REFERENCE OUTLINE

TOXICOLOGICAL REVIEW OF DIISOPROPYL ETHER (CAS No. 108-20-3)

1. INTRODUCTION

NRC (National Research Council). (1983) Risk assessment in the federal government: managing the process. Washington, DC: National Academy Press.

U.S. EPA (Environmental Protection Agency). (1986a) Guidelines for the health risk assessment of chemical mixtures. Federal Register 51(185):34014-34025.

U.S. EPA. (1986b) Guidelines for mutagenicity risk assessment. Federal Register 51(185):34006-34012.

U.S. EPA. (1988) Recommendations for and documentation of biological values for use in risk assessment. Prepared by the Environmental Criteria and Assessment Office, Office of Health and Environmental Assessment, Cincinnati, OH for the Office of Solid Waste and Emergency Response, Washington, DC; EPA 600/6-87/008. Available from: National Technical Information Service, Springfield, VA; PB88-179874/AS.

U.S. EPA. (1989) Interim methods for development of inhalation reference doses. Environmental Criteria and Assessment Office, Office of Health and Environmental Assessment, Research Triangle Park, NC; EPA/600/8-88/066F. Available online at http://www.epa.gov/iris/backgr-d.htm.

U.S. EPA. (1991) Guidelines for developmental toxicity risk assessment. Federal Register 56(234):63798-63826.

U.S. EPA. (1994a) Interim policy for particle size and limit concentration issues in inhalation toxicity studies. Federal Register 59(206):53799.

U.S. EPA. (1994b) Methods for derivation of inhalation reference concentrations and application of inhalation dosimetry. Office of Research and Development, Washington, DC; EPA/600/8-90/066F. Available from: National Technical Information Service, Springfield, VA; PB2000-500023, and online at http://www.epa.gov/iris/backgr-d.htm.

U.S. EPA. (1995) Use of the benchmark dose approach in health risk assessment. Risk Assessment Forum, Washington, DC; EPA/630/R-94/007. Available from: National Technical Information Service, Springfield, VA; PB95-213765, and online at http://www.epa.gov/iris/backgr-d.htm.

U.S. EPA. (1996) Guidelines for reproductive toxicity risk assessment. Federal Register 61(212):56274-56322.

U.S. EPA. (1998a) Guidelines for neurotoxicity risk assessment. Federal Register 63(93):26926-26954.

U.S. EPA. (1998b) Science policy council handbook: peer review. Office of Science Policy, Office of Research and Development, Washington, DC; EPA 100-B-98-001. Available from: National Technical Information Service, Springfield, VA; PB98-140726, and online at http://www.epa.gov/iris/backgr-d.htm.

U.S. EPA. (2000a) Science policy council handbook: peer review. 2nd edition. Office of Science Policy, Office of Research and Development, Washington, DC; EPA 100-B-00-001. Available online at http://www.epa.gov/iris/backgr-d.htm.

U.S. EPA. (2000b) Science policy council handbook: risk characterization. Office of Science Policy, Office of Research and Development, Washington, DC; EPA 100-B-00-002. Available online at http://www.epa.gov/iris/backgr-d.htm.

U.S. EPA. (2000c) Benchmark dose technical guidance document [external review draft]. Risk Assessment Forum, Washington, DC; EPA/630/R-00/001. Available online at http://www.epa.gov/iris/backgr-d.htm.

U.S. EPA. (2000d) Supplementary guidance for conducting for health risk assessment of chemical mixtures. Risk Assessment Forum, Washington, DC; EPA/630/R-00/002. Available online at http://www.epa.gov/iris/backgr-d.htm.

U.S. EPA. (2002) A review of the reference dose and reference concentration processes. Risk Assessment Forum, Washington, DC; EPA/630/P-02/0002F. Available online at http://www.epa.gov/iris/backgr-d.htm.

U.S. EPA. (2005a) Guidelines for carcinogen risk assessment. Risk Assessment Forum, Washington, DC; EPA/630/P-03/001B. Available online at http://www.epa.gov/iris/backgr-d.htm.

