workers, including 1,186,141 women, in 43,616 plants were potentially exposed to the compound in the workplace in 1980. Unlike NOHS, the NOES estimates were based only on observations of the use and manufacture of the compound, per se.

The American Conference of Governmental Industrial Hygienists (ACGIH) has established a threshold limit value (TLV) of 400 parts per million (ppm) as an 8-hour time-weighted average with a 15-minute short-term exposure limit of 500 ppm (Ref. 2, ACGIH, 1986b). The TLV was set on the basis of eye, nose, and throat irritation (Ref. 1, ACGIH, 1986a). The permissible exposure limit (PEL) for the workplace adopted by the Occupational Safety and Health Administration is also 400 ppm (Ref. 40, OSHA, 1983).

General dilution/ventilation and the use of personal protective equipment have been recommended as effective controls to reduce occupational exposure to isopropanol in a number of operations (Ref. 35, NIOSH/OSHA, 1978).

Isopropanol is a constituent of some commercial food flavors (Ref. 47, Stanley, 1939; Ref. 41, Pendleton, 1970). For this use and its use as an adjuvant, the Food and Drug Administration permits the use of only the minimum quantity of isopropanol necessary to produce the desired effect. No residues of the chemical may remain in foods marked with isopropanol-derived color additives (Ref. 15, FDA, 1986).

Isopropanol has been detected in trace quantities in fish meal (Ref. 21, Iida et al., 1978), white bread (Wideblatt and Kohn, 1960, cited in Ref. 16, Fenaroli, 1975), enzyme-inactivated beef (Wick, 1965, cited in Ref. 16, Fenaroli, 1975), and pressure-cooked pork liver (Mussinan and Walradt, 1974, cited in Ref. 16, Fenaroli, 1975).

Isopropanol was identified in leachates from a Southington, CT, landfill site in 1982–83 at concentrations ranging from 3.9 to 8.8 mg/L (Ref. 43, Sawhney and Kozloski, 1984). Levels of isopropanol ranging fromn 2.3 to 21.3 ug/L have been measured at a municipal effluent in a river in Oklahoma, and levels ranging from 10 to 2,000 ug/L have been found in a well in South Carolina near an industrial impoundment area (Ref. 48, STORET, 1986).

II. *Chemical fate information.* Although very large amounts of isopropanol are released to air and water, most of the releases are widely dispersed and isopropanol in the environment will be rapidly biodegraded or oxidized. Therefore, chemical fate testing is not being recommended at this time.

III. *Biological effects of concern to human health—A. Metabolism and toxicokinetics.* Isopropanol administered intravenously and orally to normal, fasting dogs was rapidly absorbed from the gastrointestinal tract; distribution to the tissues occurred within a range of 30 minutes to 1 or 2 hours (Ref. 26, Lehman et al., 1945).

Isopropanol is metabolized to acetone in rats by alcohol dehydrogenase (ADH) (Ref. 37, Nordmann, 1980). Rats were intraperitoneally administered pyrazole, an inhibitor of ADH and catalase, or amino-1,2,4-triazole, an inhibitor of catalase alone. Isopropanol was then administered either intraperitoneally or by gavage. Blood levels of isopropanol and acetone were then monitored at regular intervals. Animals receiving amino-1,2,4-triazole showed no significant difference in blood isopropanol or acetone levels from those observed in rats receiving only isopropanol. In contrast, pretreatment with pyrazole decreased isopropanol clearance and delayed the rate of acetone production (Ref. 38, Nordmann et al., 1973).

When isopropanol was perfused through rabbit liver *in situ*, a progressive rise in the acetone concentration in blood was observed (Ref. 14, Ellis, 1952).

An average of 10.2 percent of the dose of isopropanol administered by gavage to rabbits was isolated as the glucuronide from the 24-hour urine sample. Acetone (about 0.5 percent of the dose) was also identified in expired air from treated rabbits (Ref. 22, Kamil et al., 1953).

Blood levels of isopropanol and acetone in rats following inhalation exposure to isopropanol for 4 hours, in the test range of 500 to 8,000 ppm, were directly related to atmospheric concentrations of the chemical. Increasing the exposure time to 8 hours magnified the amount of acetone that could be detected even 20 hours following exposure. These results indicate a slow conversion of the alcohol to acetone (Ref. 24, Laham et al., 1980).

In rats given single intraperitoneal doses of isopropanol, the half-life of the chemical in plasma declined with decreasing dose level (Ref. 42, Rietbrock and Abshagen, 1971).

B. *Acute (short-term) effects.* The acute toxicity of isopropanol is summarized in the following Table 4.

TABLE 4.—ACUTE TOXICITY OF ISOPROPANOL IN LABORATORY ANIMALS

Animal	Route	Effect	Reference
Mouse	Orl	LD_{50}: 4.8 g/kg; CNS depression	Levy and Zakhari (1976, Ref. 28).
Do	Ihl	LD_{50}: 10.39 mg/L, 2-hr exposure	Do.
Do	Ipr	LD_{50}: 1.28 g/kg	Do.
Do	Ivn	LD_{50}: 31.0 mmol/kg (about 1.9 g/kg)	Chvapil et al. (1962, Ref. 10).
Rat	Orl	LD_{50}: 5.84 g/kg	Smyth and Carpenter (1948, Ref. 44).
Do	Orl	LD_{50}: 6.73 cm^3/kg	Lehman and Chase (1944, Ref. 25).
Rat (14-day-old)	Orl	LD_{50}: 5.6 mL/kg	Kimura et al. (1971, Ref. 23).
Rat (young adult)	Orl	LD_{50}: 6.0 mL/kg	Do.
Rat (older adult)	Orl	LD_{50}: 6.8 mL/kg	Do.
Rat	Orl	LD_{50}: 4.7 g/kg	Levy and Zakhari (1976, Ref. 28).

TABLE 4.—ACUTE TOXICITY OF ISOPROPANOL IN LABORATORY ANIMALS—Continued

Animal	Route	Effect	Reference
Do	Ihl	LD_{50}: 19,000 ppm (females), 8-hr exposure. Severe irritation to mucous membranes. Ataxia, prostration, narcosis. At levels between 20,000 and 22,000 ppm, paralysis of hind legs was observed in both sexes during first 5 days of exposure.	Laham et al. (1980, Ref. 24).
Rat	Ihl	Congestion of liver, lungs, and spleen was observed in rats exposed at 4,000 and 8,000 ppm.	
		500–16,000 ppm, 4-hr exposure: At 4,000 ppm slight hypothermia was observed. At 8,000 and 16,000 ppm, severe hypothermia recorded.	Laham et al. (1980, Ref. 24).
Do	Ipr	LD_{50}: 1.87 g/kg	Levy and Zakhari (1976, Ref. 28).
Do	Scu	LD_{50}: 5.70 g/kg	Do.
Rabbit	Orl	LD_{50}: 6.41 cm^3/kg	Lehman and Chase (1944, Ref. 25).
Do	Orl	LD_{50}: 6.15 cm^3/kg	Do.

When applied to rabbit eyes, a drop of isopropanol caused mild transitory injury (Ref. 44, Smyth and Carpenter, 1948). Isopropanol did not produce any adverse effects when applied dermally to guinea pigs, dogs, and white rats (Macht, 1922, cited in Ref. 32, NOISH, 1976a; Steele and Wilhelm, 1966, cited in Ref. 32, NIOSH, 1976a). Similarly, the chemical did not produce tissue destruction when applied to intact and abraded skin of rabbits and guinea pigs (Ref. 38, Nixon et al., 1975).

