HEALTH AND ENVIRONMENTAL EFFECT PROFILES

APRIL 30, 1980
U.S. ENVIRONMENTAL PROTECTION AGENCY
OFFICE OF SOLID WASTE

TABLE XIII-2

US METHYL ALCOHOL CONSUMPTION, 1973

	Million Pounds	Million Gallons
Formaldehyde	2,778	420
Dimethyl terephthalate	435	66
Solvent usage	565	85
Methyl halides	435	66
Methylamines	232	35
Methyl methacrylate	265	40
Inhibitor for formaldehyde	66	10
Exports	824	124
Glycol methyl ethers	81	12
Acetic acid	240	36
Miscellaneous	1,207	181
Total	7,128	1,075

From Blackford [5]

TABLE XIII-3

POTENTIAL OCCUPATIONAL EXPOSURES TO METHYL ALCOHOL

Acetic acid makers
Adhesive workers
Alcohol distillery workers
Alcohol lamp users
Aldehyde pumpmen
Antifreeze workers
Art glass workers
Automobile painters
Aviation fuel handlers
Bookbinders
Bronzers
Brushmakers
Denatured alcohol workers
Dimethyl sulfate makers
Drug makers
Drycleaners
Dye makers
Dyers
Ester makers
Explosives workers
Feather workers
Felt-hat makers
Flower makers, artificial
Formaldehyde makers
Foundry workers
Furniture polishers
Gilders
Glassmakers, safety
Hectograph operators
Incandescent lamp makers
Inkmakers
Japan makers
Japanners
Jet fuel workers
Lacquerers
Lacquer makers
Lasters
Leather workers
Linoleum makers
Lithographers
Metal polishers
Methyl acrylate makers
Methyl alcohol workers
Methyl amine makers
Methylation workers
Methyl bromide makers
Methyl chloride makers
Methyl methacrylate makers
Millinery workers
Motor fuel blenders
Organic chemical synthesizers
Painters
Paintmakers
Paint remover workers
Patent leather makers
Perfume makers
Photoengravers
Photographic film makers
Polish makers
Printers
Rayon makers
Resin makers
Rocket fuel handlers
Rocket fuel makers
Rubber shoe cementers
Rubber workers
Shellackers
Shellac makers
Shoe factory workers
Shoe finishers
Shoe heel coverers, wood
Shoe stitchers
Soapmakers
Straw-hat makers
Sugar refiners
Textile printers
Type cleaners
Vacuum tube makers
Varnish workers
Vulcanizers
Wood alcohol distillers
Wood stainers
Wood stain makers

From Gafafer [6]

TABLE XIII-4

ANIMAL EXPERIMENTATION RESULTS
OF METHYL ALCOHOL EXPOSURE

Species	Route of Exposure	Dose	Effect	Reference
Monkeys	Inhalation	5,000 ppm duration unknown	The monkey survived for an unstated period of time.	47
"	"	1,000 ppm duration unknown	The monkey died promptly upon exposure at this level.	47
Dogs	"	450-500 ppm 8 hr/day 7 days/week for 379 days	Blood levels of methyl alcohol were found to range from 10 to 15 mg/100 ml of blood and on occassion went as high as 52 mg/100 ml. No abnormal eye findings were reported.	41
"	Oral	2.5 to 9.0 g/kg body weight	Of the 9 treated dogs, 2 died at doses of 4 and 9 g/kg. CO_2 combining capacities dropped below normal in 2 dogs, and no ophthalmoscopic changes were noted.	42

TABLE XIII-4 (CONTINUED)

ANIMAL EXPERIMENTATION RESULTS
OF METHYL ALCOHOL EXPOSURE

Species	Route of Exposure	Dose	Effect	Reference
Monkeys	Oral	1.0 to 8.0 g/kg	Acidosis developed in monkeys receiving doses ranging from 3.0 to 6.0 g/kg. The animal receiving 1.0 g/kg did not develop acidosis. Definite eye-ground change occurred to 2 of the acidotic monkeys.	42
Rats	"	4.75 g/kg	70% mortality	42
"	"	4.5 g/kg	None of the 9 tested rats developed acidosis.	42
Rabbits	"	3.5 g/kg	One animal receiving this dose died in less than 24 hours. No eye fundus changes were reported.	42
Rabbits	"	2.1 g/kg	Of the 3 animals tested at this dose, all died between 24 hours and 3 days after dosing.	42
"	Intra-cutaneous	10 mg and 35 mg	At 10 mg, there was no skin reaction, whereas at 35 mg, a 9-sq mm skin reaction occurred.	49

TABLE XIII-4 (CONTINUED)

ANIMAL EXPERIMENTATION RESULTS
OF METHYL ALCOHOL EXPOSURE

Species	Route of Exposure	Dose	Effect	Reference
Monkeys	i.p. inj	0.5 g/kg of 14 C-methyl alcohol with an equimolar amount of ethyl alcohol	The ethyl alcohol reduced the oxidation of methyl alcohol 90%.	52
"	"	1.0 g/kg 14 C-methyl alcohol and 6.0 g/kg 14C-methyl alcohol	The methyl alcohol was oxidized at a rate of 37 mg/kg/hour between the first and fourth hour. The CO_2 formation was linear at the high dose; the oxidation rate was 47 mg/kg/hour which is a significant difference.	52
Rats	"	1.0/kg 14C-methyl alcohol	The oxidation rate of the methyl alcohol was 24 mg/kg/hr for the first 28 hours. At the end of 36 hours 77% of the methyl alcohol had been oxidized to 14C-labled CO_2 and 24% was excreted unchanged in approximately equal amounts by the pulmonary and combined urinary and fecal routes.	51

REFERENCES

1. Woodward HF Jr: Methanol, in Kirk-Othmer Encyclopedia of Chemical Technology, ed 2 rev. New York, John Wiley and Sons, 1967, vol 13, pp 370-98

2. American National Standards Institute: Acceptable Concentrations of Methanol, ANSI Z 37.14-1971. New York, ANSI, 1971, 8 pp

3. Chemical Safety Data Sheet SD-22--Properties and essential information for safe handling and use of methanol. Washington, DC, Manufacturing Chemists' Association Inc, 1970, 17 pp

4. Weast RC (ed): Handbook of Chemistry and Physics--A Ready-Reference Book of Chemical and Physical Data, ed 55. Cleveland, CRC Press, 1974, p D-85

5. Blackford JL: Methanol (methyl alcohol), in Chemical Economics Handbook. Menlo Park, Cal, Stanford Research Institute, 1974, pp 674.5021B-674.5021G

6. Gafafer WM: Occupational Diseases--A Guide to Their Recognition, publication No. 1097. US Department of Health, Education, and Welfare, Public Health Service, 1964, pp 176-78

7. Taylor P: On pyroligneous aether. Philos Mag J 60:315-17, 1822

8. Dumas J, Peligot E: [Organic chemistry--I. On a new alcohol and its compounds-extract from an article.] J Prakt Chem 3:369-77, 1834 (Ger)

9. MacFarlan JF: On methylated spirits, and some of its preparations. Pharm J Trans 15:310-15, 1855

10. Wood CA: Death and blindness as a result of poisoning by methyl, or wood alcohol and its various preperations. Int Clin 16:68-78, 1906

11. Wood CA, Buller F: Cases of death and blindness from Columbian spirits and other methylated preparations. JAMA 43:972-77,1058-62,1117-23, 1904

12. Baskerville C: Wood alcohol--A report of the chemistry, technology and pharmacology of and the legislation pertaining to methyl alcohol. New York State Factory Investigation Commission, Appendix 6, vol 2, pp 917-1042, 1913

13. De Schweinitz GE: A case of methyl-alcohol amaurosis, the pathway of entrance of the poison being the lungs and the cutaneous surface. Ophthalmic Rec 10:289-96, 1901

14. Dangers in the manufacture and industrial uses of wood alcohol, special bulletin No. 86. Albany, State of New York Department of Labor, Division of Industrial Hygiene, 1917, pp 1-17

15. Jelliffe SE: Multiple neuritis in wood alcohol poisoning. Med News 86:387-90, 1905

16. Hawes AT: Amblyopia from the fumes of wood alcohol. Boston Med Sur J 153:525, 1905

17. Tyson HH: Amblyopia from inhalation of methyl alcohol. Arch Ophthalmol 16:459-71, 1912

18. Wood CA: Death and blindness from methyl or wood-alcohol poisoning with means of prevention. JAMA 59:1962-66, 1912

19. Ziegler SL: The ocular menace of wood alcohol poisoning. JAMA 77:1160-66, 1921

20. Scherberger RF, Happ GP, Miller FA, Fassett DW: A dynamic apparatus for preparing air-vapor mixtures of known concentrations. Am Ind Hyg Assoc J 19:494-98, 1958

21. May J: [Odor thresholds of solvents for evaluating solvent odors in air.] Staub-Reinhalt Luft 26:385-89, 1966 (Ger)

22. Chao Chen-Tsi: [Materials on the hygienic standardization of the maximally permissible concentration of methanol vapors in the atmosphere.] Gig Sanit 24:7-12, 1959 (Rus)

23. Ubaydullayev R: A study of hygienic properties of methanol as an atmospheric air pollutant, in Levine BS (transl): USSR Literature on Air Pollution and Related Occupational Diseases--A Survey 17:39-45, 1968

24. Thies O: [Eye damage in chemical industries.] Zentralbl Gewerbehyg Unfallverhut 15:303-08, 1928 (Ger)

25. Humperdinck K: [On the problem of chronic intoxication with methanol vapors.] Arch Gewerbepathol Gewerbehyg 10:569-74, 1941 (Ger)

26. Burk M: [On chronic occupational methyl alcohol intoxication.] Klin Monatsbl Augenheilkd 130:845-50, 1957 (Ger)

27. Gimenez ER, Vallejo NE, Roy E, Lis M, Izurieta EM, Rossi S, Capuccio M: Percutaneous alcohol intoxication. Clin Toxicol 1:39-48, 1968

28. Table of normal values, in Davidsohn I, Henry JB (eds): Todd-Sanfords Clinical Diagnosis by Laboratory Methods, ed 15. Philadelphia, WB Saunders Company, 1974, Appendix 3

29. Agner K, Hook O, von Porat B: The treatment of methanol poisoning with ethanol--With report of two cases. J Stud Alcohol 9:515-22, 1949

30. Leaf G, Zatman LJ: A study of the conditions under which methanol may exert a toxic hazard in industry. Br J Ind Med 9:19-31, 1952

31. Kendal LP, Ramanathan AN: Excretion of formate after methanol ingestion in man. Biochem J 54:424-26, 1953

32. Bastrup J: Method for the determination of formic acid in urine. Acta Pharmacol 3:303-11, 1947

33. Von Wartburg JP, Bethune JL, Vallee BL: Human liver alcohol dehydrogenase--Kinetic and physiochemical properties. Biochemistry 3:1775-82, 1964

34. Blair AH, Vallee BL: Some catalytic properties of human liver alcohol dehydrogenase. Biochemistry 5:2026-34, 1966

35. Goodman JI, Tephly TR: Peroxidative oxidation of methanol in human liver--The role of hepatic microbody and soluble oxidases. Res Commun Chem Pathol Pharmacol 1:441-50, 1970

36. Ritchie JM: The aliphatic alcohols, in Goodman LS, Gilman A (eds): The Pharmacological Basis of Therapeutics, ed 4. New York, The MacMillan Co, 1970, p 141

37. Majchrowicz E, Mendelson JH: Blood methanol concentrations during experimentally induced methanol intoxication in alcoholics. J Pharmacol Exp Ther 179:293-300, 1971

38. Greenburg L, Mayers MR, Goldwater LJ, Burke WJ: Health hazards in the manufacture of "fused collars"--II. Exposure to acetone-methanol. J Ind Hyg Toxicol 20:148-54, 1938

39. Kingsley WH, Hirsch FG: Toxicologic considerations in direct process spirit duplicating machines. Compen Med 40:7-8, 1954-1955

40. Bennett IL Jr, Cary FH, Mitchell GL Jr, Cooper MN: Acute methyl alcohol poisoning--A review based on experiences in an outbreak of 323 cases. Medicine 32:431-63, 1953

41. Sayers RR, Yant WP, Schrenk HH, Chornyak J, Pearce SJ, Patty FA, Linn JG: Methanol poisoning--I. Exposure of dogs to 450-500 ppm methanol vapor in air--Report of Investigations RI 3617. US Dept of Interior, Bureau of Mines, 1942, pp 1-10

42. Gilger AP, Potts AM: Studies on the visual toxicity of methanol--V. The role of acidosis in experimental methanol poisoning. Am J Ophthalmol 39:63-86, 1955

43. Roe O: The metabolism and toxicity of methanol. Pharmacol Rev 7:399-412, 1955

44. Cooper JA, Kini MM: Editorial--Biochemical aspects of methanol poisoning. Biochem Pharmacol 11:405-16, 1962

45. Tephly TF, Watkins WD, Goodman JI: The biochemical toxicology of methanol, in Essays in Toxicology. New York, Academic Press, 1974, chap 6

46. Von Oettingen WF: The aliphatic alcohols--Their toxicity and potential dangers in relation to their chemical constitution and their fate in metabolism, bulletin No. 281. US Dept of Health, Education, and Welfare, Public Health Service, 1943

47. McCord CP: Toxicity of methyl alcohol (methanol) following skin absorption and inhalation--A progress report. Ind Eng Chem 23:931-36, 1931

48. Cooper JR, Felig P: The biochemistry of methanol poisoning--II. Metabolic acidosis in the monkey. Toxicol Appl Pharmacol 3:202-09, 1961.

49. Renkonen KO, Teir H: Studies on the local reactions of the skin to chemical compounds. Ann Med Exp Biol Fenn 35:67-69, 1957

50. Carpenter CP, Smyth HF Jr: Chemical burns of the rabbit cornea. Am J Ophthalmol 29:1363-72, 1946

51. Tephly TR, Parks RE Jr, Mannering GJ: Methanol metabolism in the rat. J Pharmacol Exp Ther 143:292-300, 1964

52. Makar AB, Tephly TR, Mannering GJ: Methanol metabolism in the monkey. Mol Pharmacol 4:471-83, 1968

53. Clay KL, Murphy RC, Watkins WD: Experimental methanol toxicity in the primate--Analysis of metabolite acidosis. Toxicol Appl Pharmacol 34:49-61, 1975

54. Saha AK, Khudabaksh AR: Chromosome aberrations induced by methanol in germinal cells of grasshopper, Oxya velox Fabricius. J Exp Biol 12:72-75, 1974

55. Technology Committee (GA Hedgecock, chmn), Working Party (SJ Silk, chmn): Chemical indicator tubes for measurement of the concentration of toxic substances in air--First report of a working party of the Technology Committee of the British Occupational Hygiene Society. Ann Occup Hyg 16:51-62, 1973

56. Smith BS, Pierce JO: The use of plastic bags for industrial air sampling. Am Ind Hyg Assoc J 31:343-48, 1970

57. Rogers GW: Sampling and determination of methanol in air. J Ind Hyg Toxicol 27:224-30, 1945

58. Documentation of NIOSH Validation Tests, NIOSH contract No. CDC 99-74-45. US Dept of Health, Education, and Welfare, Public Health Service, Center for Disease Control, National Institute for Occupational Safety and Health, 1975, pp S59-1 to S59-9

59. Feldstein M, Balestrieri S, Levaggi DA: The use of silica gel in source testing. Am Ind Hyg Assoc J 28:381-85, 1967

60. Methyl alcohol Class B, NIOSH Sampling Data Sheet #36.01. US Dept of Health, Education, and Welfare, Public Health Service, Center for Disease Control, National Institute for Occupational Safety and Health, December 15, 1975, December 16, 1975, January 26, 1976

61. Skoog DA, West DM: Fundamentals of Analytical Chemistry. New York, Holt, Rinehart and Winston, 1963, pp 667-69

62. Deniges MG: [Analytical chemistry-Study of methyl alcohol in general and especially in the presence of ethyl alcohol.] C R Acad Sci (Paris) 150:832-34, 1910 (Fr)

63. Ellvove E: A note on the detection and estimation of small amounts of methyl alcohol. J Ind Eng Chem 9:295-97, 1917

64. Wright LO: Comparison of sensitivity of various tests for methanol. Ind Eng Chem 19:750-52, 1927

65. Chapin RM: Improved Deniges test for the detection and determination of methanol in the presence of ethyl alcohol. J Ind Eng Chem 13:543-45, 1921

66. Jephcott CM: Determination of methyl alcohol in the air. Analyst 60:588-92, 1935

67. Jansson BO, Larson BT: Analysis of organic compounds in human breath by gas chromatography-mass spectrometry. J Lab Clin Med 74:961-66, 1969

68. Matsumura Y: The adsorption properties of active carbon--II. Preliminary study on adsorption of various organic vapors on active carbon by gas chromatography. Ind Health 3:121-25, 1965

69. Baker RN, Alenty LA, Zack JF Jr: Simultaneous determination of lower alcohols, acetone and acetaldehyde in blood by gas chromatography. J Chromatogr Sci 7:312-14, 1969

70. Hurst RE: A method of collecting and concentrating head space volatiles for gas-chromatographic analysis. Analyst 99:302-05, 1974

71. Occupational Health Hazards in Massachusetts Industries--IV. Wood heel covering, WPA No. 65-14-6060. Boston, Massachusetts Department of Labor and Industries, Division of Occupational Hygiene, 1937

