

BEFORE THE
UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

CHEMICAL MANUFACTURERS ASSOCIATION
VINYLIDENE CHLORIDE PROGRAM PANEL
COMMENTS ON
PROPOSED TEST RULE FOR 1,1-DICHLOROETHYLENE
(VINYLIDENE CHLORIDE)
OPTS-42082
51 Fed. Reg. 29840 August 12, 1986)
SUPPLEMENTAL MATERIALS
VOLUME 1

Geraldine V. Cox, Ph.D.
Vice President
Technical Director
Chemical Manufacturers
Association

David E. Zoll, Esq.
Vice President
General Counsel
Chemical Manufacturers
Association

Robert R. Romano, Ph.D.
Manager
Vinylidene Chloride Program
Chemical Manufacturers
Association

Of Counsel:
R. Bruce Dickson
Michael A. Wiegard
Lori Schmidt-Praul
Paul, Hastings, Janofsky & Walker
1050 Connecticut Avenue, N.W.
Suite 1200
Washington, D.C. 20036

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

January 15, 1987

SL 066408

Index to Supplementary Materials

1. Andersen, M.E., J.E. French, M.L. Gargas, R.A. Jones and L.J. Jenkins, Jr. Saturable metabolism and the acute toxicity of 1,1-dichloroethylene, Toxicol. Appl. Pharmacol. 47:385-393, 1979.
2. Andersen, M.E., M.L. Gargas, R.A. Jones and L.J. Jenkins, Jr. The use of inhalation techniques to assess the kinetic constants of 1,1-dichloroethylene metabolism, Toxicol. Appl. Pharmacol. 47:395-409, 1979.
3. Andersen, M.E., M.L. Gargas, R.A. Jones and L.J. Jenkins, Jr. Determination of the kinetic constants for metabolism of inhaled toxicants in vivo using gas uptake measurements, Toxicol. Appl. Pharmacol. 54:100-116, 1980.
4. Andersen, M.E., O.E. Thomas, M.L. Gargas, R.A. Jones and L.J. Jenkins, Jr. The significance of multiple detoxification pathways for reactive metabolites in the toxicity of 1,1-dichloroethylene, Toxicol. Appl. Pharmacol. 52:422-432, 1980.
5. Balmer, M.F., L.W. Rampy and J.F. Quast. 90-Day repeated inhalation toxicity study of vinylidene chloride in rats, Report of The Dow Chemical Company 1976.
6. Bartsch, H., C. Malaveille, A. Barbin and G. Planche. Mutagenic and alkylating metabolites of halo-ethylenes, chlorobutadienes and dichlorobutenes produced by rodent or human liver tissues, Arch. of Toxicol., 41:249-277, 1979.
7. Bartsch, H., C. Malaveille, R. Montesano and L. Tomatis. Tissue-mediated mutagenicity of vinylidene chloride and 2-chlorobutadiene in salmonella typhimurium, Nature 255:June 19, 1975.
8. Bonse, G. and D. Henschler. Chemical reactivity, biotransformation, and toxicity of polychlorinated aliphatic compounds, CRC Critical Reviews in Toxicology 4:395-409, October 1976.
9. Bonse, G., T. Urban, R. Montessano and L. Tomatis. Chemical reactivity, metabolic oxirane formation and biological activity of chlorinated ethylenes in the isolated perfused rat liver preparation, Biochem. Pharmacol. 24:1829-1834, 1975.