C. *Genotoxicity.* In the *Salmonella* microsomal assay using the spot test, isopropanol was nonmutagenic in strains TA98, TA100, TA1535, and TA1537 both with and without S-9 from Aroclor-induced rats (Ref. 17, Florin et al., 1980). The chemical was nonmutagenic in *Salmonella* strains TA97, TA98, TA100, TA1535, and TA1537 both with and without metabolic activation, when tested using a plate-incorporation modification of this microbial assay (Ref. 39, NTP CHEMTRACK, 1986).

Isopropanol yielded negative results in mutagenicity tests in *Neurospora crassa* (Ref. 6, Brockman et al., 1984). Isopropanol did not enhance simian adenovirus (SA7) transformation using Syrian hamster embryo cells when tested over a concentration range of 62 to 1,000 ug/mL (Ref. 19, Heidelberger et al., 1983).

D. *Oncogenicity.* In inhalation studies, C3H, ABC, and C57 mice were exposed to isopropanol for 3 to 7 hours per day, 5 days per week for 5 to 8 months. There was no significant increase in the number of tumors observed. Similarly, no increases in pulmonary tumors were observed in the same strains of mice received 20 to 40 weekly subcutaneous injections of 0.025 mL isopropanol (Ref. 55, Weil et al., 1952).

In skin painting studies, no tumors were observed when isopropanol was painted on the clipped backs on 30 Rockland all-purpose mice 3 times per week for 1 year (Weil, unpublished data, cited in Ref. 33, NIOSH, 1976b).

E. *Chronic (long-term) effects.* Isopropanol was administered as a 5 percent solution in tap water to male albino rats for 9 months. The average daily consumption of isopropanol was 1.9 mL/kg. There was no significant differences in the death rates of the treated animals compared to controls given tap water. Treated animals experienced a marked decrease in fluid consumption compared to controls, as well as a significant weight depression. Both of these conditions were reversed in the month following withdrawal of the alcohol. Noisy breathing and sluggishness were also noted in the treated animals. In another test, 187 daily applications of a 50 percent solution of isopropanol of the heads of male rats failed to cause injury to the skin, hair, or eyes that would differentiate the treated from the control animals (Ref. 5, Boughton, 1944).

White rats were administered 0.5, 1.0, 2.5, 5.0, and 10.0 percent solutions of isopropanol in water for 27 weeks. Rats given 10 percent isopropanol refused to drink the fluid and died early in the experiment. Some deaths occurred in two of the other exposure groups, but insufficient data were available to determine whether the deaths were treatment related. Food intake by the exposed rats was equal to or greater than that of the control rats. There was a tendency for decreasing fluid intake with increasing alcohol concentration. Gross and histopathologic examination of selected organs showed no evidence of gross or microscopic changes (Ref. 25, Lehman and Chase, 1944).

Three dogs were administered isopropanol in water daily for 7 months. The alcohol concentration was 4 percent from the end of the first month until the conclusion of the experiment. Tolerance to the alcohol developed, as manifested by an increased degree of neuromuscular coordination at similar blood levels in habituated versus control animals and by increased elimination of the alcohol. The only significant histopathologic changes were noted in the kidneys of the one dog that died (Ref. 26, Lehman et al., 1945).

F. *Reproductive and developmental effects.* In a three-generation reproductive study, male and female rats receiving 2.5 percent isopropanol daily in drinking water exhibited no deleterious effects on their reproductive function and embryonic development. Some retardation of growth was observed in the early life of first-generation rats (Ref. 26, Lehman et al., 1945).

Isopropanol was administered by inhalation to groups of 15 pregnant Sprague-Dawley rats for 7 hours per day on gestation days 1 to 19 at doses of 3,500, 7,000 and 10,000 ppm. The highest concentration produced maternal narcosis and reduced weight gain and feed intake. At 7,000 ppm isopropanol, the only observable maternal effect was decreased weight gain. No maternal effects were observed at 3,500 ppm. Following exposure to 10,000 ppm isopropanol, there was a statistically significant increase in resorptions and decrease in fetal weights. Fetal weights were also decreased at the two lower dose levels. There was a significant increase in malformations in the litters of dams exposed to 7,000 and 10,000 ppm isopropanol. No teratogenic effects were observed at the 3,5000 ppm dose level (Ref. 31, Nelson et al., 1985; Ref. 30, Nelson et al., 1986).

A single-generation reproduction study is being conducted in the Wistar rat at dose levels of 0.5, 1.0, and 2.0 percent isopropanol in drinking water. Males will be exposed 70 days prior to mating and females 21 days prior to mating. Also underway is a teratology study in female Wistar rats at does levels of 0.5, 1.5, and 2.5 percent isopropanol in drinking water. The high does was selected to produce maternal toxicity. Both studies are being conducted at the request of the government of the United Kingdom (Ref. 11, CMA, 1986).

G. *Observations in humans.* Occupational exposure to isopropanol was assessed in 12 workers employed in a printing works by testing environmental air, alveolar air, venous blood, and urine during their work shift. Isopropanol in environmental air ranged

between 7 and 645 mg/m ^{3}. It was detected in alveolar air at levels ranging between 4 and 437 mg/m ^{3}. The chemical was not detected in blood or urine. Alveolar concentration of alcohol was significantly corrected with its environmental concentration (Ref. 8, Brugnone et al., 1983).

The blood half-lives of isopropanol in two patients suffering from acute overdoses of the alcohol were estimated at 155 and 187 minutes, respectively. In both patients, acetone levels were higher than the alcohol values at the beginning of the study and remained elevated throughout the study (Ref. 13, Daniel et al., 1981).

In five persons who died as a consequence of drinking isopropanol, deep and stubborn coma was observed as well as varying degrees of shock and hypothermia. Acetonuria without glycosuria was also observed (Ref. 3, Adelson, 1962).

In a historical prospective study of 262 men who had worked at an isopropanol plant in Great Britain, the observed deaths were slightly higher than expected. There was a statistically nonsignificant increase in deaths from neoplasms. One person died from nasal cancer; the authors stated that this finding was unlikely to be due to chance even though based on small numbers (Ref. 4, Alderson and Rattan, 1980).

An increased incidence of cancer of the paranasal sinuses was observed in workers at factories manufacturing isopropanol by the strong acid process. The risk of laryngeal cancer may also have been elevated in these workers (Ref. 20, IARC, 1977).

H. *Rationale for health effects recommendations.* Annual domestic production of isopropanol is greater than 1 billion pounds. Well over 1 million persons are estimated to be exposed to the chemical in the workplace. Widespread consumer exposure results from its use in pharmaceuticals and household products. It has been detected in trace quantities in several foods. It has also been identified in leachates from a landfill site. Although several limited carcinogenicity studies have been performed, insufficient data are available to assess its long-term effects. Therefore, the Committee recommends chronic toxicity studies, including tests to assess its oncogenic potential. Additional genotoxicity studies, including tests to assess its mutagenic potential in mammalian systems and its clastogenic effects, are also recommended. The Committee is concerned about possible reproductive and developmental effects of isopropanol given the teratogenic effects observed at high doses in inhalation studies in rats. However, the Committee recommends deferring the chemical from consideration for such testing pending the outcome of relevant studies presently being conducted at the request of the government of the United Kingdom.

IV. *Ecological effects of concern.* There is sufficient information available to show that isopropanol is unlikely to persist in the environment at concentrations that would cause adverse ecological effects. Therefore, ecological effects testing is not being recommended at this time.