72. Goss AE, Vance GH: Methanol vapors from duplicating machines may be health hazard. Ind Hyg Newsletter 8:15, 1948

73. McAllister RG: Exposure to methanol from spirit duplicating machines. Am Ind Hyg Assoc Q 15:26-28, 1954

74. Dutkiewicz T, Blockowicz A: [Evaluation of exposure to methanol in view of field studies.] Med Pr 18:132-41, 1967 (Pol)

75. Methyl alcohol (methanol), AIHA Hygienic Guide Series. Southfield, Michigan, American Industrial Hygiene Association, 1957

76. Methanol, Data Sheet 407, Revision A. Chicago, National Safety Council, 1967, pp 1-5

77. American Conference of Governmental Industrial Hygienists, Committee on Industrial Ventilation: Industrial Ventilation--A Manual of Recommended Practice, ed 13. Lansing, Michigan, ACGIH, 1974

78. American National Standards Institute: Fundamentals Governing the Design and Operation of Local Exhaust Systems, Z9.2-1971. New York, American National Standards Institute Inc, 1971

79. Bowditch M, Drinker CK, Drinker P, Haggard HH, Hamilton A: Code for safe concentrations of certain common toxic substances used in industry. J Ind Hyg Toxicol 22:251, 1940

80. Cook WA: Maximum allowable concentrations of industrial atmospheric contaminants. Ind Med 14:936-46, 1945

81. Methyl alcohol (methanol), AIHA Hygienic Guide Series. Southfield, Michigan, American Industrial Hygiene Association, 1964

82. American Conference of Governmental Industrial Hygienists, Committee on Threshold Limit Values: Documentation of Threshold Limit Values for Substances in Workroom Air, ed 3. Cincinnati, ACGIH, 1971, pp 155-56

83. American Conference of Governmental Industrial Hygienists: TLVs--Threshold Limit Values for Chemical Substances and Physical Agents in the Workroom Environment with Intended Changes for 1974. Cincinnati, ACGIH, 1974

84. Winell MA: An international comparison of hygienic standards for chemicals in the work environment. Ambio 4:34-36, 1975, p 23

85. Smelyanskiy ZB, Ulanova IP: [New standards for permissible levels of toxic gases, fumes, dust in the air of work areas.] Gig Tru Prof Zabol 5:7-15, 1959 (Rus)

86. Czechoslovakia Committee of MAC (J Teisinger, chmn): Documentation of MAC in Czechoslovakia. Prague, June 1969, pp 114-15

87. Elkins, HB, in Patty FA (ed): Industrial Hygiene and Toxicology, rev ed 2; Toxicology (Fassett DW, Irish DD, eds). New York, Interscience Publishers, 1963, vol 2, pp 1409-22

88. Methyl alcohol (methanol), AIHA Hygienic Guide Series. Southfield, Michigan, American Industrial Hygiene Association, 1964

89. Methanol--Storage and Handling. Wilmington, Delaware, du Pont de Nemours Co, 1974, 10 pp

90. National Electric Code 1975, NFPA No. 70-1975. Boston, Massachusetts, National Fire Protection Association, 1975

91. American National Standards--Occupational and Educational Eye and Face Protection, Z87.1. New York, American National Standards Institute Inc, 1968

No. 127

S,S'-Methylene - o,o,o',o'-Tetraethyl Phosphorodithioate

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

-1513-

DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

PHOSPHORODITHOIC ACID,

S,S'-METHYLENE,O,O,O',O'-TETRAETHYL ESTER (ETHION)

Summary

The S,S'-methylene,O,O,O',O'-tetraethyl ester of phosphorodithoic acid, ethion, has not shown mutagenic effects in mice or teratogenic effects in fowl. Subcutaneous injection of the compound into atropinized chickens produced neurotoxic effects. There is no available information on the possible carcinogenic effects of ethion.

Ethion has shown acute toxicity in stonefly naiads at a 96-hour LC_{50} range from 1.8 to 4.2 µg/l.

I. INTRODUCTON

O,O,O',O'-Tetraethyl-S,S'-methylene bisphosphorodithioate (CAS registry number 563-12-2), also called ethion, is an insecticide and miticide made from phosphorus pentasulfide (SRI, 1976). Ethion has the following physical and chemical properties (Windholz, 1976; FAO, 1969):

Formula:	$C_9H_{22}O_4P_2S_4$
Molecular Weight:	384.48
Melting Point:	-12°C to -13°C
Density:	1.220^{20}_{4}
Vapor Pressure:	Practically non-volatile at ordinary temperatures
Solubility:	Insoluble in water, soluble in organic solvents
Consumption:	0.7 million lbs/year (SRI, 1976)

Ethion is a pre-harvest topical insecticide used primarily on citrus fruits, deciduous fruits, nuts and cotton (SRI, 1976). It is also used as a cattle dip for ticks and as a back-line treatment for buffalo flies (FAO, 1969).

II. EXPOSURE

A. Water

Pertinent data could not be located in the available literature. Water contamination from ethion manufacturing may be minimal due to the common use of industrial wastewater treatment plants (U.S. EPA, 1977).

B. Food

Residues on a variety of foods have been reported (FAO, 1969). A sampling shows the residues on fruits and vegetables range from 10.4 ppm for raisins to less than 0.1 ppm for almonds. The majority are less than 1 ppm. Treated cotton showed no residue in the seed. Tea at harvest showed residues of up to 7 ppm; since tea is blended prior to sale, residues are lower

when consumed. Lactating cows fed up to 20 ppm radioactive ethion showed no residues in their milk. In meat, the highest radioactivity was in the liver; however, chemical analysis showed these residues were not ethion but metabolites. When animals were dipped, residues from skin absorption of ethion were found in the body fat.

C. Inhalation and Dermal

Pertinent data could not be located in the available literature.

III. PHARMACOKINETICS

A. Absorption

Results of acute toxicity studies in animals indicate that ethion is absorbed following oral and dermal exposure (Gaines, 1969).

B. Distribution

Following feeding of dairy cattle with ethion, small amounts of the unchanged compound were found in milk and fatty tissues (Vettorazzi, 1976).

C. Metabolism

Rao and McKinley (1969) have reported that in vitro metabolism of ethion occurs through oxidative desulfuration of the compound by chicken liver homogenates.

D. Excretion

Pertinent data could not be located in the available literature. Based on studies of other organophosphorous insecticides, it may be anticipated that ethion metabolites would be eliminated primarily in the urine (Matsumura, 1975).

IV. EFFECTS

A. Carcinogenicity

Pertinent data could not be located in the available literature.

B. Mutagenicity

Vettorazzi (1976) has cited an unpublished study which found no dominant lethal effects in mice administered ethion.

C. Teratogenicity

Oral administration of ethion (100 ppm) to chickens, chukars, and quail failed to produce teratogenic or adverse reproductive effects (Abbott and Walker, 1972).

D. Other Reproductive Effects

Oral feeding of ethion to chickens, chukar, and quail failed to affect egg hatch (Abbott and Walker, 1972).

E. Chronic Toxicity

Subcutaneous injection of atropinized chickens with 400 mg/kg ethion produced neurotoxic effects (flaccid paralysis) (Gaines, 1969). Ethion will produce anti-cholinesterase effects in mammals (Vettorazzi, 1976).

V. AQUATIC TOXICITY

A. Acute Toxicity

Sanders and Cope (1968) observed 96-hour LC_{50} values ranging from 1.8 to 4.2 µg/l for stonefly naiads (Pteronarcys californica) exposed to ethion.

B. Chronic Toxicity, Plant Effects and Residues

Pertinent data could not be located in the available literature.

VI. EXISTING GUIDELINES AND STANDARDS

A. Human

The World Health Organization (FAO, 1969) has established an ADI level of 0.005 mg/kg for ethion based on cholinesterase inhibition studies.

B. Aquatic

Pertinent data could not be located in the available literature.

REFERENCES

Abbott, U. and N. Walker. 1972. Effects of pesticides and related compounds on several avian species, chemistry and toxicology of agricultural chemicals. Summary Report 1971. Food Protection and Toxicology Center, University of California at Davis. p. 9.

Food and Agriculture Organization/World Health Organization. 1969. Evaluations of some pesticide residues in food. The monographs FAO/WHO/PL:1968/-M/9/1.

Gaines, T. 1969. Acute toxicity of pesticides. Toxicol. Appl. Pharmacol. 14: 515.

Matsumura, F. 1975. Toxicology of Insecticides. Plenum Press, New York. p. 223.

Rao, S. and W. McKinley. 1969. Metabolism of organophosphorus insecticides by liver homogenates from different species. Can. Jour. Biochem. 47: 1155.

Sanders, H.O. and O.B. Cope. 1968. The relative toxicities of several pesticides to naiads of three species of stoneflies. Limnol. Oceanogr. 13: 112.

Stanford Research Institute. 1976. Chemical Economics Handbook, Insecticides.

U.S. EPA. 1977. Industrial process profile for environmental use: chapter 8, pesticides industry. U.S. Environ. Prot. Agency, U.S. NTIS PB 266 225.

Vettorazzi, G. 1976. State of the art of the toxicological evaluation carried out by the joint FAO/WHO meeting on pesticides residues. II. Carbamate and organophosphorus pesticides used in agriculture and public health. Residue Reviews. 63: 1.

Windholz, M. (ed.) 1976. The Merck Index, 9th ed. Merck and Co., Inc., Rahway, New Jersey.

No. 128

Methyl Ethyl Ketone

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

-1520-

DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

Methyl Ethyl Ketone

I. INTRODUCTION

Methyl ethyl ketone or (MEK) as it is commonly referred to is a clear, colorless, volatile liquid (VP of 100 mm at 25°C) with a molecular weight of 72.12. It has a melting point of -86.35°C and a boiling point of 76.6°C. It is very soluble in water (25.5 g/loo at 2 percent) and soluble in all proportions in alcohol, ether, acetone and benzene.[2] It is also highly flammable (22°F - open cup).[3]

MEK is produced and used as a solvent in nitrocellulose coatings and vinyl films; in the synthesis of colorless resins; in the manufacture of smokeless powder; in paint removers, cements, adhesives, and cleaning fluids; in printing industry; as a catalyst carrier; in lube oil dewaxing and in acrylic coatings.[2]

II. ROUTES OF EXPOSURE

MEK is rapidly absorbed through the skin by inhalation.

III. PHARMACOKINETICS

MEK occurs in trace amounts in normal human urine and may have a dietary origin.[1] Most probable precursor is - methylacetoacetic acid.[1]

Urine of rabbits exposed to MEK reported to contain glucuronide of 2-butanol.[1]

IV. EFFECTS ON MAMMALS

The chief effect of MEK is narcosis but is also a strong irritant of the mucous membranes of the eyes and nose. The oral LD50 for rats is 3.3 g/kg and the inhalation LC50 is

around 700 ppm.[1]

Repeated exposure of guinea pigs for 12 weeks to 235 ppm caused no symptoms.[1]

Lethal doses in animals caused marked congestion of internal organs and slight congestion of brain. Lungs showed emphysema (see Table 1).

Slight throat irritation in humans occured at 100 ppm and in eyes at 200 ppm.

Dermatoses among workers having direct contact and exposed to vapors are not uncommon. Some workers complained of numbness of fingers and arms.[1]

Table 1

Effects of Methyl Ethyl Ketone on Animals

	Concentration/ Duration	Animal	Effects
Methyl Ethyl Ketone	33,000-100,000 ppm/200 min.	Guinea Pigs	Gasping, death, emphysema, slight congestion of the brain, marked congestion of the systemic organs especially the lungs and corneal opacities
	3,300 ppm/810 min.	Guinea Pigs	No abnormal signs
	1,125 ppm/24 hr/3,55d	Rats	No evidence of peripheral neuropathy
	1,126 or 2,618 ppm/7 hr/d on d 6-15 of gestation	Pregnant Rats	Embryotoxicity, fetotoxicity and possible teratogenicity

References

1. Toxicity and Metabolism of Industrial Solvents.

2. Ketonic Solvents, Open File Report, Working Draft prepared by Clement Associates, Inc., September 19, 1978.

3. Sax, N. Irving, Dangerous Properties of Industrial Materials, Fourth Edition, 1975, Van Nostrand Reinhold, New York, New York 10001

4. Patty, F. A., Schrenk, H. H., Yant W. P.: Acute Respone of guinea Pigs to Vapors of Some New Commercial Organic Compounds--VIII. Butanone. U.S. Public Health Pep 50: 1217-28, 1935.

5. Spencer, P. S., Schaumburg, H. H.: Feline Nervous System Response to Chronic Intoxication With Commercial Grades of Methyl n-Butyl Ketone, Methyl Isobutyl Ketone, and Methyl Ethyl Ketone. Toxicol. Appl. Pharmacol. 37:301-11, 1976.

6. Griggs, J. H., Weller, E. M., Palmisano, P. A., Niedermeier, W.: The Effect of Noxious Vapors on Embryonic Chick Development, Ala. J Med. Sci. 8:342-45, 1971.

No. 129

Methyl Isobutyl Ketone

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WASHINGTON, D.C. 20460

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-1526-

DISCLAIMER

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Methyl Isobutyl Ketone

I. INTRODUCTION

Methyl isobutyl ketone (MIK) is a colorless, stable liquid with a molecular weight of 100.16. It has a melting point of -84.7°C and a boiling point of 116.85°C. It is slightly soluble in water, but soluble in chloroform and in all proportions in alcohol, ether, acetone and benzene.[1] MIK is also flammable (73°F).[2]

MIK is produced and used as a solvent for paints, varnishes, nitrocellulose and lacquers; in the manufacture of methyl amyl alcohol and other organic synthesis; in extraction processes, including extraction of uranium from fission products; and as a denaturant for alcohol.[1]

II. ROUTES OF EXPOSURE

Exposure occurs through the skin and by inhalation.[1]

III. EFFECTS ON MAMMALS

In a study reported on 19 employees who worked with MID for 20-30 minutes daily over an 8-hour shift, Linani et. al. concluded that MIK irritated the conjuctiva and respiratory tract and produced disturbances of the gastrointstinal tract and CNS.[3] Other reported effects due to exposure include weakness, los of appetite, headache, eye irritation, stomach ache, nausea, vomitting and sore throat.[3]

In addition, in various studies conducted on animals an increase in kidney and liver weights were reported after

repeated vapor inhalation (see Table 1).[4,5]

No information was found on the carcinogenicity, mutagenicity and teratogenicity of this compound.

Table 1

Effects of Methyl Isobutyl Ketone on Animals [4,5]

	Concentration Duration	Animal	Effects
Methyl Isobutyl Ketone	200 ppm/24 hr/d for 2 weeks	Mice, rats, dogs, and monkeys	Heavier liver and kidneys in rats
	100 ppm/24 hr/d for 2 weeks	Mice, rats, dogs, and monkeys	Heavier kidneys in rats
	100 ppm at 258 mm Hg/ 24 hr/d 90d	Monkeys, dogs, rats	Inflammation of kidneys in 1 monkey, hyaline droplet degeneration of proximal tubules in all rats, normal clinical and hematologic measurements
	150 mg/kg/twice/ d,5d/week 8.5 mo.	Cats	No evidence of peripheral neuropathy

References

1. Ketonic Solvents, Open File Report, Working Draft prepared by Clement Associates, Inc., September 19, 1978.

2. Sax, N. Irving, Dangerous Properties of Industrial Materials, Fourth Edition, 1975, Van Nostrand Reinhold, New York, New York 10001.

3. Linari, F. Perrelli, G., Varese, D: [Clinical Observations and Blood Chemistry Tests Among Workers Exposed to the Effects of a Complex Ketone--Methyl Isobutyl Ketone.] Arch. Sci. Med., 1964, pp. 226-237. (Ita).

4. MacEwen, J. D, Vernot, E. H., Haun C.C: Effect of 90-Day Continuous Exposure to Methylisobutylketone on Dogs, Monkeys and Rats, Springfield, Virginia, U.S. Department of Commerce, National Technical Information Service, 1971, 23 pp. (NTIS AD-730-291).

5. Spencer, P.S., Schaumburg, H. H.: Feline Nervous System Response to Chronic Intoxication with Commercial Grades of Methyl n-Butyl Ketone, Methyl Isobutyl Ketone, and Methyl Ethyl Ketone. Toxicol. Appl. Pharmacol. 37:301-11, 1976.

No. 130

Methyl Methacrylate

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

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METHYL METHACRYLATE

Summary

Oral or skin painting studies in rats have failed to show carcinogenic effects of administration of methyl methacrylate. Implantation of the compound in mice also failed to produce tumors.

Exposure of rats to a mixture of chloroprene and methyl methacrylate produced an increase in lymphocyte chromosome aberrations. Increased chromatid breaks and chromosome breaks have been reported in workers exposed to this same chemical mixture.

Teratogenic effects (hemangiomas) have been reported following intraperitoneal administration of methyl methacrylate to pregnant rats. Inhalation exposure of pregnant rats to an acrylic cement containing methyl methacrylate failed to produce significant teratogenic effects.

Ninety-six hour LC_{50} values for four species of fish range from 159 to 368 ppm. Inhibition of cell multiplication of an alga begins at 120 ppm.