10. Boyland, E., and L.F. Chasseaud. The role of glutathione and glutathione S-transferases in mercapturic acid biosynthesis. Adv. Enzymol. 32:173-219, 1969.
11. Cerna, M. and H. Kypenova. Mutagenic activity of chloroethylenes analyzed by screening system tests, Mutation Research 46:214-215, 1977.
12. Chieco, P., M.T. Molen and F.S. Reynolds. Effect of administrative vehicle on oral 1,1-dichloroethylene toxicity, Toxicol. Appl. Pharmacol., 57:146-155, 1981.
13. Cooper, P., The varying fate of vinylidene chloride, Fd. Cosmet.Toxicol. 18(4):435-436, 1980.
14. Costa A.K., and K.M. Ivanetich. The 1,2-dichloroethylenes: Their metabolism by hepatic cytochrome P-450 in vitro, Biochem. Pharmacol. 31:2093-2102, 1982.
15. Dallas, C.E., F.W. Weir, S. Feldman, L. Putcha and J.V. Bruckner. The uptake and distribution of 1,1-dichloroethylene in rats during inhalation exposure. Toxicol. Appl. Pharmacol. 68:140-151, 1983.
16. Drevon, C. and T. Kuroki. Mutagenicity of vinyl chloride, vinylidene chloride and chloroprene in V79 Chinese hamster cells, Mutation Research 67:173-182, 1979.
17. Filser, J.G., and H.M. Bolt. Pharmacokinetics of halogenated ethylenes in rats, Arch. Toxicol. 42:123-136, 1979.
18. Gage, J.C. The subacute inhalation toxicity of 109 industrial chemicals. Br. J. Industr. Med. 27:1-18, 1970.
19. Greim, H., G. Bouse, Z. Radman, D. Reichert and D. Henschler. Mutagenicity in vitro and potential carcinogenicity of chlorinated ethylenes as a function of metabolic oxirane formation, Biochem. Pharmacol., 24:2013-2017, 1975.
20. Hathway, D.E. Comparative mammalian metabolism of vinyl chloride and vinylidene chloride in relation to oncogenic potential, Environ. Health. Perspect. 21:55-59, 1977.
21. Hayakawa, T., R.A. Lemahieu and S. Udenfriend. Studies on glutathione-S-arene oxidase transferase - a sensitive

assay and partial purification of the enzyme from sheep liver, Arch. Biochem. Biophys. 162:223-230, 1974.

22. Henck, J.W., J.F. Quast, L.W. Rampy and J.M. Norris. A comparison of four mouse strains exposed to subchronically inhaled vinylidene chloride (VDC), Report of The Dow Chemical Company, 1980.
23. Hong, C.B., J.M. Winston, L.P. Thornberg, C.C. Lee and J.S. Woods. Follow-up study on the carcinogenicity of vinyl chloride and vinylidene chloride in rats and mice: Tumor incidence and mortality subsequent to exposure, J. Toxicol. Environ. Health 7:909-924, 1981.
24. Humiston, C.G., J.F. Quast, C.E. Wade, J. Ballard, J.E. Beyer and R.W. Lisowe. Results of a two-year toxicity and oncogenicity study with vinylidene chloride incorporated in the drinking water of rats, Report of The Dow Chemical Company, 1978.
25. Jaeger, R.J., M.J. Trabulus and S.D. Murphy. Biochemical effects of 1,1-dichloroethylene in rats: Dissociation of its hepatotoxicity from a lipoperoxidative mechanism, Toxicol. Appl. Pharmacol. 24:457-467, 1973.
26. Jaeger, R.J., R.B. Conolly and S.D. Murphy. Effect of 18 hour fast and glutathione depletion of 1,1-dichloroethylene-induced hepatotoxicity and lethality in rats, Exp. Mol. Pathol. 20:187-198, 1974.
27. Jaeger, R.J., L.G. Shoner and L.J. Coffman. 1,1-Dichloroethylene hepatotoxicity: Proposed mechanism of action of distribution and binding of ¹⁴C radioactivity following inhalation exposure in rats, Environ. Health Perspect. 21:113-119, 1977.
28. Jaeger, Rudolph J., S. Szabo and L.J. Coffman. 1,1-Dichloroethylene hepatotoxicity: Effect of altered thyroid function and evidence for the subcellular site of injury, Toxicol. Environ. Health 3:545-555, 1977.
29. Jaeger, R.J., R.B. Conolly and S.D. Murphy. Short-term inhalation toxicity of halogenated hydrocarbons, Arch. Environ. Health 30:26-31, 1975.
30. Jaeger, R.J., R.B. Conolly, E.S. Reynolds and S.D. Murphy. Biochemical toxicology of unsaturated halogenated monomers, Environ. Health Perspect. 11:121-128, 1975.