U.S. EPA. (2005b) Supplemental guidance for assessing susceptibility from early-life exposure to carcinogens. Risk Assessment Forum, Washington, DC; EPA/630/R-03/003F. Available online at http://www.epa.gov/iris/backgr-d.htm.

U.S. EPA. (2005c) Peer review handbook. 3rd edition. Review draft. Science Policy Council, Washington, DC. Available online at http://intranet.epa.gov/ospintra/scipol/prhndbk05.doc.

2. CHEMICAL AND PHYSICAL INFORMATION

Daubert, TE; Danner, RP. (1995) Physical and thermodynamic properties of pure chemicals: data compilation. (1989-) Propane, 2,2' -oxybis-. Washington, D.C.: Taylor & Francis.

Funasaki, N; Hada, S; Neya, S. (1985) Partition coefficients of aliphatic ethers - molecular surface area approach. J. Phys. Chem. 89 : 3046-3049.

Heitmann, W; Strehlke, G; Mayer, D. (2005) Ethers, Aliphatic. In: Ullmann's Encyclopedia of Industrial Chemistry. Wiley-VCH Verlag GmbH & Co., Weinheim. Available online at http://www.mrw.interscience.wiley.com.

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Karas, L; Peil, WJ. (2004) Ethers. In: Kirk-Othmer Encyclopedia of Chemical Technology. John Wiley & Sons, Inc. Available online at http://www.mrw.interscience.wiley.com.

Kwok, ESC; Atkinson, R. (1994) Estimation of hydroxyl radical reaction rate constants for gas-phase organic compounds using a structure-reactivity relationship: an update. Riverside, CA: Univ CA, Statewide Air Pollut Res Ctr., CMA Contract No. AFC-8.0-OR.

Lewis, RJ. (2001) Condensed chemical dictionary. New York, NY: John Wiley and Sons, Inc.: 631.

Lide, DR, ed. (2005) CRC handbook of chemistry and physics. Boca Raton, FL: CRC Press Inc.:3-186.

Merck Index. (2001) Merck index: an encyclopedia of chemicals, drugs, and biologicals. 13th ed. Budavari S, ed. Rahway NJ: Merck & Co., Inc. :932.

NLM. (2007) ChemID Plus Advanced. National Library of Medicine, Bethesda, MD. Online

SRI. (2007) Isopropyl Ether. Directory of chemical producers. United States. SRI Consulting, Menlo Park, CA. p. 695.

3. TOXICOKINETICS

Available toxicokinetics data for diisopropyl ether are limited to a single report in which diisopropyl ether and other gasoline oxygenates were evaluated with CASE/MULTICASE structure relational models; putative metabolites of diisopropyl ether include epoxides:

- Zhang, YP; Macina, OT; Rosenkranz, HS; et al. (1997) Prediction of the metabolism and toxicological profiles of gasoline oxygenates. Inhal. Toxicol. 9:237-54.

3.5. PHYSIOLOGICALLY-BASED TOXICOKINETIC MODELS

No PBPK models for diisopropyl ether were located.

4. HAZARD IDENTIFICATION

4.1. STUDIES IN HUMANS - EPIDEMIOLOGY, CASE REPORTS, CLINICAL CONTROLS

Oral

No studies were located regarding the toxicity of diisopropyl ether following ingestion in humans.

Inhalation

Silverman, L.; Schulte, HF; First, MW. (1946) Further studies on sensory response to certain industrial solvent vapors. J. Ind. Hyg. Toxicol. 28:262-66.

Amiot, L.G. (1932) Contribution á l'étude des propriétés anesthésiques de la function ether-oxide. Presse med. 40:300.

A reference to an unpublished report to Shell Development Company was located:

- Hine, C; Anderson, H; Kodama, J. (1955) Sensory thresholds of certain Shell organic solvents, Progress Report 1, Report to Shell Development Company, November 15, 1955, UC Report #247.

4.2. LESS-THAN-LIFETIME AND CHRONIC STUDIES AND CANCER BIOASSAYS IN ANIMALS—ORAL AND INHALATION

4.2.1. Oral Exposure

4.2.1.1. Acute Studies

Kimura, ET; Ebert, DM; Dodge, PW. (1971) Acute toxicity and limits of solvent residue for sixteen organic solvents. Toxicol. Appl. Pharmacol. 19:699-704.