I. INTRODUCTION

Methyl methacrylate, CAS registry number 80-62-6, is a colorless, clear, volatile liquid. It is made from acetone cyanohydrin which is hydrolyzed in sulfuric acid to yield methacrylamide sulfate, which is then treated with methanol to yield methyl methacrylate. It has the following physical and chemical properties (Windholz, 1976; Hawley, 1971; Weast, 1972; Verschueren, 1977):

Formula:	$C_5H_8O_2$
Molecular Weight:	100.12
Melting Point:	-48.2°C
Boiling Point:	101°C
Density:	0.9440^{20}_{4}
Vapor Pressure:	28 torr @ 20°C
Solubility:	Sparingly soluble in water, miscible in alcohol, benzene, ether, etc.
Production:	706 million lbs (1973) (Gruber, 1975)

Virtually all the methyl methacrylate produced in this country is used for polymers, e.g., surface coating resins and plastics (plexiglass, lucite), ion exchange resins, dentures, etc.

II. EXPOSURE

A. Water

According to Gruber (1975), about 1.8 g of methyl methacrylate per kilogram final product (methyl methacrylate) is present in wastewater. The amount of methyl methacrylate entering domestic water supplies is probably small.

B. Food

Polymethyl methacrylate is used for food storage. A very small amount of residual monomer may migrate into food from the polymer.

C. Inhalation

Fugitive emissions from production, storage, and transportation probably constitute the only major sources of methyl methacrylate in the air. The concentration would most likely be highest in production facilities. Production was estimated to be 7.9 million pounds in 1974 (U.S. EPA, 1976). A 550-million pound-per-year production facility with 0.5 percent loss emits 39.6 grams of methyl methacrylate per second. If this is considered to be a virtual point source, the downwind concentration 500 meters away would be 1.5 ppm one-hour average (U.S. EPA, 1976).

D. Dermal

Pertinent data could not be located in the available literature.

III. PHARMACOKINETICS

A. Absorption and Distribution

Pertinent data could not be located in the available literature.

B. Metabolism

Bratt and Hathway (1977) found that up to 88 percent of a single methyl(^{14}C)methacrylate dose of 5.7 mg/kg body weight was expired as CO_2 within 10 days. Neither the route of administration nor the specific labelling of the propylene residue changed this value. Small amounts of several metabolites were excreted in the urine, including ^{14}C-methylmalonate, ^{14}C-succinate, 2-formylpropionate, and possibly ^{14}C-β-hydroxybutyrate.

Corkill, et al. (1976) found that the disappearance of methyl methacrylate in human blood <u>in vitro</u> showed a first order dependence on methyl methacrylate concentration. The calculated half-life was 20 to 40 minutes, irrespective of the sex or age of the blood donor. More than 40 percent of the initial dose of methyl methacrylate was converted to methacrylic acid within 90 minutes.

C. Excretion

Pertinent data could not be located in the available literature.

IV. EFFECTS

A. Carcinogenicity

The International Agency for Research on Cancer (IARC, 1979) has evaluated the available data and concluded that there is not enough information to determine the potential carcinogenicity of methyl methacrylate to humans. Borzelleca, et al. (1964) observed no treatment-related tumors in male and female Wistar rats administered 6, 60, or 2,000 mg/l methyl methacrylate in their drinking water for two years. Oppenheimer, et al. (1955) found no local tumors in ten Wistar rats painted with methyl methacrylate three times per week for four months and observed for their entire life span.

Another study, by Spealman, et al. (1945), in which male and female mice received implants consisting of 0.075 gm of methyl methacrylate in a gelatin capsule also yielded negative results.

B. Mutagenicity

The only data available on the mutagenic effects of methyl methacrylate are two studies involving exposure to a mixture of chloroprene and methyl methacrylate (Bagramjan, et al. 1976; Bagramjan and Babajan, 1974). In both studies, an increased frequency of chromosomal aberrations were found in rats exposed to the mixture. Bagramjan, et al. (1976) also measured a significant increase in chromatid breaks and chromosome breaks in the lymphocytes of workers exposed to a mixture of chloroprene and methyl methacrylate.

C. Teratogenicity

Singh, et al. (1972a,b) and Autian (1975) injected intraperitoneally three groups of pregnant Sprague-Dawley rats with methyl methacrylate at doses of 0.1, 0.2, or 0.4 g/kg body weight on days 5, 10, and 15 of ges-

tation. In animals administered the two higher doses, a significantly greater number of hemangiomas were seen at various sites. All three groups exhibited reduced fetal weights, but no significant increase in skeletal defects was observed in any group.

McLaughlin, et al. (1978) exposed pregnant mice to a vapor concentration of 1,330 ppm methyl methacrylate (as acrylic cement, Simplex p) for two hours two times per day for days 6 through 15 of gestation. No fetotoxic or teratogenic effects were noted other than a slight decrease in the average fetal weight.

D. Other Reproductive Effects

Pertinent data could not be located in the available literature.

E. Chronic Toxicity

Spealman, et al. (1945) conducted a series of subchronic inhalation ex- periments involving guinea pigs and dogs. Guinea pigs exposed to 39.0 mg/l methyl methacrylate for two hours per day for three days exhibited significant liver degeneration, while dogs exposed to 46.8 mg/l methyl methacrylate for two hours per day for 8 to 15 days exhibited liver degeneration and tubular degeneration of the kidneys.

Borzelleca, et al. (1964) administered 6, 60, and 2,000 ppm of methyl methacrylate in drinking water to male and female rats for a period of two years. Weight gain was decreased for the first few weeks in animals given the highest dose. No changes in hematological values or urine concentrations of protein and reducing agents were noted. Females receiving the highest dose level exhibited an increase in kidney to body weight ratios.

Blagodatin, et al. (1970) reported symptoms of headache, pain in the extremities, fatigue, sleep disturbance, loss of memory, and irritability in 152 workers exposed to concentrations of 0.5 to 50 ppm methyl methacrylate. Most of the workers had been employed for longer than 10 years.

F. Acute Toxicity

No detectable acute effects were noted in workers employed in manufacturing polymethyl methacrylate sheets (Cromer and Kronoveter, 1976). The airborne concentrations of methyl methacrylate varied from 4 to 49 ppm.

V. AQUATIC TOXICITY

A. Acute Toxicity

Pickering and Henderson (1966) observed the following 96-hour LC_{50} values for fish exposed to methyl methacrylate: fathead minnow (Pimephales promelas) - 159 ppm in soft water (20 mg/l); fathead minnow - 311 ppm in hard water (360 mg/l); bluegill (Lepomis macrochirus) - 357 ppm in soft water (20 mg/l); goldfish (Carassius auratus) - 277 ppm in soft water (20 mg/l); guppies (Lebistes reticulatus) - 368 ppm in soft water (20 mg/l).

B. Chronic Toxicity

Pertinent data could not be located in the available literature.

C. Plant Effects

Inhibition of cell multiplication of the alga, Microcystis aeruginosa, by methyl methacrylate begins at 120 ppm (Bringmann and Kuhn 1976).

D. Residues

Pertinent data could not be located in the available literature.

VI. EXISTING GUIDELINES AND STANDARDS

A. Human

Guidelines have been established for exposure to methyl methacrylate by the American Conference of Governmental Industrial Hygienists and OSHA. Both the TLV and the federal standard have been set at 100 ppm (or 410 mg/m^3) (ACGIH, 1977; 29 CFR 1910).

8. Aquatic

No guidelines have been established for the protection of aquatic organisms from acute or chronic methyl methacrylate toxicity because of the lack of pertinent data.

REFERENCES

American Conference of Governmental Industrial Hygienists. 1977. Threshold limit values for chemical substances and physical agents in the workroom environment. Cincinnati, Ohio.

Autian, J. 1975. Structure-toxicity relationships of acrylic monomers. Environ. Health Perspect. 11: 141.

Bagramjan, S.B. and E.A. Babajan. 1974. Cytogenetic study of the mutagenic activity of chemical substances isolated from Nairit latexes MKH and LNT-1. (Russ.) Biol. Zh. Arm. 17: 102.

Bagramjan, S.B., et al. 1976. Mutagenic effect of small concentrations of volatile substances emitted from polychloroprene latexes LNT-1 and MKH, during their combined uptake by the animal. (Russ.) Biol. Zh. Arm. 19: 98.

Blagodatin, V.M., et al. 1970. Issues of industrial hygiene and occupational pathology in the manufacture of organic glass. (Russ.) Gig. Tr. Prof. Zabol. 14: 11.

Borzelleca, J.F., et al. 1964. Studies on the chronic oral toxicity of monomeric ethyl acrylate and methyl methacrylate. Toxicol. Appl. Pharmacol. 6: 29.

Bratt, H. and D.E. Hathway. 1977. Fate of methyl methacrylate in rats. Br. Jour. Cancer. 36: 114.

Bringmann, G. and R. Kuhn. 1976. Vergleichende Befunde der Schadwirkung wassergefahrdender Stoffe genen Bakterien (Speudomonas putida) und Blaualgen (Microcystis aeruginosa). Nwf-Wasser/Abwasser, (117) H.9.

Corkill, J.A., et al. 1976. Toxicology of methyl methacrylate: The rate of disappearance of methyl methacrylate in human blood in vitro. Clinica Chimica Acta. 68: 141.

Cromer, J. and K. Kronoveter. 1976. A study of methyl methacrylate exposures and employee health. National Institute for Occupational Safety and Health, Cincinnati, Ohio. DHEW 77-119.

Gruber, G.I. 1975. Assessment of industrial hazardous waste practices, organic chemicals, pesticides, and explosive industries. TRW Systems Group, NTIS PB-251 307.

Hawley, G.G. (ed.) 1971. The Condensed Chemical Dictionary. 8th ed., Van Nostrand Reinhold Co., New York.

International Agency for Research on Cancer. 1979. IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans. Vol. 19, Methyl methacrylate: 187.

McLaughlin, R.E., et al. 1978. Methyl methacrylate: a study of teratogenicity and fetal toxicity of the vapor in the mouse. Jour. Bone Jt. Surgery Am. Vol. 60A: 355.

Oppenheimer, B.S., et al. 1955. Further studies of polymers as carcinogenic agents in animals. Cancer Res. 15: 333.

Pickering, Q.H. and C. Henderson. 1966. Acute toxicity of some important petrochemicals to fish. Jour. Water Poll. Con. Fed. 38: 1419.

Singh, A.R., et al. 1972a. Embryonic-fetal toxicity and teratogenic effects of a group of methacrylate esters in rats. Jour. Dent. Res. 51: 1532.

Singh, A.R., et al. 1972b. Embryo-fetal toxicity and teratogenic effects of a group of methacrylate esters in rats (Abstract No. 106). Toxicol. Appl. Pharmacol. 22: 314.

Spealman, C.R., et al. 1945. Monomeric methyl methacrylate: Studies on toxicity. Ind. Med. 14: 292.

U.S. EPA. 1976. Assessment of methyl methacrylate as a potential air pollution problem. U.S. Environ. Prot. Agency, NTIS PB-258 361.

Verschueren, K. 1977. Handbook of Environmenal Data on Organic Chemicals. Van Nostrand Reinhold Co., New York.

Weast, R.C. 1972. Handbook of Chemistry and Physics. 53rd ed., Chemical Rubber Company, Cleveland, Ohio.

Windholz, M. (ed.) 1976. Merck Index. 9th ed., Merck and Co., Inc., Rahway, New Jersey.

No. 131

Naphthalene

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

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NAPHTHALENE

Summary

Naphthalene is present in ambient water as well as drinking water. Naphthalene can be absorbed by any route, although the efficiency of absorption has not been determined. The toxicological properties are due to the formation of highly reactive metabolites. Chronic exposure produces cataracts, hemolytic anemia, and kidney disease. Naphthalene can cross the placenta and produce these effects on newborns. Naphthalene has been found to be nonmutagenic in several microsomal/bacterial assay systems. Chronic toxicity studies of naphthalene have shown it to be noncarcinogenic.

Naphthalene has been shown to be acutely toxic in freshwater fish with LC_{50} values of 150,000 µg/l being reported in one static bioassay. Freshwater invertebrates were more sensitive with LC_{50} values of 8,570 µg/l, as were marine fish with LC_{50} values ranging from 2,350 to 2,600 µg/l.

INTRODUCTION

This profile is based on the Ambient Water Quality Criteria Document for Naphthalene (U.S. EPA, 1979).

Naphthalene ($C_{10}H_8$; molecular weight 128.16) is a bicyclic, aromatic hydrocarbon which in a pure grade, forms a white crystalline solid at room temperature (Windholz, 1976). Pure naphthalene has a melting point of 80.2°C, a boiling point of 217.96°C (Manufacturing Chemists Assoc., 1956) and a vapor pressure of 0.0492 mm Hg at 19.8°C (Gil'denblat, et al. 1960). Naphthalene is water soluble, with solubility ranging from 30,000 µg/l (Mitchell, 1926) to 40,000 µg/l (Josephy and Radt, 1948). Naphthalene vapor and dust can form explosive mixtures with air (Windholz, 1976). Naphthalene is used as an intermediary in the production of dye compounds, in the formulation of solvents, lubricants and motor fuels, and as a feedstock in the synthesis of phthalic anhydride. Naphthalene is also used directly as a moth repellant, insecticide, antihelminthic, vermicide, and an intestinal antiseptic (U.S. EPA, 1979). In 1974, production of naphthalene was approximately 2.9 x 10^5 metric tons (U.S. EPA, 1976).

II. EXPOSURE

A. Water

The two major sources of naphthalene in the aquatic environment are from industrial effluents and from oil spills. The final effluents of sewage treatment plants receiving discharges from these industrial facilities have been noted to have up to 22 µg/l naphthalene, while natural waters have up to 2.0 µg/l, and drinking water supplies have up to 1.4 µg/l naphthalene (U.S. EPA, Region IV, unpublished data).

B. Food

The U.S. EPA (1979) has estimated the weighted average bio-concentration factor for naphthalene to be 60 for the edible portions of fish and shellfish consumed by Americans. This estimate was based on octanol/water partition coefficients.

C. Inhalation

In the ambient air, inhalation of naphthalene is negligible with vapor concentrations ranging from 0.00005 to 0.0001 $\mu g/m^3$ and particulate concentrations ranging from 0.000003 to 0.00025 $\mu g/m^3$ (Krstulovic, et al. 1977). Industrial exposure can range from 0.72 $\mu g/m^3$ to 1.1×10^6 $\mu g/m^3$ in the vapor phase (Bjrseth, et al., 1978b; Robbins, 1951) and from 0.09 $\mu g/m^3$ to 4.40 $\mu g/m^3$ in particulates (Bjrseth, 1978a, 1978b). Naphthalene has also been found in cigarette smoke condensate (Akin, et al. 1976).

III. PHARMACOKINETICS

A. Absorption

Little detailed information is available on the absorption of naphthalene in man or animals. Adequate amounts of naphthalene can be absorbed when ingested as a solid, or by inhalation, to cause significant toxicity (U.S. EPA, 1979). Absorption seems to be facilitated if naphthalene is dissolved in oil (Solomon, 1957), and hindered if naphthalene is bound to protein (Sanborn and Malins, 1977).

B. Distribution

Naphthalene distributes widely after absorption. In mallards, the relative distribution of naphthalene was as follows: greatest in skin, followed by liver, brain, blood, muscle, and heart (Lawler, et al. 1978).

C. Metabolism

Naphthalene is first metabolized by hepatic mixed-function oxidases to an epoxide, which is an obligatory step in the metabolism of naphthalene. Further metabolism can occur leading to the formation of a variety of compounds. Most of these compounds are enzymatically conjugated with glucuronic acid or sulfate. During metabolism a number of highly reactive compounds are formed such as 1,2-dihydroxynaphthalene and 1,2-naphthoquinone (U.S. EPA, 1979).

Naphthalene metabolites undergo further conversions in the eye. This multi-step pathway can lead to the formation of 1,2-naphthaquinone which can irreversibly bind to lens protein and amino acids (Van Heyningen and Pirie, 1966).

D. Excretion

Naphthalene has not been identified in urine after absorption. With sufficient absorption of naphthalene to result in toxicity to an 18 month old infant, Mackell, et al. (1951) noted metabolites of naphthalene in the urine that were still identifiable two weeks after exposure but which had disappeared 18 days after exposure.

1-Napthol is the predominant spontaneous decomposition product of the epoxide of napohthalene. 1-Napthol is excreted unchanged as well as congugated with glucuronic acid or sulfate prior to excretion. The finding of 1,4-nathoquinone in the urine of a child poisoned with naphthalene (Mackell, et al. 1951) suggests that 1-napthol can also be further oxidized in mammals (Cerniglia and Gibson, 1977).

IV. EFFECTS

A. Carcinogenicity

In attempts to demonstrate its carcinogenicity, naphthalene has been given orally, subcutaneously, implanted in the bladder, and painted

on the backs of a number of animal species (U.S. EPA, 1979). In these experiments naphthalene caused no increase in tumor formation. Two experiments have produced increases in lymphosarcoma and lymphatic leukemia after treatment with coal tar derived naphthalene. The first of these studies (Knake, 1956) was complicated by the presence of 10 percent impurities in the naphthalene and the painting of the injection site with carbolfuchsin, a known experimental carcinogen, prior to injection. In the second study (Knake, 1956) where excess leukemia was noted, naphthalene was dissolved in benzene, a known human leukemogenic agent, and painted on the backs of mice. Benzene treatment resulted in no leukemia. Skin papillomas have been produced on mice following painting with 1,4-naththa-quinone, a metabolite of naphthalene (Takizawa, 1940). Also, Pirie (1968) noted abnormal mitotic figures in metaphase and cell overgrowth in the epithelial cells of the lens of rabbits given 1 g/kg/day of naphthalene by gavage.