31. Jones, B.K. and D.E. Hathaway. The Biological fate of vinylidene chloride in rats, Chem.-Biol. Interactions 20:27-41, 1978.
32. Jones, B.K. and D.E. Hathaway. Differences in metabolism of vinylidene chloride between mice and rats, Br. J. Cancer 37:411-417, 1978.
33. Krijgsheld, K.R., M.C. Lowe, E.G. Mimnaugh, M.A. Trush, E. Ginsburg and T.E. Gram. Lung-selective impairment of cythochrome P-450-dependent monooxygenases and cellular injury by 1,1-dichloroethylene in mice, Biochemical and Biophysical Research Communications 110:675-681, 1983.
34. Landau, E. and Manos N. Epidemiology studies: Estimation of population residing near vinylidene chloride plants, U.S. Environmental Protection Agency 560/6-76-022, 1976.
35. Laumbach, A.D., S. Lee, J. Wong and U.N. Streips. Studies on the mutagenicity of vinyl chloride metabolites and related chemicals, Prev. Detect. Cancer, [Proc. Int. Symp.] 3(1):155-170, 1977.
36. Lee, C.C., J.C. Bhandari, J.M. Winston, W.B. House, P.J. Peters, R.L. Dixon and J.S. Woods. Inhalation toxicity of vinyl chloride and vinylidene chloride, Environ. Health. Perspect. 21:25-32, 1977.
37. Lee, C.C., J.C. Bhandari, J.M. Winston, W.B. House, R.L. Dixon and J.S. Woods. Carcinogenicity of vinyl chloride and vinylidene chloride, J. Toxicol. Environ. Health 4:15-30. 1978.
38. Leibman, K.C. and E. Ortiz. Metabolism of halogenated ethylenes, Environ. Health Perspect. 21:91-97, 1977.
39. Liebler, D.C. and F.P. Guengerich. 1983. Olefin oxidation by cytochrome P-450: Evidence for group migration in catalytic intermediates formed with vinylidene chloride and trans-1-phenyl-1-butene, Biochemistry 22:5482-5489.
40. Liebler, D.C., M.J. Meredith and F.P. Guengerich. Formation of glutathione conjugates by reactive metabolites of vinylidene chloride in microsomes and isolated hepatocytes, Cancer Research 45:186-193, 1985.

41. Litterst, C.L., E.G. Mimnaugh, R.L. Reagan and T.E. Gram. Comparison of in vitro drug metabolism by lung, liver, and kidney of several common laboratory species, Drug Metab. Disposition 3(4):259-265, 1975.
42. Maltoni, C. Recent findings on the carcinogenicity of chlorinated olefins, Environ. Health Perspect. 21:1-5, 1977.
43. Maltoni, C., G. Cotti, L. Morisi and P. Chieco. 1980. Toxicity and carcinogenicity bioassays of vinylidene chloride, II. Chronic toxicity and carcinogenicity, Report of the Institute of Oncology & Tumor Center, Bologna, Italy.
44. Maltoni, C., G. Cotti, L. Morisi, and P. Chieco. Carcinogenicity bioassays of vinylidene chloride, Research plan and early results, La Medicina del Lavoro 68(4): 241-262, 1977.
45. McKenna, M. J., J.A. Zempel and P.J. Gehring. Covalent binding and glutathione depletion in hepatic tissue after inhalation exposure to [¹⁴C] vinylidene chloride, Abstracts: Seventeenth Annual Meeting, 257.
46. McKenna, M.J., P.G. Watanabe and P.J. Gehring. Pharmacokinetics of vinylidene chloride in the rat, Environ. Health Perspect. 21:99-105, 1977.
47. McKenna, M.J., J.A. Zempel, E.O. Madrid, W.H. Braun, and P.J. Gehring. Metabolism and pharmacokinetic profile of vinylidene chloride in rats following oral administration, Toxicol. Appl. Pharmacol. 45:821-835, 1978.
48. McKenna, M.J., J.A. Zempel and P.J. Gehring. A comparison of the pharmacokinetics of inhaled vinylidene chloride in rats and mice. Report of The Dow Chemical Company, 1979.
49. McKenna, M.J., J.F. Quast, H.O. Yakel, M.F. Balmer and L.W. Ramey. Vinylidene chloride: A chronic inhalation toxicity and oncogenicity study in rats, Report of The Dow Chemical Company, 1980.
50. McKenna, M.J., J.A. Zempel, E.O. Madrid and P.J. Gehring. The pharmacokinetics of [¹⁴C] vinylidene chloride in rats following inhalation exposure, Toxicol. Appl. Pharmacol. 45:599-610, 1978.