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2.3.b *Methyl tert-butyl ether—Summary of recommended studies.* It is recommended that methyl *tert*-butyl ether (MTBE) be tested for the following:

1. *Chemical Fate.* Monitoring studies to determine typical concentrations of MTBE at representatives sites where MTBE-containing gasoline is transferred, including gasoline terminals and service stations.

2. *Health Effects.* Chronic inhalation toxicity including neurotoxic, hematologic, and oncogenic effects.

Physical and Chemical Information

CAS Number:

1634–04–4

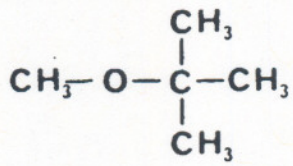
Synonyms:

Propane, 2-methoxy-2-methyl—(9 CI); Methyl 1,1-dimethylethyl ether; (2-Methyl–2–propyl) methyl ether; *tert*-Butyl methyl either

Acronym:

MTBE

Structural Formula:



Empirical Formula:

$C_5H_{12}O$

Molecular Weight:

88.15

Melting Point:

−110°C (Ref. 16, Phillips Petroleum, 1984)

Boiling Point:

55°C (Ref. 16, Phillips Petroleum, 1984)

Vapor Pressure:

414 mmHg at 38°C (Ref. 16, Phillips Petroleum, 1984)

Solubility in Water:

40,000 mg/L (Ref. 11, Hawley, 1981)
43,000 mg/L (Ref. 4, ARCO, 1986)

Solubility in Organic Solvents:

Very soluble in alcohol and ether (Ref. 12, HSDB, 1986)

Specific Gravity:

0.74 at 20/4°C (Ref. 16, Phillips Petroleum, 1984)

Log Octanol/Water Partition Coefficient: (log P):

1.30 (Ref. 13, Leo, 1982; cited in ISHOW, 1984)

Henry's Law Constant:

4.5×10^{-4} atm-m^3/mol (Ref. 20, USEPA, 1986)

Description of Chemical:

Clear liquid, pleasant hydro-carbon odor (Ref. 16, Phillips Petroleum, 1984)

Rationale for Recommendations

I. *Exposure information*—A. *Production/use.* The commercial production of MTBE uses the reaction of isobutylene and methanol, in the presence of a catalyst, at 30 to 100°C and 7 to 14 atmospheres. Production has increased dramatically since 1979 when MTBE was approved by the EPA for use as a blending component of unleaded gasoline. Current production is in the neighborhood of 2 billion pounds per year in the United States. By 1989, production is predicted to reach 3 billion pounds per year (Ref. 5, CEH, 1985).

Nearly all of the MTBE produced in the United States is used as octane-

enhancing agent in some but not all unleaded gasolines. Although it has been approved as an additive at up to all percent, typical concentrations in gasoline range from 2 to 8 percent by weight (Ref. 4, ARCO, 1986).

B. *Evidence for human exposure.* The National Occupational Exposure Survey (NOES), conducted between 1980 and 1983, indicated that 2,571 workers, including 849 women, were potentially exposed to MTBE in the workplace (Ref. 14, NIOSH, 1984).

Occupational exposures at manufacturing sites are limited because manufacturing occurs in closed systems. However, two companies have reported measured 8-hour time weighted average (TWA) workplace exposures to MTBE of 1 to 3 ppm at manufacturing sites (Ref. 16, Phillips Petroleum, 1984; Ref. 4, ARCO, 1986).

Workers involved in transportation and loading operations of MTBE-containing gasoline have been found to be exposed to less than 2 ppm MTBE (Ref. 4, ARCO, 1986). Halder et al. (Ref. 10 1986) monitored exposures of truck drivers and terminal operators at five gasoline distribution terminals. A total of 183 samples were collected at the terminals over a 12-month period. Worker exposure to C_4 and higher hydrocarbons in gasoline vapors, on a 8-hour TWA basis, varied from 0.4 to 80 ppm, with an overall 8-hour TWA geometric mean of 1.4 ppm. Some of the vapor samples were analyzed for individuals hydrocarbon constituents. No analyses were made for MTBE, but C_4 and C_5 compounds constituted 61 to 74 percent by weight of the total gasoline vapor samples. Similar hydrocarbon exposures were reported in earlier studies at terminals (Ref. 15, Phillips and Jones, 1978; Ref. 8 Diakun, 1983).

In a survey of exposures to gasoline vapors at a service station plaza, Halder, et al. (1986, Ref. 10) reported a geometric mean 8-hour TWA exposure of 1.0 ppm. Diakun (1983, Ref. 8), reporting on analyses of 74 samples obtained during self-service consumer exposures, reported a cumulative mean concentration of 59.9 ppm hydrocarbon vapor during pumping, which, projected to an 8-hour TWA exposure, is 0.28 ppm.

Tests performed in 1983 indicated that MTBE accounts for approximately 3.3 percent of the organic vapors in the head space above gasoline containing 10 percent MTBE (Ref. 4, ARCO, 1986). It is not known how that study was conducted or whether the results are useful in estimating MTBE concentrations in the hydrocarbon vapors in the "breathing zone" locations at gasoline terminals and service station plazas. However, reports that C_4 and C_5 compounds make up 61 to 74 percent by weight of the total gasoline vapors at such sites (Ref. 10, Halder, 1986) demonstrate, as might be expected, that gasoline constituents with lower molecular weights volatilize more readily than the heavier fractions. The available data are not sufficient to permit a reliable estimate of the MTBE concentration in gasoline vapors at terminals and service stations or of worker and consumer exposures at those sites.

C. *Environmental release.* North Carolina authorities have found MTBE in ground water in test wells along the Cape Fear River (Ref. 18, Taylor, 1986) at concentrations of 0.18 to 3.0 parts per million. This ground water contamination is probably due to spills during transfer of gasoline from seagoing tankers to onshore storage facilities. The largest environmental release sources appear to be through fugitive emissions at gasoline terminals and service stations where distribution to and dilution in the atmosphere will be strongly dependent on local conditions. Controls that recover gasoline vapors emitted at filling stations are used at less than 10 percent of the service stations in the nation (Ref. 19, USEPA, 1984).

II. *Chemical fate information*—A. *Transport.* Despite its relatively high water solubility, MTBE is expected to partition largely to air. The Henry's law constant of 4.5×10^{-4} atm-m^3/mol indicates that any MTBE present in surface water will have a half-life of about 9 hours before volatilizing. Furthermore, most of the MTBE released to the environment will be released directly to air during transfer operations. The low octanol/water partition coefficient and relatively high water solubility of MTBE indicate little tendency for significant partitioning to soils, sediments, or biota.

B. *Persistence.* Nearly all of the MTBE released to the environment will partition to the atmosphere where it will be degraded by hydroxy radicals, with an atmospheric half-life of about 3.5 days. The products of this oxidation are likely to include *t*-butyl formate (major product), acetone, and methyl radical (Ref. 7, Cox and Goldstone, 1981). Persistence in ground water following spills is unknown, but it may persist for long periods if volatilization is prevented, since MTBE is not likely to be readily biodegraded or otherwise transformed in ground water.