B. Mutagenicity

Naphthalene has been found to be nonmutagenic in several microsomal/bacterial assay systems (McCann, et al. 1975; Kraemer, et al. 1974).

C. Teratogenicity

Pertinent data could not be located in the available literature.

D. Other Reproductive Effects

Naphthalene or its metabolites can cross the placenta in sufficient amounts to cause fetal toxicity (Zinkham and Childs, 1958; Anziulewicz, et al. 1959). When a metabolite of naphthalene, 2-naphthol, was administered to pregnant rabbits, their offspring were born with cataracts and evidence of retinal damage (Van der Hoeve, 1913).

E. Toxicity

Oral administration of two percent naphthalene or 2-napthol to rats for at least 60 days resulted in the development of cataracts (Fitzhugh adn Busckke, 1949). Van Heyningen and Pirie (1976) dosed rabbits daily by gavage with 1000 mg/kg of naphthalene for a maximum of 28 days. Lens changes developed after the first dose, and retinal changes developed after the second dose. Rabbits fed 1000 mg/kg/day developed cataracts between day 3 and 46. Topical application of a 10 percent solution in oil to the eyes of rabbits did not produce cataracts after a period of 50 days. Intraperitoneal injection of 500 mg/kg of naphthalene in an oily solution produced weight loss over a period of 50 days (Ghetti and Mariani, 1956). Hemolytic anemia with associated jaundice and occasionally renal disease from precipitated hemoglobin has been described in newborn infants, children and adults after exposure to naphthalene by ingestion, inhalation, or possibly by skin contact (U.S. EPA, 1979). The extent or duration of exposure was not given. Mahvi, et al. (1977) noted a dose related damage to bronchiolar epithelial cells in mice given intraperintoneal injections of naphthalene in corn oil. Bronchiolar epithelial changes were not noted in two control groups. The authors noted minor bronchiolar epithelial changes in the treated group receiving 67.4 mg/kg of naphthalene. Those mice receiving higher doses (128 and 256 mg/kg of naphthalene) developed reversible necrosis of bronchiolar cells.

F. Other Relevent Information

Alexandrov and Frayssinet (1973) demonstrated that naphthalene administered intraperitoneally to rats could inhibit the mixed-function microsomal oxidase enzyme system, and could also inhibit the induction of these enzymes by 3-methylcholanthrene.

V. AQUATIC TOXICITY

A. Acute

For the freshwater mosquitofish (Gambusia affinis) a 96-hour static bioassay provided an LC_{50} value of 150,000 µg/l (Wallen, et al. 1957), while the freshwater cladoceran (Daphnia magna) was shown to have an 48-hour LC_{50} value of 8,570 µg/l (U.S. EPA, 1978). Marine organisms tended to be somewhat more sensitive to naphthalene with an 24-hour static LC_{50} value of 2,400 µg/l for the sheepshead minnow (Cyprinodon variegatus). Two 24-hour static LC_{50} values of 2,500, 2,600 were obtained for two species of marine shrimp, (Penaeus aztecus) and (Palaemonetes pugio), respectively (Anderson, et al. 1974). A 96-hour LC_{50} value of 2,350 µg/l was obtained for grass shrimp (Palaemonetes pugio) (Tatem, 1976).

B. Chronic Toxicity

A single embryo-larval test on the fathead minnow (Pimephales promelas) stated that no effects were observed at concentrations as high as 440 µg/l (U.S. EPA, 1978).

Data pertaining to the chronic toxicity of naphthalene for any marine species could not be located in the available literature.

C. Plant Effects

A 48-hour EC_{50} value of 33,000 µg/l for reduced cell numbers has been reported for the freshwater algae (Chlorella vulgaris) exposed to naphthalene. Data pertaining to the effects of naphthalene to marine plants could not be located in the available literature.

D. Residues

Using the octanol/water partition coefficient of 2,300 for naphthalene, a bioconcentration factor for aquatic organisms with an 8 percent lipid content has been estimated as 210. Bioconcentration

factors determined for marine invertebrates ranged from 50 to 60 in the marine copepod Calanus helgolandicus after one day (Harris, et al. 1977a, 1977b) to 5,000 in the copepod Eurytemora affinis, after nine days, (Harris, et al. 1977b) indicating that equilibrium may not occur rapidly. Bioconcentration factors of 32 to 77 after 1 to 24 hours were reported for these 3 species of marine fish and one species of mussel (Lee, et al. 1972a; 1972b).

VI. EXISTING GUIDELINES AND STANDARDS

Neither the human health nor aquatic criteria derived by U.S. EPA (1979), which are summarized below, have gone through the process of public review; therefore, there is a possibiliity that these criteria will be changed.

A. Human

The Occupational Safety and Health Administration standard for exposure to vapor for a time-weighted industrial exposure is 50 mg/m^3. The American Conference of Governmental Industrial Hygienists (ACGIH, 1971) threshold limit value is 75 mg/m^3, while at present the ACGIH also suggests a maximum 15 minute exposure value of 75 mg/m^3 (ACGIH, 1978). The acceptable daily intake for naphthalene is 448 μg/day for a 70 kg person. The U.S. EPA (1979) draft ambient water criterion for naphthalene is 143 μg/l.

B. Aquatic

Criterion can not be derived for naphthalene for either fresh-water or marine organisms, because of the lack of sufficient toxicological data.

NAPHTHALENE

REFERENCES

Akin, F.J., et al. 1976. Identification of polynuclear aromatic hydrocarbons in cigarrette smoke and their importance as tumorigens. Jour. Natl. Cancer Inst. 57: 191.

Alexandrov, K. and C. Frayssinet. 1973. In vitro effect of some naphthalene-related compounds on aryl hyrocarbon (benzo(a)pyrene) hydroxylase. Jour. Natl. Cancer Inst. 51: 1067.

American Conference of Governmental Industrial Hygienists. 1971. Documentation of the threshold limit values for substances in workroom air. 3rd ed. Cincinnati, Ohio.

American Conference of Governmental Industrial Hygienists. 1978. Threshold limit values for chemical substances and physical agents in the workroom environment with intended changes for 1978. Cincinnati, Ohio.

Anderson, J.W. et al. 1974. The effects of oil on estuarine animals: Toxicity uptake and depuration, respiration. In: pollution and physiology of marine orgasnisms. Adademic Press. New York

Anziulewicz, J.A., et al. 1959. Transplacental naphthalene poisoning. Am. Jour. Obstet. Gynecol. 78: 519.

Bjorseth, A. et al. 1978a. Polycyclic aromatic hydrocarbons in the work atmosphere. II. Determination in a coke plant. Scand. Jour. Work. Environ. Health. 4: 212.

Bjorseth, A. et al. 1978b. Polycyclic aromatic hydrocarbons in the work atmosphere. I. Determination in an aluminum reduction plant. Scand. Jour. Work Environ. Health. 4: 212.

Cerniglia, C.E. and D.T. Gibson. 1977. Metabolism of napthalene by Cunninghamella elegans. Appl. Environ. Microbiol. 34: 363.

Fitzhugh, O.G. and W.H. Buschke. 1949. Production of cataract in rats by beta-tetralol and other derivatives of naphthalene. Arch. Ophthal. 41: 572.

Ghetti, G. and L. Mariani. 1956. Eye changes due to naphthalene. Med. Lavoro. 47: 524.

Gil'denblat, I.A., et al. 1960. Vapor pressure over crystalline naphthalene. Jour. Appl. Chem. USSR. 33: 245.

Harris, R.P. et al. 1977a. Factors affecting the retention of a petroleum hydrocarbon by marine planktonic copepods. In: Fate and Effects of petroleum hydrocarbons in marine ecosystems and organisms. Proc. Symp. 286.

Harris, R.P. et al. 1977b. Accumulation of carbon-14-1-napthalene by an oceanic and an estuarine copepod during long-term exposure to low-level concentrations. Mar. Biol. 42: 187.

Josephy, E. and F. Radt, (eds.) 1948. Encyclopedia of organic chemistry: Series III. Elsevier Publishing Co., Inc., New York.

Knake, E. 1956. Uber schwache geschwulsterzengende Wirkung von Naphthalin und Benzol. Virchows Archiv. Pathol. Anat. Physiol. 329: 141.

Kraemer, M., et al. 1974. S. typhimurium and E. coli to detect chemical mutagens. Arch. Pharmacol. 284: 846.

Krstulovic, A.M., et al. 1977. Distribution of some atmospheric polynuclear aromatic hydrocarbons. Am. Lab. 9(7): 11.

Lawler, G.C., et al. 1978. Accumulation of aromatic hydrocarbons in tissues of petroleum-exposed mallard ducks (Anas platyrhynchos). Environ. Sci. Technol. 12: 51.

Lee, R.F. et al. 1972a. Uptake, metabolism and discharge of polycyclic aromatic hydrocarbons by marine fish. Mar. Biol. 17: 201.

Lee, R.F. et al. 1972b. Petroleum hydrocarbons: uptake and discharge by the marine mussel Mytilus edulis. Science. 177: 344.

Mackell, J.V., et al. 1951. Acute hemolytic anemia due to ingestion of napthalene moth balls. Pediatrics. 7: 722.

Mahvi, D., et al. 1977. Morphology of a naphthalene-induced bronchiolar lesion. Am. Jour. Pathol. 86: 559.

Manufacturing Chemists Assoc. 1956. Chemical safety data sheets SD-58: Napthalene. Washington, D.C.

McCann, J., et al. 1975. Detection of carcinogens as mutagen in the Salmonella/microsome test. Assay of 300 chemicals. Proc. Natl. Acad. Sci. 72: 5135.

Mitchell, S. 1926. A method for determining the solubility of sparingly soluble substances. Jour. Chem. Soc. 129: 1333.

Pirie, A. 1968. Pathology in the eye of the naphthalene-fed rabbit. Exp. Eye Tes. 7: 354.

Robbins, M.C. 1951. Determination of Napthalene in air. Arch. Ind. Hyg. Occup. Med. 4: 85.

Sanborn, H.R. and D.C. Malins. 1977. Toxicity and metabolism of naphthalene: a study with marine larval invertebrates. Proc. Soc. Exp. Biol. Med. 154: 151.

Solomon, T. 1957. A manual of pharmacology and its applications to therapeutics and toxicology. 8th ed. W.B. Saunders Co., Philadelphia.

Takizawa, N. 1940. Carcinogenic action of certain quinones. Proc. Imp. Acad. (Tokyo) 16: 309.

Tatem, H.E. 1976. Toxicity and physiological affects of oil and petroleum hydrocarbons on estuarine grass shrimp, Palaeminetes pugio. Holthuis Ph.D. dissertation. Texas A and M University. 133 pp.

U.S. EPA. 1971-1977. Unpublished data from Region IV, Atlanta, Ga.

U.S. EPA. 1976. Organic chemical producer's data base program. Chemical No. 2701. Radian Corporation.

U.S. EPA. 1978. In-depth studies on health and environmental impacts of selected water pollutants. Contract No. 68-01-4646, U.S. Environ. Prot. Agency.

U.S. EPA. 1979. Naphthalene: Ambient Water Quality Criteria. (Draft)

Van Heyningen, R. and A. Pirie. 1966. Naphthalene cataract. In: M.U.S. Dardenne, ed. Symposium on the biochemistry of the eye. Karger, Asel, Switzerland.

Van Heyningen, R. and A. Pirie. 1976. Naphthalene cataract in pigmented and albino rabbits. Exp. Eye Res. 22: 393.

Van der Hoeve, J. 1913. Wirkung von napbthol auf die augen von menschen, tieren, und auf fatale augen. Graele Arch. Ophthal. 85: 305.

Wallen, I.E., et al. 1957. Toxicity of Gambusia affinis of certain pure chemicals in turbid waters. Sewage Ind. Wastes. 29: 695.

Windholz, M., ed. 1976. The Muck Index, 9th ed. Muck and Co. Rahway, N.J.

Zinkham, W.J. and B. Childs. 1958. A defect of glutathione metabolism in erythrocytes from patients with a naphthalene-induced hemolytic anemia. Pediatrics 22: 461.

No. 132

1,4-Naphthoquinone

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

-1556-

DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

1,4-NAPHTHOQUINONE

SUMMARY

1,4-Naphthoquinone is used as a polymerization regulator and an intermediate. Some data are available which indicate that 1,4-naphthoquinone is biodegradable.

The most consistent findings reported in the literature for health effects of 1,4-naphthoquinone involve hematological changes, irritant and allergenic activity, and inhibition of biochemical oxidation processes. One study found 1,4-naphthoquinone to be oncogenic. Some evidence of inhibition of *in vitro* endocrine function and of nerve activity was reported.

I. INTRODUCTION

1,4-Naphthoquinone (1,4-naphthalenedione; $C_{10}H_6O_2$; molecular weight 158.15) is a solid at room temperature. It occurs as a greenish yellow powder or as yellow triclinic needles. It has a melting point of 123-126°C and begins to sublime at 100°C; its density is 1.422. 1,4-Naphthoquinone is only slightly soluble in water; it is soluble in a variety of organic solvents (Windholz 1976; Hawley 1971).

Current production (including importation) statistics for 1,4-naphthoquinone (CAS No. 130-15-4) listed in the initial TSCA Inventory (U.S. EPA 1979) show that between 1,000,000 and 9,000,000 pounds of this chemical were produced/imported in 1977.*

1,4-Naphthoquinone is used as a polymerization regulator for rubber and polyester resins, in the synthesis of dyes and pharmaceuticals, and as a fungicide and algicide (Hawley 1971).

II. EXPOSURE

A. Environmental Fate

No specific information on the biological, chemical or photochemical transformation of 1,4-naphthoquinone under environmental conditions was identified in the literature. Napthoquinones undergo few substitution

* This production range information does not include any production/importation data claimed as confidential by the person(s) reporting for the TSCA Inventory, nor does it include any information which would compromise Confidential Business Information. The data submitted for the TSCA Inventory, including production range information, are subject to the limitations contained in the Inventory Reporting Regulations (40 CFR 710).

reactions (Thirtle 1965). Like other quinones, 1,4-naphthoquinone can interconvert with its corresponding hydroquinone in an oxidation-reduction system.

Talakin (1964) reported that 1,4-naphthoquinone in river water apparently undergoes slow biochemical oxidation, based on an observed increase in BOD. Verschueren (1977) reports that the BOD_5 is 0.81, using the standard dilution technique with normal sewage as seed material, and that the theoretical oxidation demand is 2.1.

B. Bioconcentration

No information was found on the bioconcentration potential of 1,4-naphthoquinone. Based on its low water solubility and its solubility in organic solvents, 1,4-naphthoquinone could be expected to bioconcentrate to some extent.

C. Environmental Occurrence

No information was found on the presence of 1,4-naphthoquinone in environmental media.

In addition to its potential entry into the environment from its manufacture, processing and uses, 1,4-naphthoquinone may also enter the environment as a degradation product of certain naphthalene derivatives. For example, the U.S. EPA (1975) reported studies showing that the pesticide carbaryl (1-naphthyl-n-methyl-carbamate) undergoes hydrolysis to 1-naphthol, which is then converted by bacteria to 1,4-naphthoquinone and other products.

III. PHARMACOKINETICS

No information was obtained.

IV. HEALTH EFFECTS

A. Carcinogenicity

1,4-Naphthoquinone was found to induce neoplasm when applied dermally to mice for 28 weeks. The total dose applied was 2000 mg/kg. (Proceedings of the Imperial Academy of Tokyo 16:309, 1940, as cited in NIOSH 1975).

B. Reproductive Effects

1,4-Naphthoquinone completely inhibited the gametokinetic effect of human chorionic gonadotropin in toads (Pakrashi 1963).

C. Other Toxicity

The oral LD_{50} for rats was reported as 190 mg/kg (NIOSH, 1975). The LD_{100} of 1,4-naphthoquinone in rats was 0.5 g/kg, 0.25 g/kg, and 0.5 g/kg for intraventricular, subcutaneous, and intraperitoneal administrations, respectively. The LC_{100} in air was 0.45 mg/L for a one-hour exposure. Acute (0.5 g/kg) and subchronic (0.3 g/kg for 4 days) exposure of rats resulted in the formation of 39 and 18% methemoglobin, respectively, followed by the appearance of Heinz bodies and development of hemolytic anemia. A decrease in total respiration and hypothermia due to disturbances in oxidation-reduction processes was also observed. According to the authors, "threshold concentrations of 1,4-naphthoquinone detected for rats and rabbits in single-exposure and chronic experiments were 0.0004 and 0.0007 mg/L with respect to their irritant and toxic effects" (Slyusar et al. 1964).

D. Other Relevant Information

1,4-Naphthoquinone exerted an allergenic effect in guinea pigs (Kryzhanovskaya et al. 1966). A possible role for 1,4-naphthoquinone in drug-induced thrombocytopenia was suggested by Niewig et al. (1973) as 1,4-naphthoquinone was found to be involved in the destruction of normal blood platelets by serum antibodies *in vitro*. 1,4-Naphthoquinone blocks the biosynthesis of adrenal steroids by bovine adrenal cortex *in vitro* (Kahnt and Neher 1966), and has an inhibitory effect on mixtures of cytochrome *c* and dehydrated succinate oxidase from beef heart (Heymann and Feiser 1966). 1,4-Naphthoquinone inhibited ATPase and nerve activity in the (American) cockroach (Baker and Norris 1971, Baker 1972).