51. McKenna, M.J. Letters to the Editor, Environ. Health Perspect. 28:311-314, 1979.
52. Moore, L. 1,1-Dichloroethylene inhibition of liver endoplasmic reticulum calcium pump function, Biochem. Pharmacol. 31:1463-1465, 1982.
53. Moore, L. Inhibition of liver-microsome calcium pump by in vivo administration of CCl₄, CHCl₃, and 1,1-dichloroethylene (vinylidene chloride), Biochem. Pharmacol. 29:2505-2511, 1980.
54. Murray, F.J., K.D. Nitschke, L.W. Rapp and B.A. Schwetz. Embryotoxicity and fetotoxicity of inhaled or ingested vinylidene chloride in rats and rabbits, Toxicol. and Appl. Pharmacol. 49:189-202, 1979.
55. Murray, F.J., K.D. Nitschke, F.A. Smith, J.A. John, C.G. Humiston, J.F. Quast, and B.A. Schwetz. Teratology and reproduction studies of vinylidene chloride in rats and rabbits, Abstracts: Seventeenth Annual Meeting, 341.
56. Nitschke, K.D., F.A. Smith, J.F. Quast, J.M. Norris and B.A. Schwetz. A three-generation rat reproductive toxicity study of vinylidene chloride in the drinking water, Fundam. and Appl. Toxicol. 3:75-79, 1983.
57. Norris, J.M. Toxicological and pharmacokinetic studies on inhaled and ingested vinylidene chloride in laboratory animals, 1977 Paper Synthetics Conference, September 26-28.
58. Oesch, F. Mammalian epoxide hydrolases: Inducible enzymes catalyzing the inactivation of carcinogenic and cytotoxic metabolites derived from aromatic and olefinic compounds, Xenobiotica 3:305-340, 1973.
59. Oesch, F., D. Raphael, H. Schwind, and H.R. Glatt. Species differences in activating and inactivating enzymes related to the control of mutagenic metabolites, Arch. Toxicol. 39:97-108, 1977.
60. Ott, M.G., W.A. Fishbeck, J.C. Townshend and E.J. Schneider. A health study of employees exposed to vinylidene chloride, J. Occupational Med. 18(11):737-738, 1976.
61. Ponomarev, V. and L. Tomatis. Long-term testing of vinylidene chloride and chloroprene for carcinogenicity in rats, Oncology 37:136-141, 1980.