Machle, W; Scott, EW; Treon, K.(1939) The physiological response to isopropyl ether and to a mixture of isopropyl ether and gasoline. J. Ind. Hyg. Toxicol. 21:72-96.

4.2.1.2. Short-Term Studies

Machle, W; Scott, EW; Treon, K.(1939) The physiological response to isopropyl ether and to a mixture of isopropyl ether and gasoline. J. Ind. Hyg. Toxicol. 21:72-96.

4.2.1.3. Longer-Term Studies

No longer-term repeated-dose oral studies were located.

4.2.1.4. Chronic and Cancer Studies

Information regarding the chronic toxicity and carcinogenicity of diisopropyl ether is restricted to a single carcinogenicity bioassay of male and female rats administered the test chemical by oral gavage (in olive oil) at doses of 0, 250, or 1000 mg/kg/day, 4 days/week for 78 weeks and observed until spontaneous death; results include statistically significantly increased incidences of lymphomas and leukemias in low- and high-dose females and high-dose males:

- Belpoggi, F; Soffritti, M; Minardi, F; et al. (2002) Results of long-term carcinogenicity bioassays on *tert*-amyl-methyl-ether (TAME) and di-isopropyl-ether (DIPE) in rats. Ann. N.Y. Acad. Sci. 982:70-86.

4.2.2. Inhalation Exposure

4.2.2.1. Acute Studies

Machle, W; Scott, EW; Treon, K.(1939) The physiological response to isopropyl ether and to a mixture of isopropyl ether and gasoline. J. Ind. Hyg. Toxicol. 21:72-96.

Jackson, D.E. (1933) The pharmacological action of isopropyl ether. J. Pharm. Exper. Therap. 48:267.

CDC (2007) includes acute LC_{50} values for rats and rabbits from a study (Pavlova et al., 1963) in Russian and an acute LC_{50} value for rats from an unpublished study performed for the Union Carbide Corporation:

- CDC (Center for Disease Control). (2007) Documentation for immediately dangerous to life or health concentrations (IDLHs) – isopropyl ether. Available online at http://www.cdc.gov/Niosh/idlh/108203.html.

Lewis (2000) includes acute LC_{50} values for rats, mice, and rabbits, the original source of which appears to be Pavlova et al. (1963):

- Lewis, R.J., ed. (2000) Sax's Dangerous Properties of Industrial Materials. Isopropyl Ether. Vol. 3. New York, NY: John Wiley & Sons, Inc. pp. 2160-2161.

4.2.2.2. Short-Term Studies

Machle, W; Scott, EW; Treon, K.(1939) The physiological response to isopropyl ether and to a mixture of isopropyl ether and gasoline. J. Ind. Hyg. Toxicol. 21:72-96.

4.2.2.3. Longer-Term Studies

Dalbey, W; Feuston, M. (1996) Subchronic and developmental toxicity studies of vaporized diisopropyl ether in rats. J. Toxicol. Environ. Health. 49:29-43. (Note: TSCATS Submission OTS0556020 includes the developmental toxicity study reported by Dalbey and Feuston, 1996)

Rodriguez, SC; Dalbey, WE. (1997) Subchronic neurotoxicity of vaporized diisopropyl ether in rats. Int. J. Toxicol. 16:599-610.

4.2.2.4. Chronic Studies

No chronic inhalation studies were located.

4.3. REPRODUCTIVE/DEVELOPMENTAL STUDIES - ORAL AND INHALATION

Dalbey, W; Feuston, M. (1996) Subchronic and developmental toxicity studies of vaporized diisopropyl ether in rats. J. Toxicol. Environ. Health. 49:29-43. (Note: TSCATS Submission OTS0556020 includes the developmental toxicity study reported by Dalbey and Feuston, 1996)

Feuston, M.H.; Dalbey, W.E. (1996) Developmental toxicity of vaporized diisopropyl ether in rats. J. Am. Coll. Toxicol. 15(3):267. (Note: The report is an abstract for the 16th meeting of ACT; the results appear to be the same as those reported by Dalbey and Feuston, 1996, although there were slight differences in the reported exposure levels)

4.4. OTHER ENDPOINT-SPECIFIC STUDIES [*e.g., in vivo neurological, immunological studies*]

4.4.1. Neurological

Rodriguez, SC; Dalbey, WE. (1997) Subchronic neurotoxicity of vaporized diisopropyl ether in rats. Int. J. Toxicol. 16:599-610.