C. *Rationale for chemical fate recommendations.* MTBE released to the environment will partition to the atmosphere (except at spill and leak sites) where it will be degraded by reaction with hydroxy radicals. Other fate pathways are expected to be less significant. The major concern for MTBE involves exposures in the "breathing zone" of workers and consumers handling MTBE-containing gasoline during transfer operations. In view of this and the lack of data on exposure concentrations, it is recommended that appropriate monitoring studies be conducted to evaluate the concentration of MTBE at representative sites where MTBE-containing gasoline is transferred from shipping units (e.g., tankers, barges) into storage facilities, from storage facilities into shipping units, and from service station plaza pumps into motor vehicles.

III. *Biological effects of concern to human health*—A. *Metabolism and toxicokinetics.* Over 90 percent of an intraperitoneal dose of MTBE (232 mg/kg) was excreted untransformed in rat breath (Ref. 3, API, 1985). A fraction of the dose was also excreted as CO_2 in the breath and as formic acid in the feces and urine.

B. *Acute and subchronic effects.* In rats, the oral LD_{50} (short-term) was reported as 3,865.9 mg/kg. Acute oral exposure resulted in central nervous system depression, ataxia, tremors, labored breathing, and loss of righting reflex. In rats exposed by inhalation, eye irritation, irregular respiration, incoordination and prostration were noted. The inhalation LD_{50} in rats was found to be approximately 120 mg/L (Ref. 3, Atlantic Richfield Co., cited in API, 1985).

In tests with rabbits, MTBE was not found to be a primary skin irritant. It was irritating to the rabbit eye (Ref. 3, Atlantic Richfield Co., cited in API, 1985).

A 9-day inhalation toxicity study was conducted on fasted and unfasted rats. Rats (20 per sex per group) were exposed for 6 hours per day, 5 days per week for 9 days at concentrations of 0, 100, 300, 1,000, or 3,000 ppm. No dose-related mortality was noted. Phosphorus levels were significantly increased in the fasted females in the 1,000 and 3,000 ppm groups. An increase in relative liver weight in both sexes of fasted rats at 3,000 ppm was noted. The same trend was seen in the unfasted high-does male rats. Microscopic pathology revealed chronic inflammation in the nasal mucosa and trachea in the 1,000 and 3,000 ppm groups. (Ref. 3, API 1985)

In a 90-day inhalation study in rats, MTBE was administered at 250, 500, and 1,000 ppm does levels for 6 hours per day, 5 days per week for 3 months. The principal pharmacotoxic sign was increased anesthesia with increased

concentration. A slight decrease in body weight was seen at 1,000 ppm. An increase in hemoglobin levels in male rats was noted at 1,000 ppm at the end of the study, but this was not considered toxicologically significant (Ref. 3, API, 1985).

C. *Genotoxicity.* MTBE was tested in several *in vitro* systems (Atlantic Richfield Co., cited in API, 1985). Negative results were reported in the *Salmonella* and *Saccharomyces* tests with and without metabolic activation. In the mouse lymphoma forward mutation assay both with and without metabolic activation, a dose-related mutagenic effect was noted with S9 activation.

Sister chromatid exchange (SCE) and chromosomal aberration assays produced negative results. An increase in SCE was observed at 0.2 and 1.0 uL/mL in one activated sample. In an *in vitro* cytrogenetic study in rats, negative results were noted.

D. *Oncogenicity.* No information was found.

E. *Reproductive and development effects.* Tests to determine the reproductive and developmental effects of MTBE were conducted in female rats. The animals were exposed to 0, 250, 1,000, and 2,500 ppm for 6 hours per day during gestation days 6 to 15. Dams were sacrificed at day 20. No treatment-related effects were noted. In another study, female mice were exposed to the same concentrations but were sacrificed at day 18 of gestation. No adverse effects were noted in the dams. Minor fetal skeletal malformations were noted, but in the absence of vertebral rib defects these malformations were not considered to be teratogenic (Ref. 6, Conaway et al., 1985).

An inhalation study was conducted on the effects of MTBE on the reproduction of rats through one generation. The animals were exposed to 0. 250, 1,000 or 2,500 ppm MTBE for 6 hours per day, 5 days per week for 12 weeks, including both premating and postmating periods. Males were exposed for 6 hours during the mating period. Female rats were exposed for 6 hours per day, 5 days per week for 3 weeks during premating and daily for 6 hours during mating. After mating, females were exposed 6 hours daily during gestation days 0 to 20 and lactation days 5 to 21. The study involved two litter intervals, and females were exposed for 5 days per week, 6 hours per day during a 2-week period between litter rest intervals. No dose-related adverse effects were noted (Ref. 3, API, 1985).

F. *Chronic (long-term) effects.* No information was found.

G. *Observations in humans. In vivo* dissolution of gallstones by MTBE in four patients was reported (Ref. 2, Allen et al., 1985b). Dissolution occurred within 4 to 7 hours after direct instillation. Hematology and blood chemistry profiles showed no abnormalities. Results of both urinalysis and 24-hour urine collection for measurement of total protein were normal.

The Food and Drug Administration has classified MTBE as an Investigational New Drug. It is currently being used by one team of investigators to dissolve gallstones (Ref. 22, Wyngaarden, 1986).

H. *Rationale for health effects recommendations.* Almost all MTBE produced in the United States is used as a gasoline enhancer in certain unleaded blends, and the annual production is on the rise, with a projected volume of 3 billion pounds in 1989, Consequently, human exposure to MTBE low-level fugitive emissions at gasoline pumps is expected to occur. The major routes of expose would be via the skin and inhalation. In view of this potential exposure and the lack of chronic health effects information, the Committee recommends chronic health effects testing. Special emphasis should be given to neurotoxic, hematologic, and oncogenic effects.

IV. *Ecological effects of concern*—A. *Acute and subchronic (short-term) effects.* Using a flow-through system, Veith et al. (1983, Ref. 21) reported a 96-hour LC_{50} with the fathead minnow of 760 mg/L MTBE. Using static systems, Tarkpea and Svanberg (1982, Ref. 17) found a 24-hour LC_{50} of 1,700 to 1,800 mg/L with the bleak *Alburnus alburnus,* and a 96-hour LC_{50} greater than 10,000 mg/L with the copepod *Nitocra spinipes.*

B. *Chronic (long-term) effects.* No information was found.

C. *Other ecological effects (biological, behavioral, or ecosystem processes).* No information was found.

D. *Bioconcontration and food-chain transport.* Using carp in a flow-through system, Fujiwara et al. (1984, Ref. 9) reported a bioconcentration factor of 1.5. MTBE was rapidly eliminated from the fish when they were transferred to fresh water. No other information was found.

E. *Rationale for ecological effects recommendations.* It does not appear that MTBE will be toxic to biota at concentrations likely to be found in the environment except at spill and leaking storage tank sites. Therefore, ecological effects testing is not being recommended at this time.

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2.4 *Chemicals and groups of chemicals recommended without being designated for response within 12 months*—2.4.a *C.I. Disperse Blue 79—Summary of recommended studies.* It is recommended that C.I. Disperse Blue 79 be tested for the following:

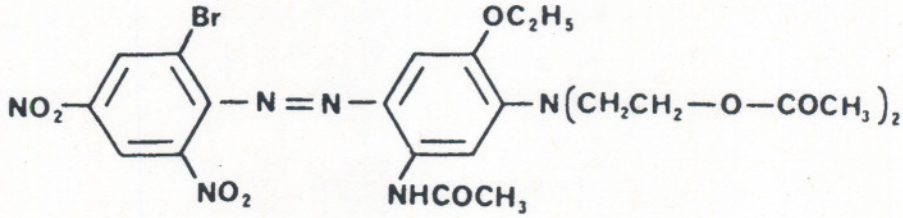
1. *Chemical Fate.* Solubility in water at 25° C. biodegradation under aerobic and anaerobic conditions and the identification of any relatively persistent biodegradation intermediates.