V. AQUATIC TOXICITY

Very little information was available. For 1,4-naphthoquinone, a median threshold limit value (TLM:24-28 hr) of 0.3-0.6 mg/L was listed for an unspecified species of fish (Verschueren 1977).

VI. GUIDELINES

No guidelines for exposure to 1,4-naphthoquinone were located.

References

Baker JE. 1972. Effects of feeding-inhibitory quinones on the nervous system of Periplaneta. Experientia. 28(1):31-32.

Baker JE, Norris DM. 1971. Neurophysiological and biochemical effects of naphthoquinones on the central nervous system of Periplaneta. J. Insect Physiol. 17:2383-2394.

Hawley GG. 1971. Condensed Chemical Dictionary, 8th edition. Van Nostrand Reinhold Co.

Heymann H, Feiser LF. 1948. Naphthoquinone antimalarials. XXI. Anti-succinate oxidase activity. Jour. Biol. Chem. 176(3):1359-1369.

Kahnt FW, Neher R. 1966. Biosynthesis of adrenal steroids in vitro. II. Importance of steroids as inhibitors. Helv. Chim. Acta 49(1):123-133. (Ger.)

Kotsifopoulos PN. 1975. In vitro effect of oxidizing and analgesic agents on the erythrocyte membrane protein electrophoretic pattern. Nouv. Rev. Fr. Hematol. 15(1):141-146. (Abstract in Chemical Abstracts, 83,72709Z).

Kryzhanovskaya MV, et al. 1966. Allergenic activity of some atmospheric pollutants of a chemical nature. Gig. Sanit. 31(3):8-11.

National Institute of Occupational Safety and Health. Registry of Toxic Effects of Chemical Substances. 1975.

Nieweg HO, et al. 1973. Drugs and thrombocytes. Proc. Eur. Soc. Study Drug Toxic. 14:101-109.

Pakrashi A. 1963. Endocrinological studies of plant products. IV. Effect of certain coumarins upon the biological potency of human chorionic gonadotropin. Ann. Biochem. Exptl. Med. (Calcutta) 23:357-370.

Slyusar MP, et al. 1964. Data on the toxicology of alpha-naphthoquinones and its permissible concentration in a working area. Gigiena 95-100. (Abstract in Zh. Farmakol. Toksikol. 11.54.373, 1965).

Talakin YN. 1965. The experimental determination of the maximum permissible concentration of alpha-naphthoquinone in water resources. Hyg. and Sanit. 30:184.

Thirtle JR. 1965. Quinones. In: Kirk-Othmer Encyclopedia of Chemical Technology. 2nd Edition. John Wiley and Sons, Inc., New York.

U.S. EPA 1975. Microbial degradation and accumulation of pesticides in aquatic systems. EPA 660/3-75-007, PB 241 293.

U.S. EPA 1979. Toxic Substances Control Act Chemical Substance Inventory, Production Statistics for Chemicals on the Non-Confidential TSCA Inventory.

Verschueren, K. 1977. Handbook of Environmental Data on Organic Chemicals, Van Nostrand Reinhold Co.

Windholz, M. ed. 1976. The Merck Index, Merck & Co., Inc., Rahway, New Jersey.

No. 133

Nickel

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

SPECIAL NOTATION

U.S. EPA's Carcinogen Assessment Group (CAG) has evaluated nickel and has found sufficient evidence to indicate that this compound is carcinogenic.

NICKEL

Summary

Nickel is a ubiquitous multi-media environmental contaminant. Although nickel is toxic and appears to be a carcinogen to man, there is an increasingly strong indication that nickel is an essential element. The route of exposure to nickel is very important, since oral intake of nickel metal is comparatively nontoxic. However, exposure to nickel by inhalation or parenteral administration as well as cutaneous contact can produce toxic effects. In terms of human health effects, probably the most acutely toxic nickel compound is nickel carbonyl. Nickel in several chemical forms has been associated with lung cancer in man and experimental animals upon inhalation; carcinogenic effects, however, are not indicated by the oral route. The acceptable daily intake (ADI) of nickel is 294 µg per day for a 70 kg man.

The toxicity of nickel to aquatic life is affected by water hardness. In the aquatic environment nickel is acutely toxic to freshwater fishes at a concentration of 2,480 µg/l (26 mg/l hardness). Chronic toxicity to fishes has been reported at 527 µg/l (210 mg/l hardness). Nickel toxicity is affected by water hardness. Algae appears to be more sensitive to nickel than fish. Based on the limited number of studies performed, the bioconcentration factor for fish is 61, for algae the factor is 9.8, and the weighted average bioconcentration factor is 11 for fish and shellfish.

NICKEL

I. INTRODUCTION

This profile is based on the Ambient Water Quality Criteria Document for Nickel (U.S. EPA, 1979).

Nickel (Ni; atomic weight 58.71), a bright, silver metal of the iron-cobalt-nickel triad, is a hard and malleable metal with a high tensile strength used in virtually all areas of metallurgy. Nickel does not readily form chloro-complexes under environmental conditions and would not be expected to form significant amounts of sulfate complexes (U.S. EPA, 1979).

In 1972, U.S. consumption of nickel, exclusive of scrap, was estimated to total about 160,000 tons (Reno, 1974). The estimate consisted mainly of commercially pure nickel (about 110,000 tons) which is used in stainless steel, electroplating, and various other alloys.

II. EXPOSURE

The route by which most people in the general population receive the largest portion of daily nickel intake is through foods. Total daily dietary intake values may range up to 900 µg nickel, depending on the nature of the diet, with average values of 300 to 500 µg daily (NAS, 1975). The U.S. EPA (1979) has estimated a weighted average bioconcentration factor for nickel to be 11 for the edible portions of fish and shellfish consumed by Americans. This estimate is based on measured steady-state bioconcentration studies in fathead minnow larvae (Pimephales promelas) (Lind, et al. Manuscript). The values for nickel levels in 969 U.S. public water supplies for 1969-1970 was 4.8 µg/l, with only 11 systems of this total exceeding 25 µg/l (NAS, 1975). The levels of nickel in the air are also low, with a 1974 arithmetic mean level for urban air of 9 ng/m^3 (U.S. EPA, 1976).

III. PHARMACOKINETICS

A. Absorption

The major routes of nickel absorption are inhalation and ingestion via the diet. Percutaneous absorption is a less significant factor for nickel's systemic effects but important in the allergenic responses to nickel. Collectively the data of Tedeschi and Sunderman (1957), Perry and Perry (1959), Nomoto and Sunderman (1970), Nodiya (1972), and Horak and Sunderman (1973) indicate that 1 to 10 percent of dietary nickel is absorbed. Skin penetration of nickel has been demonstrated with nickel entering at sweat-duct and hair-follicle ostia (Wells, 1956). The extent to which nickel enters the bloodstream by way of the skin cannot be stated at the present time (U.S. EPA, 1979).

Respiratory absorption of various forms of nickel is probably the major route of nickel entry into man under conditions of occupational exposure. Pulmonary absorption into the bloodstream is probably greatest for nickel carbonyl vapor, with animal studies suggesting that as much as half of the inhaled amount is absorbed (Sunderman and Selin, 1968). Nickel in particulate matter is absorbed from the pulmonary tract to a lesser degree than nickel carbonyl (Leslie, et al. 1976). Based on animal studies, nickel appears to have a half-life of several days in the body, yet there is little evidence for tissue accumulation.

B. Distribution

Blood is the main vehicle for transport of absorbed nickel, with serum albumin being the main carrier protein, although a specific nickelrich metalloprotein has been identified in man (NAS, 1975). Tissue distribution of absorbed nickel appears to be dependent on the route of intake. Inhaled nickel carbonyl leads to highest levels in the lung, brain, kidney, liver,

and adrenals (Armit, 1908; Sunderman and Selin, 1968; Mikheyev, 1971). Parenteral administration of nickel salts usually results in highest levels in the kidney, with significant uptake shown by endocrine glands, liver and lung (Wase, et al. 1954; Smith and Hackley, 1968).

C. Metabolism

A number of disease states and other physiological stresses are reported to alter the movement and tissue distribution of nickel in man as well as experimental animals. In man, increased levels of serum nickel are seen in cases of acute myocardial infarction (D'Alonzo and Pell, 1963; Sunderman, et al. 1972), acute stroke and extensive burn injury (McNeely, et al. 1971). Reduction is seen in hepatic cirrhosis or uremia, possibly secondary to hypoalbuminemia.

Nickel appears to be an essential element, at least in experimental animals. Nickel deficient diets have produced decreased growth rates and impaired reproduction in swine (Anke, et al. 1974) and rats (Schnegg and Kirchgessner, 1975).

D. Excretion

The routes of elimination for nickel in man and animals depend in part on the chemical forms of nickel and the mode of nickel intake. Dietary nickel, due to the low extent of gastrointestinal absorption, is simply lost in the feces (U.S. EPA, 1979). Urinary excretion in man and animals is usually the major clearance route for absorbed nickel. In some instances sweat can constitute a major route of nickel elimination (Hohnadel, et al. 1973). Nodiya (1972) reported a fecal excretion average of 258 µg in Russian students. Horak and Sunderman (1973) determined fecal excretion of nickel in 10 healthy subjects and arrived at a value identical to that found in the Russian study.

IV. EFFECTS

A. Carcinogenicity

A carcinogenic response to various nickel compounds upon injection has been observed in a number of animal studies (Lau, et al. 1972; Stoner, et al. 1976; IARC, 1976). In nickel refinery workers, an excess risk of nasal and lung cancer has been demonstrated (IARC, 1976). However, there is no evidence at present to indicate that orally ingested nickel is tumorigenic.

The qualitative and quantitative character of the carcinogenic effects of nickel as seen in experimental animal models has been shown to vary with the chemical form of the nickel, the route of exposure, the animal model employed, and the amounts of the substance administered (U.S. EPA, 1979).

B. Mutagenicity

Pertinent information could not be located in the available literature.

C. Teratogenicity

While Ferm (1972) has claimed unspecified malformations in surviving hamster embryos when mothers were exposed to parenteral nickel (0.7 to 10.0 mg/kg), Sunderman, et al. (1978) found no teratogenic effects from oral administration of either nickel chloride (16 mg/kg) or nickel subsulfide (80 mg/kg) in rats. Exposure of pregnant rats by inhalation to nickel carbonyl on days 7 or 8 of gestation frequently caused the progeny to develop ocular anomalies, including anophthalmia and microphthalmia. The incidence of extraocular anomalies is very low. The specificity of nickel carbonyl for induction of ocular anomalies in rats appears to be unique among known teratogenic agents (Sunderman, et al. 1979).

D. Other Reproductive Effects

Schroeder and Mitchner (1971) have demonstrated adverse affects in a three generation study with rats at a level of 5 mg/l (5 ppm) nickel in drinking water. In each of the generations, increased numbers of runts and enhanced neonatal mortality were seen. A significant reduction in litter size and a reduced proportion of males in the third generation were also observed. Nickel sulfate (25 mg/kg) has been demonstrated to be gametotoxic in rats, with complete obliteration of spermatozoa following exposure for 120 days (Hoey, 1966; Waltschewa, et al. 1972).

E. Chronic Toxicity

Chronic exposure to nickel has resulted in injury to both the upper and lower respiratory tract in man (Tolot, et al. 1956; McConnell, et al. 1973). Inhalation of nickel particulate matter is likely to play a role in chronic respiratory infections by effects on alveolar macrophages. Contact dermatitis in man with nickel sulfate has been observed (Fregert, et al. 1969; Brun, 1975). Also, dietary nickel can elicit a dermatitic response (Kaaber, et al. 1978).

F. Other Relevant Information

There are experimental data that demonstrate that nickel has a synergistic effect on the carcinogenicities of polycyclic hydrocarbons (Toda, 1962; Maenza, et al. 1971; Kasprzak, et al. 1973). Nickel and other elements are known to be present in asbestos and may possibly be a factor in asbestos carcinogenicity (Cralley, 1971). Also, a synergistic action between nickel and viruses has been suggested (Treagon and Furst, 1970).

V. AQUATIC TOXICITY

A. Acute Toxicity

Water hardness significantly influences the acute toxicity of nickel to freshwater fish. For fish, observed LC_{50} values range from 2,480

µg/l for the rock bass (Amblophites rupestris) (hardness = 26 mg/l) to 110,385 µg/l for the bluegill (Lepomis macrochirus) (hardness = 42 mg/l). At a hardness of 20-29 mg/l, six freshwater species have LC_{50} values of between 2,916 and 5,360 µg/l (Pickering and Henderson, 1966; Lind et al., manuscript). At a hardness of 360 µg/l, values range from 39,600 to 44,500 µg/l. In comparison, acute tests with freshwater invertebrate species have a greater range of LC_{50} values at a fixed hardness. The stonefly (Acroneuria lycorias) exhibited the highest LC_{50} of 33,500 µg/l (Warnick and Bell, 1969) and Daphnia magna gave the lowest value of 510 µg/l (Biesinger and Christensen, 1972). Lind, et al. (1979) provide the only data obtained under relatively high hardness conditions (244 mg/l), an LC_{50} value of 2409 µg/l for Daphnia pulicaria.

Data on the acute toxicity of nickel to saltwater fishes is limited. The LC_{50} values range from 29,000 µg/l for the Atlantic Silverside (Menidia menidia) to 350,000 µg/l for the mummichog (Fundulus heteroclitus) (Eisler and Hennekey, 1977). The invertebrate acute toxicity data base consists of 14 results, with a range of LC_{50} values from 310 µg/l for larvae of the hard clam (Mercenaria mercenaria) (Calabrese and Nelson, 1974) to 500,000 µg/l for adults of the cockle Cardium edule (Portmann, 1968).

B. Chronic Toxicity

A life cycle test (Pickering, 1974) and an embryo-larval test (Lind, et al., manuscript) have been conducted with the fathead minnow (Pimephales promelas). The chronic values are 527 µg/l (210 mg/l hardness) and 109 µg/l (44 mg/l hardness) respectively. Biesinger and Christensen (1972) conducted a life cycle test with Daphnia magna resulting in a chronic value of 53 µg/l at a hardness of 45 mg/l. There are no chronic saltwater data available (U.S. EPA, 1979).

C. Plant Effects

Hutchinson (1973) and Hutchinson and Stokes (1975) observed reduced growth of several algae species at concentrations ranging from 100 to 700 µg/l. A decrease in diatom diversity was observed by Patrick, et al. (1975) to occur at concentrations as low as 2 µg/l.

D. Residues

Bioconcentration data is limited to the fathead minnow, Pimephales promelas, (Lind, et al., manuscript) and the alga, Scenedesmes acuminata (Hutchinson and Stokes, 1975). The bioconcentration factor for the whole body of the fathead minnow is 61 and for the alga the factor is 9.8.

VI. EXISTING GUIDELINES AND STANDARDS

Neither the human health nor the aquatic criteria derived by U.S. EPA (1979a), which are summarized below, have gone through the process of public review; therefore, there is a possibility that these criteria will be changed.

A. Human

The American Conference of Governmental Industrial Hygienists (ACGIH, 1971) has adopted a threshold limit value (TLV) for a workday exposure of 1 ppb. The acceptable daily intake (ADI) for man has been determined to be 294 µg/day (U.S. EPA, 1979). The U.S. EPA (1979) draft water quality criterion for nickel is 133 µg/l.

B. Aquatic

For nickel, the draft criterion (U.S. EPA, 1979) to protect freshwater aquatic life is:

$$e^{(1.01 \cdot \ln(\text{hardness}) - 1.02)}$$

as a 24-hour average, and the concentration should not exceed at any time:

$$e^{(0.47 \cdot \ln(\text{hardness}) + 4.19)}.$$

The draft criterion to protect saltwater aquatic life is 220 µg/l as a 24-hour average, not to exceed 510 µg/l at any time (U.S. EPA, 1979).

NICKEL

REFERENCES

American Conference of Governmental Industrial Hygienists. Threshold limit values for chemical substances and physical agents in the workroom environment with intended changes for 1978. 94 pp.

Anke, M., et al. 1974. Low nickel rations for growth and reproduction in pigs. In: Trace Element Metabolism in Animals-2. W.G. Hoekstra, J.W. Suttie, H.E. Ganther and W. Mertz (eds.). University Park Press, Baltimore, MD., pp. 715.

Armit, H.W. 1908. The toxicology of nickel carbonyl. Part II. Jour. Hygiene 8: 565.

Biesinger, K.E., and G.M. Christensen. 1972. Effects of various metals on survival, growth, reproduction, and metabolism of Daphnia magna. Jour. Fish. Res. Board Can. 29: 1691.

Brun, R. 1975. Epidemiology of contact dermatitis in Geneva (1,000 cases). Dermatol. 150: 193. (French)

Calabrese, A., and D.A. Nelson. 1974. Inhibition of embryonic development of the hard shell clam, Mercenaria mercenaria, by heavy metals. Bull. Environ. Contam. Toxicol. 2: 92.

Cralley, L.J. 1971. Electromotive phenomenon in metal and mineral particulate exposures. Relevance to exposure to asbestos and occurrence of cancer. Am. Ind. Hyg. Assoc. Jour. 32: 653.

D'Alonzo, C.A., and S. Pell. 1963. A study of trace metals in myocardial infarction. Arch. Environ. Health 6: 381.