4.4.2. Mixture studies of gasoline and diisopropyl ether (Note: Only abstracts are available)

Gray, T.M.; Hazelden, K.P.; Steup, D.R.; et al. (2004) Inhalation toxicity of gasoline and fuel oxygenates – reproductive toxicity assessment. Toxicologist. 78(1-S):146.

Hoffman, G.; Schreiner, C.A.; Parker, C; et al. (2004) Inhalation toxicity of gasoline and fuel oxygenates – 13-week subchronic/neurotoxicity study. Toxicologist. 78(1-S):147.

O'Callaghan, J.P.; Felton, C.M.; Mutansky, B.K.; et al. (2004) Inhalation toxicity of gasoline and fuel oxygenates – neurotoxicity. Toxicologist. 78(1-S):146.

Schreiner, C.; Hoffman, G.; Mason, C.; et al. (2004) Inhalation toxicity of gasoline and fuel oxygenates – micronucleus and sister chromatid exchange tests. Toxicologist. 78(1-S):147.

White, K.L.; Peachee V.L.; Armstrong, S.R.; et al. (2004) Inhalation toxicity of gasoline and fuel oxygenates – immunotoxicity. Toxicologist. 78(1-S):148.

4.5. MECHANISTIC DATA AND OTHER STUDIES IN SUPPORT OF THE MODE OF ACTION [*e.g., in vitro and ex vivo studies using isolated target tissues/organs or cells, metabolite studies, genotoxicity, SAR, etc.*]

Genotoxicity

Brooks, TM; Meyer, AL; Hutson, DH. (1988) The genetic toxicology of some hydrocarbon and oxygenated solvents. Mutagenesis. 3:227-232.

Mechanisms

No relevant studies were located.

4.6. SYNTHESIS OF MAJOR NONCANCER EFFECTS

4.7. EVALUATION OF CARCINOGENICITY

4.8. SUSCEPTIBLE POPULATIONS AND LIFE STAGES

4.8.1. Possible Childhood Susceptibility

Available data are limited to acute oral LD_{50} values of 6.4, 16.5, and 16.0 mL/kg in 14-day-old, young adult (80-160 g bodyweight), and older adult (300-470 g bodyweight) Sprague-Dawley rats, indicating that immature rats may be more acutely susceptible than adult rats to diisopropyl ether toxicity:

- Kimura, ET; Ebert, DM; Dodge, PW. (1971) Acute toxicity and limits of solvent residue for sixteen organic solvents. Toxicol. Appl. Pharmacol. 19:699-704.

4.8.2. Possible Gender Differences

Limited data indicate that male rats may be somewhat more susceptible than female rats to diisopropyl ether toxicity:

- Dalbey, W; Feuston, M. (1996) Subchronic and developmental toxicity studies of vaporized diisopropyl ether in rats. J. Toxicol. Environ. Health. 49:29-43. (Note: TSCATS Submission OTS0556020 includes the developmental toxicity study reported by Dalbey and Feuston, 1996)

- Rodriguez, SC; Dalbey, WE. (1997) Subchronic neurotoxicity of vaporized diisopropyl ether in rats. Int. J. Toxicol. 16:599-610.

Secondary Sources to be Reviewed

ACGIH (American Conference of Governmental Industrial Hygienists). (2001) Documentation of the threshold limit values and biological exposure indices Vol:7th Ed. ACGIH, Cincinnati, OH.

Lewis, R.J., ed. (2000) Sax's Dangerous Properties of Industrial Materials. Isopropyl Ether. Vol. 3. New York, NY: John Wiley & Sons, Inc. pp. 2160-2161.

Mehlman, M.A. (2001) Ethers. In: Bingham, E.; Cohrssen, B.; Powell, C.H.; eds. Patty's Toxicology. Fifth Edition. Volume 1. New York, NY: John Wiley & Sons, Inc.: pp. 883-885.