2. *Health Effects.* Absorption and chemical disposition via oral route of administration. Subchronic toxicity (90-day study).

3. *Ecological Effects.* Acute toxicity to fish, aquatic invertebrates, algae, and benthic organisms, including filter feeders. bioconcentration in fish. Chronic effects on aquatic and benthic biota if the acute studies show toxicity at low mg/L concentrations or if the dye bioconcentrates.

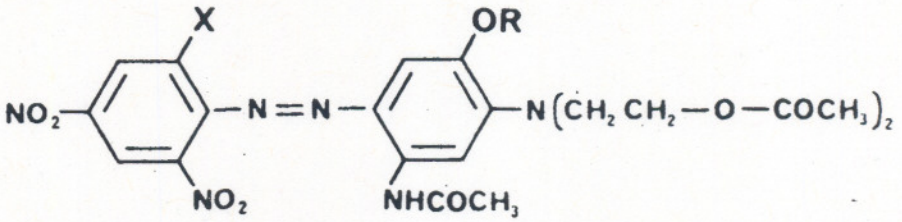
Physical and Chemical Information

CAS Number:
3956-55-6
Synonym:
Acetamide, *N*-[5-[bis[2-(acetyloxy)ethyl]amino]-2-[(2-bromo-4,6-dinitrophenyl)azo]-4-ethoxyphenyl](9CI)
Structural Formula:



Description of Chemical:
Blue powder with characteristic odor (Ref. 12, Mobay Chemical, 1985)
Empirical Formula:
$C_{24}H_{27}BrN_6O_{10}$
Molecular Weight:
639.44
Melting Point:
143 °C (estimated; Ref. 19, USEPA, 1986a)
Boiling Point:
476 °C (estimated; Ref. 19, USEPA, 1986a)
Vapor Pressure:
3.4×10^{-9} mmHg at 25 °C (estimated; Ref. 19, USEPA, 1986a)
Solubility in Water:
5.4 mg/L (estimated; Ref. 19, USEPA, 1986a)
Solubility in Organic Solvents:
No information was found.
Specific Gravity:
No information was found
Log Octanol/Water Partition Coefficient: (log P):
4.1 (estimated; Ref. 19, USEPA, 1986a)
Henry's Law Constant:
5.9×10^{-10} atm-m^3/mol (estimated; Ref. 19, USEPA, 1986a)
Log Adsorption Coefficient (log K_{oc})
3.6 (estimated; Ref. 19, USEPA, 1986a)
Bioconcentration Factor (fish)
757 (estimated; Ref. 19, USEPA, 1986a)

According to the Ecological and Toxicological Association of the Dyestuffs Manufacturing Industry (Ref. 6, ETAD, 1986), the bromoethoxy compound described above, which has the Colour Index (C.I.) Constitution No. 11345, is the only derivative properly referred to as C.I. Disperse Blue 79. However, there appear to be three other closely related derivatives that have been and may still be called Disperse Blue 79. The concerns expressed in this report for the bromoethoxy derivative apply also to these other derivatives which are expected to have physical and chemical properties similar to the bromoethoxy derivative and which have the following structures:



where, for derivative 1, X=Br and R=CH_3; for derivative 2, X=Cl and R=CH_3, and for derivative 3, X=Cl and R=C_2H_5.

Rationale for Recommendations

I. *Exposure information*—A. *Production/use/environmental release.* The U.S. International Trade Commission listed the annual production of C.I. Disperse Blue 79 at 5 to 10 million pounds per year in the United States from 1980 through 1984 (Refs. 23 through 27, USITC, 1981–1985). Heath (Ref. 21, USEPA, 1986c) has estimated the current annual production at 0.9 to 1.4 million kilograms (2 to 3 million pounds), as active colorant, which is a large production for a dye. Disperse Blue 79 appears to be the major blue dye for textile use and a major component of green, brown, and black dyes. About 40 percent of production is sold to users in a paste or liquid formulation and about 60 percent as a solid, mainly as low dusting granules (Ref. 6, ETAD, 1986).

Heath (Ref. 21 USEPA, 1986c) estimated that during the manufacture of Disperse Blue 79, there would be releases of 4,500 to 14,000 kilograms (10,000 to 30,000 pounds) per year at a total of nine sites, with an estimated 3 to 20 kilograms (7 to 45 pounds) per site per day. Heath estimated releases of 2 to 18 kg (4.4 to 40 pounds) per site per day at 400 to 600 textile dyeing operations.

B. *Evidence for human exposure.* According to the National Occupational Exposure Survey (NOES) 1,450 workers at 25 plants in the chemical and allied products industry were potentially exposed to C.I. Disperse Blue 79 in the workplace in 1980 (Ref. 13, NIOSH, 1984). Workplace exposure limtis have not been established for C.I. Disperse Blue 79 by American Conference of Governmental Industrial Hygienists (Ref. 1, ACGIH, 1986) or the Occupational Safety and Health Administration (Ref. 15, OSHA, 1983). Farris (Ref. 20, USEPA, 1986b) estimated significant worker exposure during manufacture and use. Occupational exposure to this dye is expected from inhalation of dye-containing dust particles, swallowing inhaled particles trapped in saliva and mucous, and from dermal exposure during open batch manufacture (Ref. 20, USEPA, 1986b; Ref. 21, USEPA, 1986c). Consumer exposures should be very low since this is a fast dye which is relatively insoluble in water and not likely to leach from the fabrics.

C. *Environmental exposure.* No published information was found. However, an assessment (based on mathematical modeling) has been made for the ITC by the Office of Toxic Substances (Ref. 22, USEPA, 1986d). The assessment used estimates of releases (Ref. 21, USEPA, 1986c) and took into consideration plant locations, receiving stream characteristics, and the locations of downstream drinking water treatment plants. The assessment also assumed 50 percent removal of the dye during passage through biological treatment plants by adsorption to sludge solids. Mean surface water concentrations downstream from manufacturing plants and fabric dyeing operations were estimated to range from 0.02 to 40 ug/L. A high receiving stream concentration of 306 ug/L was predicted for low flow conditions at one site. Drinking water exposures resulting from releases during manufacture and dyeing were calculated and were estimated to range from 0.06 to 43 ug/kg/year. Variations are due to site features, releases per day, and the number of days per year that releases occur. These estimates assumed no loss of the dye through biodegradation on other transformation processes.

II. *Chemical fate information*—A. *Transport.* The low estimated vapor pressure and Henry's law constant indicate that volatilization of Disperse Blue 79 will not be significant. The estimated log K_{oc} value of 3.6 indicates that about 50 to 60 percent of the dye will adsorb to the organic matter of waste treatment sludges and that about 40 to 50 percent will be released to receiving streams.

B. *Persistence.* Information supplied by ETAD (Ref. 6, 1986) indicates that in static tests, where the disappearance of total organic carbon (TOC) was followed, 29 to 68 percent of the TOC disappeared over a 2-week period in solutions containing Disperse Blue 79. No data were presented on the specific features of the tests or on whether the TOC disappearance might have been due to some factors other than biodegradation, such as adsorption onto suspended and settled particulates or the walls of test vessels. In standard 5-day biological oxygen demand (BOD) tests, the BOD_5 was 6.8 pounds O_2 per 100 pounds dye (Ref. 7, ETAD, 1986), which is about 4 percent of the theoretical oxygen uptake for complete oxidation. None of this biodegradation information is sufficient to evaluate the biodegradability of Disperse Blue 79. Studies currently underway or planned at the EPA Water Engineering Research Laboratory in Cincinnati, OH, and at the Georgia Institute of Technology (Ref. 6, ETAD, 1986) may provide useful information on both adsorption and biodegradation.