Eisler, R., and R.J. Hennekey. 1977. Acute toxicities of Cd^{2+}, Cr^{2+}, Ni^{2+}. amd Zn^{2+} to estaurine macro fauna. Arch. Environ. Contam. Toxicol. 6: 315.

Ferm, V.H. 1972. The teratogenic effects of metals on mammalian embryos. In: Advances in Teratology, Vol. 5. D.H.M. Wollam (ed.) Academic Press, New York. pp. 51-75.

Fregert, S., et al. 1969. Epidemiology of contact dermatitis. Trans. St. Johns Hosp. Derm. Soc. 55: 71.

Hoey, M.J. 1966. The effects of metallic salts on the histology and functioning of the rat testes. Jour. Reprod. Fertil. 12: 461.

Hohnadel, D.C., et al. 1973. Atomic absorption spectrometry of nickel, copper, zinc, and lead in sweat collected from health subjects during sauna bathing. Clin. Chem. 19: 1288.

Horak, E., and F.W. Sunderman. 1973. Fecal nickel excretion by healthy adults. Clin. Chem. 29: 429.

Hutchinson, T.C. 1973. Comparative studies of the toxicity of heavy metals to phytoplankton and their synergistic interactions. Water Pollut. Res. (Canada) 8: 68.

Hutchinson, T.C., and P.M. Stokes. 1975. Heavy metal toxicity and algal bioassays. ASTM STP 573, Am. Soc. Test. Mater. pp. 320-343.

International Agency for Research on Cancer. 1976. Nickel and nickel compounds. In: Evaluation of Carcinogenic Risk of Chemicals to Man (International Agency for Research on Cancer Monographs, 11) IARC, Lyon, p. 111.

Kaaber, K., et al. 1978. Low nickel diet in the treatment of patients with chronic nickel dermatitis. Brit. Jour. Derm. 98: 197.

Kasprzak, K.S., et al. 1973. Pathological reactions in rat lungs following intratracheal injection of nickel subsulfide and 3,4-benzpyrene. Res. Comm. Chem. Pathol. Pharmacol. 6: 237.

Lau, T.J., et al. 1972. The carcinogenicity of intravenous nickel carbonyl in rats. Cancer Res. 32: 2253.

Leslie, A.C.D., et al. 1976. Prediction of health effect of pollution aerosols. In: Trace Substances in Environmental Health - X. D.D. Hemphill (ed.), University of Missouri, Columbia, Mo. pp. 497-504.

Lind, D., et al. Regional copper-nickel study, Aquatic Toxicology Study, Minnesota Environmental Quality Board, State of Minnesota (Manuscript).

Maenza, R.M. et al. 1971. Rapid induction of sarcomas in rats by combination of nickel sulfide and 3,4-benzypyrene. Cancer Res. 31: 2067.

McConnell, L.H., et al. 1973. Asthma caused by nickel sensitivity. Ann. Ind. Med. 78: 888.

McNeely, M.D., et al. 1971. Abnormal concentrations of nickel in serum in cases of myocardial infarction, stroke, burns, hepatic cirrhosis, and uremia. Clin. Chem. 17: 1123.

Mikheyev, M.I. 1971. Distribution and excretion of nickel carbonyl. Gig. Tr. Prof. Zabol. 15: 35.

National Academy of Sciences. 1975. Nickel. National Academy of Sciences Committee of Medical and Biological Effects of Environmental Pollutants. Washington, DC.

Nodiya, P.I. 1972. Cobalt and nickel balance in students of an occupational technical school. Gig. Sanit. 37: 108.

Nomoto, S., and F.W. Sunderman, Jr. 1970. Atomic absorption spectrometry of nickel in serum, urine, and other biological materials. Clim. Chem. 16: 477.

Patrick, R., et al. 1975. The role of trace elements in management of nuisance growths. U.S. Environ. Prot. Agency, EPA 660/2-75-008, 250 p.

Perry, H.M., Jr., and E.F. Perry. 1959. Normal concentrations of some trace metals in human urine: Changes produced by ethylenediametetracetate. Jour. Clin. Invest. 38: 1452.

Pickering, Q.H. 1974. Chronic toxicity of nickel to the fathead minnow. Jour. Water Pollut. Control Fed. 46: 760.

Pickering, Q.H., and C. Henderson. 1966. The acute toxicity of some heavy metals to different species of warmwater fishes. Air Water Pollut. Int. Jour. 10: 453.

Portmann, J.E. 1968. Progress report on a program of insecticide analysis and toxicity testing in relation to the marine environment. Helgolander wiss. Meeresunters 17: 247.

Reno, H.T. 1974. Nickel. In: Minerals Yearbook 1972, Vol. I. Metals, Minerals and Fuels. Washington, DC, U.S. Government Printing Office, pp. 871.

Schnegg, A., and M. Kirchgessner. 1975. The essentiality of nickel for the growth of animals. Z. Tierphysiol., Tierer naehr. Futtermittelkd. 36: 63.

Schroeder, H.A., and M. Mitchner. 1971. Toxic effects of trace elements on the reproduction of mice and rats. Arch. Environ. Health 23: 102.

Smith, J.C., and B. Hackley. 1968. Distribution and excretion of nickel-63 administered intravenously to rats. Jour. Nutr. 95: 541.

Stoner, G.D., et al. 1976. Test for carcinogenicity of metallic compounds by the pulmonary tumor response in strain A mice. Cancer Res. 36: 1744.

Sunderman, F.W., et al. 1978. Embryotoxicity and fetal toxicity of nickel in rats. Toxicol. Appl. Pharmacol. 43: 381.

Sunderman, F.W., Jr. 1978. Carcinogenic effects of metals. Fed. Proc. 37: 40.

Sunderman, F.W., Jr., and C.E. Selin. 1968. The metabolism of nickel-63 carbonyl Toxicol. Appl. Pharmacol. 12: 207.

Sunderman, F.W., Jr., et al. 1972. Nickel metabolism in health and disease. Ann. N.Y. Acad. Sci. 199: 300.

Sunderman, F.W., Jr., et al. 1979. Eye malformation in rats: Induction by prenatal exposure to nickel carbonyl. Science 203: 550.

Tedeschi, R.E., and F.W. Sunderman. 1957. Nickel poisoning. V. The metabolism of nickel under normal conditions and after exposure to nickel carbonyl. Arch. Ind. Health 16: 486.

Toda, M. 1962. Experimental studies of occupational lung cancer. Bull. Tokoya Med. Dent. Univ. 9: 441.

Tolot, F., et al. 1956. Asthmatic forms of lung disease in workers exposed to chromium, nickel and aniline inhalation. Arch. Mol. Prof. Med. Tran. Secur. Soc. 18: 288.

Treagon, L., and A. Furst. 1970. Inhibition of interferon synthesis in mammalian cell cultures after nickel treatment. Res. Comm. Chem. Pathol. Pharmacol. 1: 395.

U.S. EPA. 1976 (August). Air quality data for metals 1970 through 1974 from the national air surveillance network. EPA-600/4-76-041, U.S. Environ. Prot. Agency, Research Triangle Park, NC.

U.S. EPA. 1979. Nickel: Ambient Water Quality Criteria.

Waltschewa, V.W. et al. 1972. Hodenveranderungen bei weissen Ratten durch chronische Verabreichung von Nickel sulfate. (Testicular changes due to long-term administration of nickel sulphate in rats.) Exp. Pathol. 6: 116. In German with Engl. abstr.

Warnick, S.L., and H.L. Bell. 1969. The acute toxicity of some heavy metals to different species of aquatic insects. Jour. Water Pollut. Control Fed. 40: 280.

Wase, A.W., et al. 1954. The metabolism of nickel. I. Spatial and temporal distribution of Ni^{63} in the mouse. Arch. Biochem. Biophys. 51: 1.

Wells, G.C. 1956. Effects of nickel on the skin. Brit. Jour. Dermatol. 68: 237.

No. 134

Nitrobenzene

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

-1579-

DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

NITROBENZENE

Summary

Nitrobenzene is a pale yellow oily liquid with an almond-like odor. There is little or no information available on its teratogenic, mutagenic or carcinogenic effects. Nitrobenzene yielded negative results in the Ames assay for mutagenicity. Gross abnormalities were observed in 4 fetuses of 30 rats administered nitrobenzene.

Chronic exposure to nitrobenzene produces cyanosis, methemoglobinemia, jaundice, anemia, and sulfhemoglobinemia in man.

Static tests with the bluegill, sunfish, *Daphnia magna*, and an alga, *Selenestrum capricornutum*, indicates little difference in sensitivity with no 50 percent effective concentration lower than 27,000 µg/l. An embryo-larval test with the fathead minnow demonstrated no adverse chronic effects at the highest concentration tested (32,000 µg/l). Static tests with salt-water fish, shrimp, and alga gave repeated 96-hour LC_{50} or EC_{50} values of 58,538 µg/l, 6,676 µg/l and 9,600 µg/l, respectively.

I. INTRODUCTION

This profile is based on the Ambient Water Quality Criteria Document for Nitrobenzene (U.S. EPA, 1979). The principal uses of nitrobenzene are for reduction to aniline (97 percent), solvent for Friedel-Crafts reaction, metal polishes, shoe black, perfume, dye intermediates, crystallizing solvent for some substances, and as a combustible propellant (Dorigan and Hushon, 1976).

Nitrobenzene ($C_6H_5NO_2$) is a pale yellow oily liquid with an almond-like odor. Its physical properties include: melting point, 6^oC; vapor pressure, 0.340 mm Hg at 25^oC; and solubility in water of 1000 mg/l at 20^oC (U.S. EPA, 1979). Nitrobenzene is miscible with most organic solvents, a fairly strong oxidizing agent, and undergoes photoreduction when irradiated with ultraviolet light in organic solvents that contain abstractable hydrogen atoms.

II. EXPOSURE

A. Water

Levels of nitrobenzene in wastewater are monitored by plants producing and using the chemical, but nitrobenzene levels in city water systems are usually too low to measure (Pierce, 1979).

B. Food

Nitrobenzene is not an approved food additive (Dorigan and Hushon, 1976). There have been reports of nitrobenzene poisoning resulting from its contamination of alcoholic drinks and food (Nabarro, 1948).

The U.S. EPA (1979) has estimated the weighted average bioconcentration factor for nitrobenzene to be 4.3 for the edible portions of fish and shellfish consumed by Americans. This estimate was based on octanol/water partition coefficients.

C. Inhalation

Atmospheric nitrobenzene levels outside a plant are not monitored by industry. Since inner plant levels are below the Threshold Limit Value (TLV) of 5 mg/m^3 and nitrobenzene vapors accumulate at the floor level due to their high density, the external concentrations are expected to be very low (Dorigan and Hushon, 1976).

III. PHARMACOKINETICS

A. Absorption

Nitrobenzene absorption can occur by all possible routes, but it takes place mainly through the respiratory tract and skin. On the average, 80 percent of the nitrobenzene vapors are retained in the human respiratory tract (Piotrowski, 1977).

Nitrobenzene, as liquid and vapor, will pass directly through the skin. The rate of vapor absorption depends on the air concentration, ranging from 1 mg/hr at 5 mg/m^3 concentration to 9 mg/hr at 20 mg/m^3. Maximal cutaneous absorption of liquid nitrobenzene is 0.2 to 3 $mg/cm^2/hr$ depending on skin temperature.

B. Distribution

Upon entry into the body, nitrobenzene enters the bloodstream. Nitrobenzene is a very lipid soluble with an oil to water coefficient of 800. In a rat study, the ratio of concentration of nitrobenzene in adipose tissue versus blood in internal organs and muscle was approximately 10:1 one hour after an intravenous injection (Piotrowski, 1977). Dorigan and Hushon (1976) found that 50 percent of the nitrobenzene administered to rabbits accumulated unchanged in tissues within two days after intubation.

C. Metabolism

There are two main pathways for the metabolism of nitrobenzene: 1) reduction to aniline followed by hydroxylation to aminophenols, and 2) direct hydroxylation of nitrobenzene to form nitrophenols. Further reduction of nitrophenols to aminophenols may also occur (Piotrowski, 1977). The first pathway proceeds via the unstable intermediates, nitrosobenzene and phenylhydroxylamine, both of which are toxic and have pronounced methemoglobinemic capacity. These reactions occur in the cytoplasmic and microsomal fractions of liver cells by the nitro-reductase enzyme system (Fouts and Brodie, 1957). The aniline is then excreted as an acetyl derivative, or hydroxylated and excreted as an aminophenol. The second pathway does not occur in the microsomal fraction. This reaction proceeds via peroxidase in the presence of oxygen (Piotrowski, 1977).

Robinson, et al. (1951) found p-aminophenol to be the main metabolic product of nitrobenzene metabolism in rabbits. Little unchanged nitrobenzene was excreted in the urine and only 1 percent was expired as carbon dioxide. Together with nitrophenols and nitrocatechol, p-aminophenol constituted 55 percent of the urinary metabolites. Metabolites were detected in the urine up to one week after dosing.

D. Excretion

In man, the primary known excretion products of nitrobenzene are p-aminophenol and p-nitrophenol which appear in the urine after chronic or acute exposure. In experimental inhalation exposure to nitrobenzene, p-nitrophenol was formed with the efficiency of 6 to 21 percent. The efficiency of p-aminophenol formation is estimated from acute poisoning

cases where the molar ratio of excreted p-nitrophenol to p-aminophenol is two to one, since p-aminophenol is not formed at a detectable level in short subacute exposure (Piotrowski, 1977).

Ikeda and Kita (1964) found the rate of excretion of these two metabolites to parallel the level of methemoglobin in the blood.

Nitrobenzene remains in the human body for a prolonged period of time. The excretion coefficient of urinary p-nitrophenol (followed for three weeks) in man is about 0.008 per hour. The extended systemic retention and slow excretion of metabolites in man is determined by the low rates of metabolic transformation (reduction and hydroxylation) of the nitrobenzene itself. The conjugation and excretion of the metabolites, p-nitrophenol and p-aminophenol, is rapid (Piotrowski, 1977). The urinary metabolites in man account for only 20 to 30 percent of the nitrobenzene dose; the fate of the rest of the metabolites is not known (Piotrowski, 1977).

IV. EFFECTS

A. Carcinogenicity

The available literature does not demonstrate the carcinogenicity of nitrobenzene, although it is suspect (Dorigan and Hushon, 1976).

Some nitrobenzene derivatives have demonstrated carcinogenic capacities. Pentachloronitrobenzene (PCNB) induced hepatomas and papillomas in mice (Courtney, et al. 1976).

1-Fluoro-2,4-dinitrobenzene (DNFB) was found to be a promoter of skin tumors in mice, although it does not induce them when administered alone (Bock, et al 1969).

B. Teratogenicity

There is a paucity of information on the teratogenic effects of nitrobenzene. In one study, 125 mg/kg was administered to pregnant rats

during preimplantation and placentation periods (Kazanina, 1968). Delay of embryogensis, alteration of normal placentation, and abnormalities in the fetuses were observed. Gross morphogenic defects were seen in 4 of 30 fetuses examined.

C. Mutagenicity

Nitrobenzene was not found to be mutagenic in the Ames Salmonella assay (Chiu, et al., 1978). Trinitrobenzene and other nitrobenzene derivatives have demonstrated mutagenicity in the Ames Salmonella microsome assay and the mitotic recombination assay in yeast (Simmon, et al. 1977), thus raising questions concerning the mutagenicity of nitrobenzene.

D. Other Reproductive Effects

Changes in the tissues of the chorion and placenta of pregnant women who worked in the production of a rubber catalyst that used nitrobenzene were observed. No mention was made of the effects on fetal development or viability (Dorigan and Hushon, 1976). Menstrual disturbances after chronic nitrobenzene exposure have been reported.

Garg, et al. (1976) tested substituted nitrobenzene derivatives for their ability to inhibit pregnancy in albino rats. Two of the compounds tested (p-methoxy and p-ethoxy derivatives) inhibited implantation and pregnancy 100 percent when administered on days 1 through 7 after impregnation.

E. Chronic Toxicity

Symptoms of chronic occupational nitrobenzene absorption are cyanosis, methemoglobinemia, jaundice, anemia, sulfhemoglobinemia, presence of Heinz bodies in the erythrocytes, dark colored urine, and the presence of nitrobenzene metabolites (e.g., nitrophenol) in the urine (Pacseri and Magos, 1958; Hamilton, 1919; Wuertz, et al. 1964; Browning, 1950; Malden, 1907; Piotrowski, 1967).

Chronic exposure of laboratory animals to nitrobenzene (via inhalation, ingestion or subcutaneous injection) produced symptoms similar to those mentioned above for humans as well as tissue degeneration of the heart, liver, and kidney, and reductions in erythrocytes and hemoglobin levels in the blood (U.S. EPA, 1979).

F. Other Relevant Information

Alcohol ingestion has been found to act synergistically with nitrobenzene in man and animals (Dorigan and Hushon, 1976; Smyth, et al., 1969).

Kaplan, et al. (1974) showed that caffeine, an inducer of microsomal enzymes, increases the rate of metabolism and excretion of nitrobenzene thus causing a rapid decline in nitrobenzene induced methemoglobin levels.

Metabolism and excretion of nitrobenzene in humans is slower by an order of magnitude than in rats or rabbits (Piotrowski, 1977).