62. Quast, J.F. Pathology report on male and female rats exposed to vinylidene chloride vapors for six hours per day, five days per week during a 30-day period, Report of The Dow Chemical Company, 1976.
63. Quast, J.F., M.J. McKenna, L.W. Rampy and J.M. Norris. Chronic toxicity and oncogenicity study on inhaled vinylidene chloride in rats, Fundam. Appl. Toxicol. 6:105-144, 1986.
64. Quast, J.F., M.J. McKenna, L.W. Rampy and J.M. Norris. A chronic toxicity and oncogenicity study in rats and subchronic toxicity study in dogs on ingested vinylidene chloride, Fundam. and Appl. Toxicol. 3:55-62, 1983.
65. Rampy, J.W., J.F. Quast, C.G. Humiston, M.F. Balmer and B.A. Schwetz. Interim results of two-year toxicological studies in rats of vinylidene chloride incorporated in the drinking water or administered by repeated inhalation, Environ. Health. Perspect. 21:33-43, 1977.
66. Ray, P.L. and L. Moore. 1,1-Dichloroethylene inhibition of liver microsomal calcium pump in vitro, Arch. of Biochem. Biophys. 218:26-30, 1982.
67. Reichert, D., H.W. Werner and D. Henschler. Role of liver glutathione in 1,1-dichloroethylene metabolism and hepatotoxicity in intact rats and isolated perfused rat liver, Arch. Toxicol. 41:169-178, 1978.
68. Reichert, D., H.W. Werner, M. Metzler and D. Henschler. Molecular mechanism of 1,1-dichloroethylene toxicity: Excreted metabolites reveal different pathways of reactive intermediates, Arch. Toxicol. 42:159-169, 1979.
69. Reichert, D., and H.W. Werner. 1978. Disposition and metabolism of (¹⁴C) 1,1-dichloroethylene after single oral administration in rats (Abstract) Naunyn-Schmiedeberg's Arch. Pharmacol. 302(Suppl), R-22.
70. Reitz, R.H., P.G. Watanabe, M.J. McKenna, J.F. Quast, and P.J. Gehring. Effects of vinylidene chloride on DNA synthesis and DNA repair in the rat and mouse: A comparative study with dimethylnitrosamine, Toxicol. Appl. Pharmacol. 52:357-370, 1980.
71. Reynolds, E.S. and M.T. Moslen. Damage to hepatic cellular membranes by chlorinated olefins with emphasis on synergism and antagonism, Environ. Health Perspect. 21:137-147, 1977.

72. Reynolds, E.S., M.T. Moslen, P.J. Boor, R.J. Jaeger. 1,1-Dichloroethylene hepatotoxicity, time course of GSH changes and biochemical aberrations, Am. J. Path. 101(2):331-343, 1980.
73. Short, R.D., J.M. Winston, J.L. Minor, C.B. Hong, J. Seifter and C.C. Lee. Toxicity of vinylidene chloride in mice and rats and its alteration by various treatments. J. Toxicol. Environ. Health 3:913-921, 1977.
74. Short, R.D., J.M. Winston, J.L. Minor, J. Seifter and C.C. Lee. Effect of various treatments on toxicity of inhaled vinylidene chloride, Environm. Health Perspect. 21:125-129, 1977.
75. Short, R.D., J. L. Minor, J.M. Winston and C.C. Lee. A dominant lethal study in male rats after repeated exposures to vinyl chloride or vinylidene chloride, J. of Toxicol. and Environ. Health 3:965-968, 1977.
76. Simmon, V.F., H.S. Rosenkranz, E. Zeiger and L.A. Poirier. Mutagenic activity of chemical carcinogens and related compounds in the intraperitoneal host-mediated assay, Natl. Cancer Inst. 62:911-918, 1979.
77. Simmon, V.F., K. Kauhanen and R.G. Tardiff. Mutagenic activity of chemicals identified in drinking water, In: Progress in Genetic Toxicology (D. Scott, B.A. Bridges and F.H. Sobels, eds.), 249-258, Elsevier/North Holland Biomedical Press, 1977.
78. Szabo, S., R.J. Jaeger, M.T. Moslen and E.S. Reynolds. Modification of 1,1-dichloroethylene hepatotoxicity by hypothyroidism, Toxicol. and Appl. Pharmacol. 42:367-376, 1977.
79. Van Duuren, B.L., B.M. Goldschmidt, G. Loewengart, A.C. Smith, S. Melchionne, I. Seldman and D. Roth. Carcinogenicity of halogenated olefinic and aliphatic hydrocarbons in mice, JNCI 63:1433-1439, 1979.
80. Viola, P.L. and A. Caputo. Carcinogenicity studies on vinylidene chloride, Environ. Health. Perspect. 21:45-47, 1977.
81. Walker, C.H. Species differences in microsomal monooxygenase activity and their relationship to biological half-lives, Drug Metab. Rev. 7(2):295-323, 1978.

82. Watanabe, P.G., R.H. Reitz, A.M. Schumann, M.J. McKenna, J.F. Quast and P.J. Gehring. Implications of the mechanisms of tumorigenicity for risk assessment, In: The Scientific Basis of Toxicity Assessment (H. Witschi, ed), 69-89, Elsevier/ North-Holland Biomedical Press, 1980.