Azo dyes in general are relatively resistant to biodegradation and Disperse Blue 79 is likely to persist during biological treatment, with a portion adsorbing to the sludge solids and the rest being discharged in the effluent. Under anaerobic conditions, microbial processes may cleave the azo bond to form two aromatic amines. The 2-bromo-4,6-dinitroaniline produced by this reaction may be of concern by itself.

In its Fourth Report to the EPA Administrator (44 FR 31867), the ITC recommended and designated certain anilines, including 2-chloro-4,6-dinitroaniline (CAS No. 3531-19-9) and 2-bromo-4,6-dinitroaniline (CAS No. 1817-73-8). In an Advance Notice of Proposed Rulemaking (ANPR) on January 3, 1984 (49 FR 108), the EPA noted that there appeared to be no current production of 2-chloro-4,6-dinitroaniline, but that the 2-bromo compound was being produced and that it was being considered for a battery of chemical fate, health effects and environmental effects testing.

The potential for Disperse Blue 79 to be cleaved to release 2-bromo-4,6-dinitroaniline, both in the environment and *in vivo* following ingestion, needs to be investigated. If this product is formed via microbial processes in sediments, waste treatment facilities, and intestinal tracts, then added emphasis should be placed on testing of the sort described by the EPA in the ANPR of January 3, 1984.

Other transformation processes (e.g., hydrolysis and photolysis) are not expected to be major factors in the transformation of this dye.

C. *Rationale for chemical fate recommendations.* The lack of measured values on physical and chemical properties for C.I. Disperse Blue 79 increases the uncertainty with respect to chemical fate predictions. At a minimum, water solubility values at 25 °C should be obtained for any commercially important forms of Disperse Blue 79.

Disperse Blue 79 released to the environment is likely to partition to both water and sediments. In sediments, it may degrade anaerobically and release 2-bromo-4,6-dinitroaniline. No data have been found to substantiate or refute these predictions. Since the dye has widespread large use in the United States and is likely to be released to the environment during both manufacture and use, it is recommended that biodegradation studies be conducted to determine (1) the potential for aerobic and anaerobic biodegradation, and (2) the identify of relatively persistent intermediates, if any, resulting from biodegradation.

III. *Biological effects of concern to human health*—A. *Metabolism and toxicokinetics.* No information was found on the metabolism of C.I. Disperse Blue 79. The dye is likely to split at the azo bond into 2-bromo-4,6-dinitroaniline, and 2-diethanolamino-4-methoxy-5-amino-6-acetanilide by azoreductases present in the intestinal flora. Many azo dyes are split at the azo bond by the intestinal flora (Ref. 4, Chung et al., 1978; Ref. 7, Grasso and Golberg, 1968; Ref. 9, Honohan et al., 1976; Ref. 15, Pritchard et al., 1976; Ref. 16, Radomski, 1961; Ref 17, Roxon et al., 1967) and liver enzymes (Ref. 5, Daniel, 1967). Studies on the metabolism and disposition of 2-bromo-4,6-dinitroaniline, (BDNA) in male F344 rats were reported by Chopade and Matthews (1986, Ref 3). The gastrointestinal absorption of ^{14}C-BDNA was nearly complete, and approximately 80 percent of the

radioactivity was cleared from most tissues within 6 hours.

B. *Acute and subchronic (short-term) effects.* The acute oral LD_{50} of Disperse Blue 79 in rats was greater than 5,000 mg per kg of body weight (Ref. 6, ETAD, 1986). It was found to be nonirritating in primary skin irritation and eye irritation tests (Ref. 6, ETAD, 1986).

C. *Genotoxicity.* Disperse Blue 79 was found to be strongly mutagenic in the standard *Salmonella* S–9 assay in four tester strains TA1535, TA1537, TA98, and TA100 (Ref. 11, Mishra et al., 1981). It was also found to be negative in the V79 mammalian cell and mouse micronucleus assays (Ref. 6, ETAD, 1986).

D. *Oncogenicity.* No data were found on oncogenicity testing of C.I. Disperse Blue 79. 2,6-Dichloro-4-nitro-aniline, a structural analog of 2-bromo-4,6-dinitroaniline (one of the fragments of azo bond cleavage of the dye), was found to be negative in cancer bioassays in mice (Ref. 16, Innes et al., 1969) and rats (Ref. 8, Hadidian et al., 1968).

2-Chloro-4,6-dinitroaniline and 2-bromo-4,6-dinitroaniline (CAS No. 3531–19–9 and 1817–73–18, respectively) were recommended by the ITC in its Fourth Report to the EPA Administrator for carcinogenicity, mutagenicity, teratogenicity, and other chronic effects studies (see Part IIB, above).

E. *Chronic (long-term) effects.* No information was found.

F. *Reproductive and developmental effects.* No information was found.

G. *Observations in humans.* No information was found.

H. *Rationale for health effects recommendations.* Because of the potential bioavailability of C.I. Disperse Blue 79 to workers from ingestion of inhaled dye-containing dust, it is recommended that the dye be tested for subchronic toxicity (90-day study) and for absorption and chemical dispositon following the oral route of administration. A chemical disposition study is recommended to determine the potential for liberation of 2-bromo-4,6-dinitroaniline in the intestines due to azo bond cleavage of the dye.

IV. *Ecological effects of concern*—A. *Acute and subchronic (short-term) effects.* Acute toxicity studies using rainbow trout and Disperse Blue 79 formulations were reported as follows (Ref. 6, ETAD, 1986):

Granule formulation, containing approximately 26% Disperse Blue 79, LC_{50} = 320 mg/L.
Granule formulation, containing approximately 52% Disperse Blue 79, LC_{50} = 400 mg/L.
Liquid formulation, containing approximately 13% Disperse Blue 79, LC_{50} = 700 mg/L.

Without additional details, it is not possible to evaluate the validity of these test data. The Committee is concerned about the reported LC_{50} concentrations, since the values cited are about 100 times the estimated water solubility of Disperse Blue 79 and the test data are only for a 48-hour exposure time, whereas 96 hours is the minimal exposure period for acute toxicitiy tests in fish.

B. *Chronic (long-term) effects.* No information was found.

C. *Other ecological effects (biological, behavioral or ecosystem processes).* No effects on activated sludge respiration were observed when Disperse Blue 79 was present at concentrations up to 100 mg/L (Ref. 2, Brown et al., 1981).

D. *Bioconcentration and food-chain transport.* No data were found for Disperse Blue 79.

E. *Rationale for ecological effects recommendations.* Although the estimated concentration levels for C.I. Disperse Blue 79 in surface waters are relatively low, ranging from 0.02 to 306 μg/L, the lack of adequate data on ecological effects and the nature of this dye molecule raise concerns for potential effects. Acute toxicity tests should be run with fish, aquatic invertebrates, algae, and benthic organisms. If biodegradation studies demonstrate the formation of 2-bromo-4,6-dinitroaniline, then this transformation product should also be evaluated as noted in the EPA Advance Notice of Proposed Rulemaking of January 2, 1984 (49 FR 108). The estimated log P value of 4.1 for Disperse Blue 79, and an estimated bioconcentration factor in fish of 757, indicate a potential for some sorption and bioconcentration of the dye in biolipids. Bioconcentration studies with fish are recommended to confirm or refute the prediction of Disperse Blue 79 uptake. Chronic studies with aquatic and benthic organisms are recommended if the results of the studies show toxicity at low mg/L concentrations or if the dye bioconcentrates.