V. AQUATIC TOXICITY

A. Acute Toxicity

The 96-hour LC_{50} reported value for the bluegill (Lepomis macrochirus) is 42,600 µg/l and the observed 48-hour LC_{50} for Daphnia magna is 27,000 µg/l. Saltwater species tested are the sheepshead minnow, Cyprinodon variegatus, which has a reported 96-hour LC_{50} of 58,539 µg/l and the mysid shrimp, Mysidopsis bahia, with a reported 96-hour LC_{50} of 6,676 µg/l (U.S. EPA, 1979).

B. Chronic Toxicity

In the only chronic data available, no adverse effects were observed during an embryo-larval test with the fathead minnow (Pimephales promelas) at nitrobenzene test concentrations as high as 32,000 µg/l (U.S. EPA, 1978).

C. Plant Effect

Based on cell numbers and chlorophyll a concentration, reported EC_{50} values for the freshwater alga, Selenastrum capricornutum, are 42,000 and 44,100 µg/l; and for the marine alga, Skeletonema costatum, there are reported EC_{50} values of 9,600 and 10,300 µg/l (U.S. EPA, 1979).

D. Residues

A bioconcentration factor of 15 was estimated for aquatic organisms that contain 8 percent lipids.

VI. EXISTING GUIDELINES AND STANDARDS

Neither the human health nor the aquatic criteria derived by U.S. EPA (1979), which are summarized below, have gone through the process of public review; therefore, there is a possibility that these criteria will be changed.

A. Human

The TLV for nitrobenzene is 5 mg/m^3. This is the OSHA Federal standard, the value set by the ILO/WHO committee on Occupational Health, and the TLV suggested by the American Conference of Governmental and Industrial Hygienists (Goldstein, 1975, ACGIH, 1977).

The draft water quality criteria for nitrobenzene is 30 µg/l (U.S. EPA, 1979). This value is based on the TLV and organoleptic level (minimum detectable odor limit in water) of nitrobenzene.

B. Aquatic

For nitrobenzene the drafted criterion to protect freshwater aquatic life is 480 µg/l as a 24-hour average concentration not to exceed 1,100 µg/l at any time. To protect saltwater aquatic life, the 24-hour average is 53 µg/l and this concentration should not exceed 120 µg/l at any time (U.S. EPA, 1979).

NITROBENZENE

REFERENCES

American Conference of Governmental Industrial Hygiensts. 1977. Documentation of the threshold limit value for substances in workroom air. Cincinnati, Ohio.

Bock, A.G., et al. 1969. Tumor promotion by 1-fluoro-2, 4-dinitrobenzene, a potent skin sensitizer. Cancer Res. 29: 179.

Browning, E. 1950. Occupational jaundice and anemia. Practitioner 164: 397.

Chiu, C.W., et al. 1978. Mutagenicity of some commercially available nitro compounds for Salmonella typhinurium. Mut. Res. 58: 11.

Courtney, K.D., et al. 1976. The effects of pentachloronitrobenzene, hexachlorobenzene, and related compounds on fetal development. Toxicol. Appl. Pharmacol. 35: 239.

Dorigan, J., and J. Hushon. 1976. Air pollution assessment of nitrobenzene. U.S. Environ. Prot. Agency.

Fouts, J.R., and B.B. Brodie, 1957. The enzymatic reduction of cloramphenicol, p-nitrobenzoic acid and other aromatic nitro compounds in mammals. Jour. Pharmacol. Exp. Ther. 119: 197.

Garg, S.K., et al. 1976. Potent female antifertility agents. Indian Jour. Med. Res. 64: 244.

Goldstein, I. 1975. Studies on MAC values of nitro and amino-derivatives of aromatic hydrocarbons. Adverse Effects Environ. Chem. Psychotropic Drugs 1: 153.

Hamilton, A. 1919. Industrial poisoning by compounds of the aromatic series. Jour. Industr. Hyg. 1: 200.

Ikeda, M., and A. Kita. 1964. Excretion of p-nitrophenol and p-aminophenol in the urine of a patient exposed to nitrobenzene. Br. Jour. Ind. Med. 21: 210.

Kaplan, A.M., et al. 1974. Methemoglobinemia and metabolism of nitro compounds. Toxicol. Appl. Pharmacol. 29: 113.

Kazanina, S.S. 1968. Morphology and histochemistry of hemochorial placentas of white rats during poisoning of the maternal organisms by nitrobenzene. Bull. Exp. Biol. Med. (U.S.S.R.) 65: 93.

Malden, W. 1907. Some observations on the condition of the blood in men engaged in aniline dyeing and the manufacture of nitrobenzene and its compounds. Jour. Hyg. 7: 672.

Nabarro, J.D.N. 1948. A case of acute mononitrobenzene poisoning. Br. Med. Jour. 1: 929.

Pacseri, I., and L. Magos. 1958. Determination of the measure of exposure to aromatic nitro and amino compounds. Jour. Hyg. Epidemiol. Microbiol. Immunol. 2: 92.

Pierce, M. 1979. Personal communication. Quality Control Dep., Philadelphia Water Treatment Div., Philadelphia, Pa.

Piotrowski, J. 1967. Further investigations on the evaluation of exposure to nitrobenzene. Br. Jour. Ind. Med. 24: 60.

Piotrowksi, J. 1977. Exposure tests for organic compounds in industrial toxicology. NIOSH 77-144. U.S. Dep. Health, Edu. Welfare.

Robinson, D., et al. 1951. Studies in detoxication. 40. The metabolism of nitrobenzene in the rabbit. o-, m-, and p-nitrophenols, o-, m-, and p-aminophenols and 4-nitrocatechol as metabolites of nitrobenzene. Biochem. Jour. 50: 228.

Simmon, V.F., et al. 1977. Munitions wastewater treatments: Does chlorination or ozonation of individual components produce microbial mutagens? Toxicol. Appl. Pharmacol. 41: 197.

Smyth, H.F., Jr., et al. 1969. An exploration of joint toxic action: Twenty-seven industrial chemicals intubated in rats in all possible pairs. Toxicol. Appl. Pharmacol. 14: 340.

U.S. EPA. 1978. In-depth studies on health and environmental impacts of selected water pollutants. Contract No. 68-01-4646.

U.S. EPA. 1979. Nitrobenzenes. Ambient Water Quality Criteria (Draft).

Wuertz, R.L., et al. 1964. Chemical cyanosis - anemia syndrome. Diagnosis, treatment, and recovery. Arch. Environ. Health 9: 478.

No. 135

4-Nitrophenol

Health and Environmental Effects

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-1591-

DISCLAIMER

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4-NITROPHENOL

SUMMARY

There is no evidence to indicate that 4-nitrophenol is carcinogenic.

Weak mutagenic effects in *Saccharomyces* and in *Proteus* have been observed. Results from the Ames assay, the *E. coli*, and the dominant lethal assay failed to show mutagenic effects from 4-nitrophenol.

No information on the teratogenic or adverse reproductive effects of 4-nitrophenol is available.

A single animal study indicates cumulative chronic toxicity; the methodology of this study was not available for review.

For freshwater organisms, acute values for the toxic effects of 4-nitrophenol ranged from 8,280 to 60,500 µg/l, and 7,170 to 27,100 µg/l for marine organisms. Effective concentrations for aquatic plants fall within these ranges of concentrations.

4-NITROPHENOL

I. INTRODUCTION

This profile is based on the Ambient Water Quality Criteria Document for Nitrophenols (U.S. EPA, 1979).

The mononitrophenols are a family of compounds composed of the isomers resulting from nitro group substitution at the 2,3, and 4 position of phenol (the ortho, meta, and para isomers, respectively). The para isomer, 4-nitrophenol, has a molecular weight of 139.11, a boiling point of 279°C, a melting point of 113-114°C, a density of 1.479 g/ml; it is soluble in water (U.S. EPA, 1979).

Uses of the mononitrophenols include the following: production of dyes, pigments, pharmaceuticals, rubber chemicals, lumber preservatives, photographic chemicals, and pesticidal and fungicidal agents (U.S. EPA, 1979). Production was 17.5×10^3 tons per year in 1976 (Chem. Market. Reporter, 1976).

The nitrophenols may be formed via microbial degradation or photodegradation of pesticides (e.g., parathion) containing the nitrophenol moiety. 4-Nitrophenol may be produced in the atmosphere through the photochemical reaction between benzene and nitrogen monoxide (U.S. EPA, 1979). Partial microbial degradation of certain nitrophenols has been shown, particularly by acclimated microorganisms. Mononitrophenols appear to be efficiently degraded by unacclimated microorganisms (Haller, 1978).

II. EXPOSURE

The lack of monitoring data on the mononitrophenols makes it difficult to assess exposure from water, inhalation, and foods.

Mononitrophenols in water have been detected in the effluents of chemical plants (U.S. EPA, 1976, 1979). 4-Nitrophenol has been shown to penetrate the skin and to produce damage at threshold concentrations of 0.8 and 0.9 percent (w/v), respectively (U.S. EPA, 1979).

Exposure to nitrophenols appears to be primarily through occupational contact (chemical plants, pesticide applications). Contaminated water may result in isolated poisoning incidents.

The U.S. EPA (1979) has estimated the weighted average bioconcentration factor for 4-nitrophenol to be 4.9 for the edible portions of fish and shellfish consumed by Americans. This estimate is based on the octanol/water partition coefficient.

III. PHARMACOKINETICS

A. Absorption and Distribution

Pertinent data could not be located in the available literature regarding absorption or distribution.

B. Metabolism

Metabolism of the mononitrophenols occurs primarily by conjugation. Other possible routes are reduction of the nitro group to an amino group or oxidation to dihydric-nitrophenols (U.S. EPA, 1979). These reactions are mediated primarily by liver enzyme systems, although other tissues show lower metabolizing activity (U.S. EPA, 1979).

B. Excretion

An animal study has indicated that oral or intraperitoneal administration of 4-nitrophenol leads to rapid elimination in all species tested, and that the total elimination period is not likely to exceed one week (Lawford, et al. 1954).

IV. EFFECTS

A. Carcinogenicity

There is no evidence available regarding the carcinogenicity of mononitrophenols.

B. Mutagenicity

A weak mutagenic effect was detected in *Saccharomyces cerevisiae* by 4-nitrophenol (Fahrig, 1974); this was also indicated by testing 4-nitrophenol for growth inhibition in a DNA repair deficient strain of *Proteus mirabilis* (Adler, et al., 1976). This compound has also induced chromosome breaks in plants (U.S. EPA, 1979). 4-Nitrophenol has failed to show mutagenic effects in the Ames assay, in *E. coli*, or in the dominant lethal assay (U.S. EPA, 1979).

C. Teratogenicity and Other Reproductive Effects

Pertinent data could not be located in the available literature regarding teratogenicity and other reproductive effects.

D. Chronic Toxicity

A single Russian study (Makhinya, 1969) reported that chronic administration of mononitrophenol to mammals produced hepatitis, splenic hyperplasia, and neurological symptoms. Methodology of this study was not available for review.

V. AQUATIC TOXICITY

A. Acute Toxicity

LC_{50} values have been obtained for two species of freshwater fish: 8,280 µg/l for bluegills, *Lepomis macrochirus*, in a 96-hour static assay (U.S. EPA, 1978), and 60,510 µg/l for the fathead minnow, *Pimephales promelas*, in a 96-hour flow-through assay (Phipps, et al. unpublished manuscript). For the fresh-

water invertebrate, Daphnia magna, determined LC_{50} values range from 8,396 to 21,900 µg/l (U.S. EPA, 1979). The marine fish, sheepshead minnow, Cyprinodon variegatus, has produced determined LC_{50} value of 27,100 816 µg/l in a 96-hour static assay, while the marine mysid shrimp, Mysidopis bahia, was more sensitive, with a reported LC_{50} value of 7,170 µg/l.

B. Chronic Toxicity

No chronic studies on freshwater organisms are available. In an embryo-larval test of the marine fish, sheepshead minnow, a chronic value of 6,325 µg/l was obtained. No chronic testing for marine invertebrates was available.

C. Plant Effects

Four species of freshwater plants have been tested with 4-nitrophenol. The algae, Selenastrum capricornutum and Chlorella vulgaris, and the duckweed, Lemna minor, were most sensitive with effective concentrations of 4,190, 6,950, and 9,452 µg/l, respectively; while the alga, Chlorella pyrenoidosa, was much more resistant, with an effective concentration of 25,000 µg/l. The marine alga, Skeletonema costatum, provided effective concentrations of 7,370 to 7,570 µg/l (U.S. EPA, 1979).

D. Residues

No bioconcentration factors for either freshwater or marine species were available.

VI. EXISTING GUIDELINES AND STANDARDS

Neither the human health nor aquatic criteria derived by U.S. EPA (1979), which are summarized below, have gone through the process of review; therefore, there is a possibility that these criteria will be changed.

A. Human

Available data pertaining to 4-nitrophenol is insufficient for deriving a criterion to protect human health.

B. Aquatic

A criterion for protecting freshwater organisms has been drafted as 240 µg/l, for a 24-hour average concentration, not to exceed 550 µg/l. For marine life, a criterion has been drafted as 53 µg/l for a 24-hour average, not to exceed 120 µg/l (U.S. EPA, 1979).

4-NITROPHENOL

REFERENCES

Adler, B., et al. 1976. Repair-defective mutants of Proteus mirabilis as a prescreening system for the detection of potential carcinogens. Biol. Zbl. 95: 463.

Chemical Marketing Reporter. 1976. Chemical profile: p-nitrophenol. Chem. Market. Reporter p. 9.

Fahrig, R. 1974. Comparative mutagenicity studies with Pesticides. Pages 161-181 In: R. Montesano and L. Tomatis eds. Chemical carcinogenesis essays. Proc. workshop on approaches to assess the significance of experimental chemical carcinogenesis data for man organized by IARC and the Catholic University of Louvain, Brussels, Belgium. IARC Sci. Publ. No. 10. Int. Agency Res. Cancer, World Health Organization.

Haller, H.D. 1978. Degradation of mono-substituted benzoates and phenols by wastewater. Jour. Water Pollut. Control Fed. 50: 2771.

Lawford, D.J., et al. 1954. On the metabolism of some aromatic nitro-compounds by different species of animals. Jour. Pharm. Pharmacol. 6: 619.

Makhinya, A.P. 1969. Comparative hygienic and sanitary-toxicological studies of nitrophenol isomers in relation to their normalization in reservoir waters. Prom Zagryazneniya Vodoemov. 9: 84.

Phipps, G.L., et al. The acute toxicity of phenol and substituted phenols to the fathead minnow. (Manuscript).

U.S. EPA. 1976. Frequency of organic compounds identified in water. U.S. Environ. Prot. Agency. Contract No. EPA 600/4-76-062.

U.S. EPA. 1978. In-depth studies on health and environmental impacts of selected water pollutants. Contract No. 68-01-4646.

U.S. EPA. 1979. Nitrophenols: Ambient Water Quality Criteria (Draft).

No. 136

Nitrophenols

Health and Environmental Effects

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-1600-

DISCLAIMER

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NITROPHENOLS

SUMMARY

None of the nitrophenols have shown carcinogenic activity.

Mutagenicity testing has indicated positive effects of: 2,4-dinitrophenol in mouse bone marrow cells and *E. coli*; 2,4,6-trinitrophenol in *E. coli* and *Salmonella*; and 4,6-dinitro-ortho-cresol in *Proteus*. Weak mutagenic effects of 4-nitrophenol have been reported in *Saccharomyces* and in *Proteus*. Other mutagenic test assays have shown negative results for these compounds.

Teratogenic effects have been reported in the developing chick embryo following administration of 2,4-dinitrophenol. This compound did not produce teratogenic effects in mammalian studies. Adverse reproductive effects (embryo toxicity) were seen in rats exposed to 2,4-dinitrophenol.

The chronic effects of 2,4-dinitrophenol ingestion have included cases of agranulocytosis, neuritis, functional heart damage, and cataract formation. Ingestion of 4,6-dinitro-ortho-cresol has also produced cataracts in humans.

One Russian study has reported cumulative toxic effects in animals produced by the mononitrophenols; methodology of this study was not available for review.

Freshwater fish appeared to be the most sensitive organism to the action of nitrophenols, with acute values ranging from 230 to 167,000 μg/l. The reactivities of various nitrophenols in order of decreasing toxicity are, in general: 2,4-dinitro-6-methylphenol, 2,4-dinitrophenol, 2-nitrophenol, 4-nitrophenol, and 2,4,6-trinitrophenol.

NITROPHENOLS

I. INTRODUCTION

This profile is based on the Ambient Water Quality Criteria Document for Nitrophenols (U.S. EPA, 1979).

The nitrophenols are a family of compounds which, depending on the extent and position of nitro group substituents, include the mononitrophenols, dinitrophenols, and trinitrophenols. Dinitrocresols are related compounds bearing an additional 2-position methyl group. The mononitrophenols (molecular weight 139.11) show boiling points from 194-279°C (depending on the isomeric form) and melting points of 44-114°C. They have a density of 1.485 and are soluble in water. The dinitrophenols (molecular weight 184.11) have melting points from 63.5-144°C and show a density of 1.67 to 1.70. Water solubility is from 0.42 to 2.3 g/l. Trinitrophenols (molecular weight 229.11) have melting points from 96-123°C; they are slightly soluble in water. 2,4,6-Trinitrophenol, the most widely used isomer, has a density of 1.763 g/ml and a solubility of 1.28 g/l. Of the six isomers of dinitrocresol, 4,6-dinitro-o-cresol is the only one of any commercial importance. The physical properties of 4,6-dinitro-o-cresol, hereafter referred to as dinitro-ortho-cresol, include a molecular weight of 198.13, a melting point of 85.8°C and a solubility of 100 mg/l in water (U.S. EPA, 1979).