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2.4.b *Methyl Ethyl Ketoxime—Summary of recommended studies.* It is recommended that methyl ethyl ketoxime (MEKO) be tested for the following:

1. *Health Effects.* Chronic toxicity, with special emphasis on hematopoietic and oncogenic effects.

Physical and Chemical Information

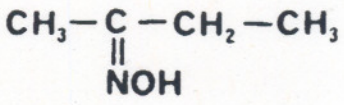
CAS Number:

96–29–7

Synonyms:

2-Butanone oxime (9 CI); MEK–OXIME; MEKO

Structural Formula:



Empirical Formula:

C_4H_9NO

Molecular Weight:

87.12

Melting Point:

−29.5 °C (Ref. 25, Verschueren, 1983)

Boiling Point:

152 °C (Ref. 25, Verschueren, 1983)

Vapor Pressure:

1.06 mmHg at 20 °C 7.6 mmHg at 50 °C (Ref. 7, Kurita, 1967)

Solubility in Water:

100 g/L at unspecified temperature (Ref. 25, Verschueren, 1983)

Solubility in Organic Solvents:

Miscible with alcohol and ether (Ref. 26, Weast, 1984)

Secific Gravity

0.923 at 20/4 °C (Ref. 25, Verschueren, 1983)

Log Octanol/Water Partition Coefficient (log P):

0.8 (Ref. 6, Leo, 1982, cited in ISHOW, 1985)

Description of Chemical:

Clear, colorless to light-yellow liquid at ambient conditions (Ref. 7, Kurita, 1967; Ref. 2, Allied, 1984a)

Rationale for Recommendations

I. *Exposure information*—A. *Production/use/environmental release.* The public portion of the TSCA Inventory listed on aggregate production volume of 520,000 to 5,202,000 pounds of MEKO in 1977 Ref. 23, USEPA, 1986a). In 1982, approximately 1.9 to 2.7 million pounds of MEKO were produced in the United States and in 1983, 2.0 to 2.9 million pounds were produced (Refs. 27 and 28, Zacharias, 1985, 1986; Ref. 17, SRI, 1984). Imports of MEKO totaled 2.6 million pounds in 1984 (Ref. 21, USDOC, 1985) and 2.2 million pounds in 1985 (Ref. 22, USDOC, 1986).

MEKO is used almost exclusively as the major antiskinning agent in alkyd and coatings. (Ref. 4, CEH, 1981). Antiskinning agents are added at less than 1 percent concentration to typical solvent-thinned paint formulations (Ref. 15, Scofield et al., 1975), prevent oxidation of the paint while in the can and volatilize while the coating is drying (Ref. 10, NIOSH, 1984a). Alkyd paints containing MEKO are used in interior semigloss and gloss paints and exterior enamels, in auto refinishing, and in product finishes for metal furniture, machinery, and appliances (Ref. 16, SRI, 1982).

B. *Evidence for human and enviornmental exposure.* The National Occupational Hazard Survey (NOHS), conducted by the Natioal Institute for Occupational Safety and Health (NIOSH) from 1972 to 1974, estimated that 12,114 workers in 1,540 plants were potentially exposed to MEKO in the workplace in 1970 (Ref 10, NIOSH, 1976).

NIOSH conducted a second survey, the National Occupational Exposure Survey (NOES), from 1980 to 1983. Preliminary data from NOES indicated that 2,145 workers (including 209 women) in the chemical and allied products industry were potentially exposed to MEKO in 1980 (Ref. 11, NIOSH. 1984b).

It has been conservatively estimated that more than 900,000 individuals were potentially exposed to MEKO as professional painters in end-use applications in 1984 (Ref. 19, Stoecklein, 1986). This estimate is exclusive of consumers incidentally exposed during routine painting/decorating activities.

Workplace exposure limits have not been recommended for MEKO by the American Conference of Governmental Industrial Hygienists (Ref. 1, ACGIH, 1986) or established by the Occupational Safety and Health Administration (Ref. 13, OSHA, 1983).

In a montoring study (Ref. 5, Himmelsbach, 1984), a MEKO-containing paint was applied by nonpowered equipment in an interior hall in an office building by four painters. During a 4-hour sampling period, the airborne concentration of MEKO ranged from approximately 0.27 to 0.46 ppm.

There are 764 products listed in the U.S. Consumer Product Safety Commission's Chemicals in Products data base that contained MEKO at concentrations of 0.1 to 0.8 percent (Ref. 20, USCPSC, 1985). Of these, all but 16 are in the paints and coatings category, which includes house and trim finish products, floor paints, wood stains, enamel finishes, yacht bottom and marine paints, traffic paints, heavy-duty equipment enamels, varnishes, interior paints, and primers. Some of the products identified in the nonpaint category are bathroom bowl cleaners, aluminum cleaners, adhesives, and caulking compounds.

No information was found on general population exposure to MEKO. However, it appears that consumers as well as professional painters would potentially be exposed to MEKO via the dermal and inhalation routes, principally through contact with alkyd paints (e.g., interior semigloss and gloss paints, exterior enamels).

An exposure assessment (based on mathematical modeling) has been made for the ITC by the Office of Toxic Substances (Ref. 24, USEPA, 1986b). Based on this analysis, the level to which consumers might be exposed to MEKO was estimated. In this analysis, two coats of a solvent-based alkyd paint containing 1 percent MEKO were applied by roller to most of the interior of a house. The total exposure to MEKO resulting from such an activity was estimated to be 432 mg. While consumers could be exposed to this level on a casual basis, the exposure to professional painters would be more frequent. Hence, the levels to which this group could be exposed to MEKO would be considerably higher.

II. *Chemical fate information.* If released tothe environment, it is likely that MEKO will be photooxidized in the atmosphere and photolyzed or biodegraded in the aquatic environment. Therefore, chemical fate testing is not being recommended at this time.

III. *Biological effects of concern to human health*—A. *Metabolism and toxicokinetics.* It is expected that MEKO would metabolize to methyl ethyl ketone and hydroxylamine (Ref. 3, Allied, 1984b).

A summary of an unpublished study on tissue distribution (REF. 3, allied, 1984b), reported that pregnant female mice were administered a single oral (unspecified) dose of ^{14}C-MEKO on day 14 of gestation, and one male mouse was administered an unspecified dose of the compound by intratracheal instillation. The following data were reported:

Whole body autoradiography revealed that MEKO was rapidly absorbed from the stomach and lungs. Widespread uptake and distribution of the label over the entire body of the animal were noted. The tissues with the highest concentration of MEKO included bone, bone marrow, liver, gallbladder, nasal and bronchial epithelium, pancreas, seromucous and salivary glands, spleen, intestinal wall, and thymus. Urine and bile contained significant activity throughout the study. Interstinal activity was minimal. This suggests that MEKO is primarily excreted via the kidneys . . . high concentrations of MEKO were detected in the liver of the fetuses at 24 hours. This concentration was greater than that seen in the livers of the mothers.

B. *Acute and subchronic effects.* The acute toxicity of MEKO is summarized in Table 5 which follows:

TABLE 5.—ACUTE TOXICITY OF METHYL ETHYL KETOXIME IN LABORATORY ANIMALS

Animal	Route	Effects	Reference
Mouse	Orl	LD_{50}: 1.0 g/kg[1]	Allied (1984b, Ref. 3).
Mouse	Ipr	Approx. LD_{50}: 1 g/kg	Pizak and Doull (1969, Ref. 14).
Rat	Orl	LD_{50}: 2.3 g/kg	Allied (1984b, Ref. 3).
Rat	Orl	LD_{50}: 3.7 g/kg	Allied (1984b, Ref. 3).
Rat	Ihl	Saturated vapors for 35 min. Agitation by 2 min and then drowsiness by 35 min when exposed to vapors for 35 min.	Kurita (1967, Ref. 7).
Rat	Ihl	0.19, 1.45, and 4.83 mg/L of MEKO vapors for 4 hr produced no mortality. The high dose group showed evidence of anesthesia after exposure. Methemoglobin formation was noted for the mid- and high-dose levels. Minor changes were noted in hematology or clinical chemistry for all groups.	Allied (1984b, Ref. 3).
Rat	Skn	Doses of 0.02, 0.2, or 2.0 mL/kg for 24 hr produced 100 percent mortality at 2.0 mL/kg; no mortality at lower doses. Methemoglobin was noted at 0.2 and 2.0 mL/kg and a small increase in reticulocytes at 0.2 mL/kg. Nervous system depression was the predominant sign for acute doses. There was no effect at 0.02 mL/kg.	Allied (1984b, Ref. 3).
Rat	Scn	LD_{50}: 2.7 g/kg, LD_{50}: 2.8 g/kg.	Kurita (1967, Ref. 7).

[1] "Oral" LD_{50} reported as cited in Allied (1984b).

In a study in which MEKO in vaseline was applied to rat skin (Ref. 7, Kurita, 1967), transient dermatitis was noted. Mild dermal irritation in the rabbit, usually disappearing within 72 hours of exposure, has also been reported (Ref. 3, Allied, 1984b). Data obtained using the guinea pig maximization test indicated that MEKO has a strong sensitization potential (Ref. 3, Allied, 1984b). Marked hyperemia of the eyelid and bulb conjunctiva was observed in rats following instillation of MEKO into one of the eyes of each of three rats. The observed effects disappeared after 6 to 9 hours (Ref. 7, Kurita, 1967).

The effects of MEKO on various hematologic parameters in rats have been studied (Ref. 7, Kurita, 1967). In one study, five male albino rats received subcutaneous doses of MEKO in olive oil (1.5 mL per kg every other day for 4 weeks). Five control rats were similarly treated with olive oil alone (1.5 mL per kg). At the end of the treatment period, the only statistically significant ($p < 0.05$) effect noted was inhibition of erythrocyte and plasma cholinesterease activity.

In another study (Ref. 7, Kurita, 1967), four groups of male albino rats each received MEKO in olive oil at dose levels of 0.1, 0.5, or 1.0 mL per kg body weight, respectively. The control group received olive oil only. The test material was injected subcutaneously once daily for 4 weeks. Clinical examinations, including body weight and hematologic measurements were performed throughout the experimental period. After 4 weeks, the rats were sacrificed, with blood samples taken and gross and microscopic pathological examinations performed. Dose-related effects were observed at the two highest doses but not at the lowest dose level (0.1 mL per kg per day). According to the author, the effects associated with exposure to MEKO included growth inhibition, increases in the absolute and/or relative weights of the spleen, liver, and kidneys, decreased erythrocyte count and hemoglobin content, secondary leukocytoses, lymphopenia, splenic hypertrophy, impairment of clotting function, atrophy of lymphatic tissue, pulmonary atelectasis, pulmonary emphysema, and bronchial pneumonia. A statistically significant ($p < 0.01$) decrease in serum protein concentration also was noted.

A summary of an unpublished study (Ref. 3, Allied, 1984b) reported that rats were administered MEKO by gavage at doses of 25, 75, and 225 mg per kg per day for 13 weeks. The following data were reported:

No mortality, changes in appearance or behavior, or abnormalities in urine values were observed in the rats during the study. Slight to moderately lower mean body weights and food consumption were noted at the high dose level at eight and thirteen weeks in the males. All of the treated groups from both sexes showed dose related decreases in erythrocyte count, hematocrit and hemoglobin values and displayed a moderate to market reticulocytosis. Heinz bodies, occasional siderocytes, polychromasia, basophilic stippling and Howell-Jolly bodies were generally present in the mid and high dose groups. Blood chemistries revealed an elevation of total bilirubin and erythrocyte cholinesterase in mid dose males and high dose males and females. Alkaline phosphatase levels of high dose males also increased. A slight depression in blood urea nitrogen and plasma cholinesterase levels were noted in the high dose level female group.

Dose related increases in the absolute and/or relative weight of the spleen, liver and kidney were observed in all treatment groups. The spleens and livers appeared large and/or darkened upon necropsy. Histopathological examination revealed extramedullary

hematopoiesis and increased amounts of greenish-brown pigment located in macrophages of the spleen and liver.

Kidney sections revealed an accumulation of greenish-brown pigment in the epithelial cells lining the proximal convoluted tubules. These data suggest that MEKO induces a hemolytic anemia in the rat with compensatory erythropoiesis. A NOEL (no observable effect level) was not established but was predicted to be less than 25 mg kg/day.

C. *Genotoxicity.* This chemical has been selected by the National Toxicology Program for testing in the Ames assay and is currently on test for *in vitro* cytogenetics (Ref. 12, NTP, 1986). In previously conducted assays, however, MEKO was nonmutagenic in both the Ames and sister chromatid exchange assays (Ref. 3, Allied, 1984b). In another study, MEKO was nonmutagenic in *Salmonella* strains TA98, TA100 TA1535, TA1537, and TA1538 (Ref. 8, NCI, 1985a). MEKO has also been tested in the mouse lymphoma assay (Ref. 9, NCI, 1985b). Under the conditions of the assay, MEKO produced a positive response without metabolic activation and a negative response with metabolic activation.

D. *Oncogenicity.* No information was found.

E. *Chronic (long-term) effects.* No information was found.

F. *Reproductive and developmental effects.* No information was found.

G. *Observations in humans.* No information was found.

H. *Rationale for health effects recommendations.* MEKO is the major antiskinning agent in alkyd coating resins for use in interior semigloss and gloss paints and exterior enamels, in auto refinishing and in product finishes for metal furniture, machinery, and appliances. It volatilizes while the coating is drying and may be inhaled in indoor settings by professional painters and consumers. Apart from the workers exposed to MEKO in the chemical and allied products industry, more than 900,000 professional painters are conservatively estimated to be exposed to this chemical at low levels on a continuous basis in end-use applications. The number of consumers exposed to MEKO through casual painting and decorating activities is assumed to be high, though data do not exist to provide a precise estimate.

Although several short-term toxicity studies have been performed, limited data exist to evaluate its long-term toxicologic effects, particularly on the hematopoietic system. In addition, no data are available that address the oncogenic potential of this compound. Therefore, the Committee recommends the performance of chronic toxicity studies with special emphasis on potential hematopoietic and oncogenic effects.

IV. *Ecological effects of concern.* MEKO is unlikely to persist in the environment at concentrations likely to cause adverse ecological effects. Therefore, ecological effects testing is not being recommended at this time.

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