Uses of the mononitrophenols include the following: production of dyes, pigments, pharmaceuticals, rubber chemi-

cals, lumber preservatives, photographic chemicals, and pesticidal and fungicidal agents. The dinitrophenols are used as chemical intermediates for sulfur dyes, azo dyes, photochemicals, pest control agents, wood preservatives, and explosives. 2,4,6-Trinitrophenol (picric acid) is used for dye intermediates, germicides, tanning agents, fungicides, tissue fixative, photochemicals, pharmaceuticals, and for the etching of metal surfaces. Dinitro-ortho-cresol is used primarily as a blossom-thinning agent on fruit trees and as a fungicide, insecticide, and miticide on fruit trees during the dormant season (U.S. EPA, 1979).

Current Production:	2-nitrophenol	5- 7.5x1[illegible] tons/year	(1976)
	4-nitrophenol	17.5×10^3 tons/year	(1976)
	2,4-dinitrophenol	4.3×10^2 tons/year	(1968)

The nitrophenols may be formed via microbial degradation or photodegradation of pesticides (e.g., parathion) containing the nitrophenol moiety (U.S. EPA, 1979). Partial microbial degradation of certain nitrophenols has been shown, particularly by acclimated microorganisms. Mononitrophenols appear to be efficiently degraded by unacclimated microorganisms (Haller, 1978).

II. EXPOSURE

The lack of monitoring data on the nitrophenols makes it difficult to assess exposure from water, inhalation, and foods. Nitrophenols in water have been detected in

effluents from chemical plants (U.S. EPA, 1976; 1979) or following dumping of explosives (Harris, et al. 1946). Dermal absorption of mononitrophenols, dinitrophenols, trinitrophenols (picric acid), and dinitro-ortho-cresol (DNOC) has been detected (U.S. EPA, 1979).

Exposure to nitrophenols appears to be primarily through occupational contact (chemical plants, pesticide application). Contaminated water may result in isolated poisoning incidents.

The U.S. EPA (1979) has estimated weighted average bioconcentration factors for the following nitrophenols: 2-nitrophenol, 4.0; 4-nitrophenol, 4.9; 2,4-dinitrophenol, 2.4; 2,4,6-trinitrophenol, 6.0; and 4,6-dinitrocresol, 7.5 for fish and shellfish consumed by Americans. This estimate is based on octanol/water partition coefficients.

III. PHARMACOKINETICS

A. Absorption

Specific data on the absorption of the mononitrophenols is not available. The dinitrophenols are readily absorbed following oral, inhalation, or dermal administration. Data on the absorption of trinitrophenols is not available. Animal studies with oral administration of 2,4,6-trinitrophenol indicate that it is readily absorbed from the gastrointestinal tract. Dinitro-ortho-cresol is readily absorbed through the skin, the respiratory tract, and the gastrointestinal tract in humans (NIOSH, 1978).

B. Distribution

No information on the distribution of the mono-nitrophenols is available. Dinitrophenol blood levels rise rapidly after absorption, with little subsequent distribution or storage at tissue sites (U.S. EPA, 1979). 2,4,6-Trinitrophenol and dinitro-ortho-cresol have been found to stain several body tissues; however, the compounds may be bound to serum proteins, thus producing non-specific organ distribution (U.S. EPA, 1979).

C. Metabolism

Metabolism of the nitrophenols occurs through conjugation, reduction of nitro groups to amino groups, or oxidation to dihydric-nitrophenols (U.S. EPA, 1979). These reactions are mediated primarily by liver enzyme systems, although other tissues show lower metabolizing activity (U.S. EPA, 1979). The metabolism of dinitro-ortho-cresol is very slow in man as compared to that observed in animal studies (King and Harvey, 1953).

D. Excretion

Evidence from human poisoning with parathion indicates that excretion of 4-nitrophenol in the urine is quite rapid (Arteberry, et al. 1961). Experiments with urinary clearance of dinitrophenols in several animal species indicate rapid elimination of these compounds (Harvey, 1959). 2,4,6-Trinitrophenol has been detected in the urine of exposed human subjects indicating at least partial urinary elimination (Harris, et al. 1946). The experiments of Parker

and coworkers (1951) in several animal species indicate that dinitro-ortho-cresol is rapidly excreted following injection; however, Harvey, et al. (1951) have shown slow excretion of dinitro-ortho-cresol in human volunteers given the compound orally.

IV. EFFECTS

A. Carcinogenicity

There are no available data to indicate that the mononitrophenols are carcinogenic. Both 2- and 4-nitrophenol failed to show promoting activity for mouse skin tumors (Boutwell and Bosch, 1959); this same study failed to show promoting activity for 2,4-dinitrophenol. No evidence is available to indicate that dinitrophenols, trinitrophenols, or dinitro-ortho-cresol produce any carcinogenic effects (U.S. EPA, 1979).

B. Mutagenicity

A weak mutagenic effect was detected in *Saccharomyces cerevisiae* for 4-nitrophenol (Fahrig, 1974); this was also indicated by testing 4-nitrophenol for growth inhibition in a DNA repair deficient strain of *Proteus mirabilis* (Adler, et al. 1976). This compound has also induced chromosome breaks in plants (U.S. EPA, 1979). 4-Nitrophenol has failed to show mutagenic effects in the Ames assay, in *E. coli*, or in the dominant lethal assay (U.S. EPA, 1979).

Testing of 2,4-dinitrophenol has indicated mutagenic effects in *E. coli* (Demerec, et al. 1951) and damage in murine bone marrow cells (chromatid breaks) (Mitra and Manna, 1971). *In vitro* assays of unscheduled DNA synthesis

(Friedman and Staub, 1976) and DNA damage induced during cell culture (Swenberg, et al. 1976) failed to show positive results with this compound.

2,4,6-Trinitrophenol has produced mutations in E. coli and Salmonella assays (Demerec, et al. 1951; Yoshikawa, et al. 1976). Testing in Drosophila has failed to indicate mutagenic activity.

Adler, et al. (1976) have reported that dinitro-ortho-cresol shows some evidence of producing DNA damage in Proteus mirabilis. Testing of this compound in the Ames Salmonella system (Anderson, et al. 1972) or in E. coli (Nagy, et al. 1975) failed to show any mutagenic effects.

C. Teratogenicity

No information is available to indicate that mono-nitrophenols, 2,4,6-trinitrophenol, or dinitro-ortho-cresol produce teratogenic effects.

2,4-Dinitrophenol has produced developmental abnormalities in the chick embryo (Bowman, 1967; Miyamoto, et al. 1975). No teratogenic effects were observed following intragastric administration to rats (Wulff, et al. 1935) or intraperitoneal administration to mice (Gibson, 1973).

D. Other Reproductive Effects

Feeding of 2,4-dinitrophenol to pregnant rats produced an increased mortality in offspring (Wulff, et al. 1935); similarly, intraperitoneal administration of the compound to mice induced embryotoxicity (Gibson, 1973).

Influence of the compound on maternal health may have contributed to these effects (U.S. EPA, 1979).

E. Chronic Toxicity

Chronic administration of mononitrophenols to mammals has been reported to produce hepatitis, splenic hyperplasia, and neurological symptoms in a single Russian study (Makhinya, 1969). Methodology of this study was not available for review.

Use of 2,4-dinitrophenol as a human dieting aid has produced some cases of agranulocytosis, neuritis, functional heart damage, and a large number of cases of cataracts (Horner, 1942). Cataracts have also been reported in patients poisoned with dinitro-ortho-cresol (NIOSH, 1978).

Human effects resulting from 2,4,6-trinitrophenol exposure have been reported as temporary impairment of speech, memory, walking, and reflexes (Dennie, et al. 1929).

F. Other Relevant Information

A synergistic action in producing teratogenic effects in the developing chick embryo has been reported with a combination of 2,4-dinitrophenol and insulin (Landauer and Clark, 1964).

The combination of 2,4,6-trinitrophenol and opioids or minor analgesics produced an increase in analgesia (Huidobro, 1971).

2,4-Dinitrophenol is a classical uncoupler of oxidative phosphorylation, which accounts for its marked acute toxicity. Dinitro-ortho-cresol is also well known for its activity as an uncoupler.

V. AQUATIC TOXICITY

A. Acute Toxicity

Freshwater fish LC_{50} values reported for the bluegill (Lepomis macrochinus) ranged from 230 to 167,000 µg/l and for the juvenile fathead minnow (Pimephales promelas), from 2,040 to 60,510 µg/l. The order of decreasing toxicity for five nitrophenols examined was: 2,4-dinitro-6-methyl phenol, 2,4-dinitrophenol, 2-nitrophenol, 4-nitrophenol, 2,4,6-trinitrophenol (U.S. EPA, 1979). For three of the phenols tested with both the bluegill and fathead minnow, the bluegill appeared more sensitive. In static bioassays with the freshwater invertebrate, Daphnia magna, 48-hour LC_{50} values of 4,090 to 4,710; 8,396 to 21,900; and 84,700 µg/l were reported for 2,4-dinitrophenol, 4-nitrophenol and 2,4,6-trinitrophenol, respectively (U.S. EPA, 1979). The marine fish, sheepshead minnow (Cyprinodon variegatus), was the only fish species acutely tested for three nitrophenols, with reported LC_{50} values of 29,400; 27,100 and 134,000 µg/l being obtained for 2,4-dinitrophenol, 4-nitrophenol, and 2,4,6-trinitrophenol. Observed LC_{50} values of 4,350; 7,170 and 19,700 µg/l were reported for the mysid shrimp (Mysidopsis bahia) for the same three formulations, respectively.

B. Chronic Toxicity

Pertinent information on the chronic effects on freshwater species could not be located in the available literature searches. The only chronic test on a marine

species was an embryo-larval assay of the sheepshead minnow that produced a chronic value of 6,325 µg/l (U.S. EPA, 1978). Pertinent information relative to chronic effects on marine invertebrates could not be located in the available literature.

C. Plant Effects

The effects of various nitrophenols vary widely among species of freshwater plants and according to the formulation of nitrophenol tested. The duckweed, Lemna minor, was the most sensitive plant tested with 2,4-dinitrophenol and was the most resistant with 2-nitrophenol, having effective concentrations (50 percent growth reduction, time unspecified) ranging from 1,472 to 62,550 µg/l for the two respective formulations. The marine alga, Skeletonema costatum, appeared to be slightly more resistant than freshwater species tested, with effective concentrations ranging from 7,370 to 141,000 µg/l for 4-nitrophenol and 2,4,6-trinitrophenol, respectively.

D. Residues

Bioconcentration factors were not determined for any freshwater or marine species. However, based on octanol/water partition coefficients, bioconcentration factors were estimated as 8.1, 21, and 26 for 2,4-dinitrophenol, 2,4,6-trinitrophenol, and 2,4-dinitro-6-dimethylphenol, respectively.

VI. EXISTING GUIDELINES AND STANDARDS

The human health and aquatic criteria derived by U.S. EPA (1979), which are summarized below, have not yet gone through the process of public review; therefore, there is a possibility that these criteria may be changed.

A. Human

Eight-hour TWA exposures for 2,4,6-trinitrophenol (0.1 mg/m^3) and 4,6-dinitro-ortho-cresol (0.2 mg/m^3) have been established by the ACGIH (1971).

Draft water quality criteria for the following nitrophenols have been estimated by U.S. EPA (1979) based on adverse effects data: dinitrophenols - 68.6 µg/l; trinitrophenols - 10 µg/l; and dinitrocresols - 12.8 µg/l.

B. Aquatic

Criteria drafted to protect freshwater life from nitrophenols follow: 57 µg/l as a 24-hour average concentration, not to exceed 130 µg/l, for 2,4-dinitro-6-methylphenol; 79 µg/l, not to exceed 180 µg/l, for 2,4-dinitrophenol; 240 µg/l, not to exceed 550 µg/l, for 4-nitrophenol; 2,700 µg/l, not to exceed 6,200 µg/l, for 2-nitrophenol; and 1,500 µg/l, not to exceed 3,400 µg/l, for 2,4,6-trinitrophenol. For marine life the following criteria have been drafted as 24-hour average concentrations: 37 µg/l, not to exceed 84 µg/l, for 2,4-dinitrophenol; 53 µg/l, not to exceed 120 µg/l, for 4-nitrophenol; and 150 µg/l, not to exceed 340 µg/l, for 2,4,6-trinitrophenol.

NITROPHENOLS

REFERENCES

Adler, B., et al. 1976. Repair-defective mutants of Proteus mirabilis as a prescreening system for the detection of potential carcinogens. Biol. Zbl. 95: 463.

American Conference of Governmental Industrial Hygienists. 1971. Documentation of the threshold limit values for substances in workroom air. Vol. 1. 3rd ed. Cincinnati, Ohio.

Anderson, K.J., et al. 1972. Evaluation of herbicides for possible mutagenic properties. Jour. Agric. Food Chem. 20: 649.

Arterberry, J.D., et al. 1961. Exposure to parathion: Measurement by blood cholinesterase level and urinary p-nitrophenol excretion. Arch. Environ. Health 3: 476.

Boutwell, R.K., and D.K. Bosch. 1959. The tumor-promoting action of phenol and related compounds for mouse skin. Cancer Res. 19: 413.

Bowman, P. 1967. The effect of 2,4-dinitrophenol on the development of early chick embryos. Jour. Embryol. Exp. Morphol. 17: 425.

Demerec, M., et al. 1951. A survey of chemicals for mutagenic action on E. coli. Am. Natur. 85: 119.

Dennie, C.C., et al. 1929. Toxic reactions produced by the application of trinitrophenol (picric acid). Arch. Dermatol. Sypnilol. 20: 698.

Fahrig, R. 1974. Comparative mutagenicity studies with Pesticides. Pages 161-181 In: R. Montesano and L. Tomatis. (eds.) Chemical carcinogenesis essays. Proc. workshop on approaches to assess the significance of experimental chemical carcinogenesis data for man. Organized by IARC and the Catholic University of Louvain, Brussels, Belgium. IARC Sci. Publ. No. 10. Int. Agency Res. Cancer, World Health Organization.

Friedman, M.A., and J. Staub. 1976. Inhibition of mouse testicular DNA synthesis by mutagens and carcinogens as a potential simple mammalian assay for mutagenesis. Mutat. Res. 37: 67.

Gibson, J.E. 1973. Teratology studies in mice with 2-sac-butyl-4, 6-dinitrophenol (dinoseb). Food Cosmet. Toxicol. 11: 31.

Haller, H.D. 1978. Degradation of mono-substituted benzoates and phenols by wastewater. Jour. Water Pollut. Control Fed. 50: 2771.

Harris, A.H., et al. 1946. Hematuria due to picric acid poisoning at a naval anchorage in Japan. Am. Jour. Pub. Health 36: 727.

Harvey, D.G. 1959. On the metabolism of some aromatic nitro compounds by different species of animal. Part III. The toxicity of the dinitrophenols, with a note on the effects of high environmental temperatures. Jour. Pharm. Pharmacol. 11: 462.

Harvey, D.G., et al. 1951. Poisoning by dinitro-ortho-cresol. Some observations on the effects of dinitro-ortho-cresol administration by mouth to human volunteers. Br. Med. Jour. 2: 13.

Horner, W.D. 1942. Dinitrophenol and its relation to formation to cataracts. Arch. Ophthal. 27: 1097.

Huidobro, F. 1971. Action of picric acid on the effects of some drugs acting on the central nervous system, with special reference to opiods. Arch. Int. Pharmacodyn Ther. 192: 362.

King, E., and D.G. Harvey. 1953. Some observations on the absorption and excretion of 4,6-dinitro-o-creosol (DNOC). I. Blood dinitro-o-cresol levels in the rat and rabbit following different methods of absorption. Biochem. Jour. 53: 185.

Landauer, W., and E. Clark. 1964. Uncouplers of oxidative phosphorylation and teratogenic activity of insulin. Nature 204: 285.

Makhinya, A.P. 1969. Comparative hygienic and sanitary toxicological studies of nitrophenol isomers in relation to their normalization in reservoir waters. Prom. Zagryazneniya Vodoemov. 9: 84. (Translation).

Mitra, A.B., and G.K. Manna. 1971. Effect of some phenolic compounds on chromosomes of bone marrow cells of mice. Indian Jour. Med. Res. 59: 1442.

Miyamoto, K., et al. 1975. Deficient myelination by 2,4-dinitrophenol administration in early stage of development. Teratology 12: 204.

Nagy, A., et al. 1975. The correct mutagenic effect of pesticides on Escherichia coli WP2 strain. Acta. Microbiol. Acad. Sci. Hung. 22: 309.

National Institute for Occupational Safety and Health. 1978. Criteria for a recommended standard: Occupational exposure to dinitro-ortho-creosol. Dep.. Health Edu. Welfare, Washington, D.C.

Parker, V.H., et al. 1951. Some observations on the toxic properties of 3,5-dinitro-ortho-cresol. Br. Jour. Ind. Med. 9: 226.

Swenberg, J.A., et al. 1976. In vitro DNA damage/akaline elution assay for predicting carcinogenic potential. Biochem. Biophys. Res. Commun. 72: 732.

U.S. EPA. 1976. Frequency of organic compounds identified in water. U.S. Environ. Prot. Agency. Contract No. EPA 600/4-76-062.

U.S. EPA. 1978. In-depth studies on health and environmental impacts of selected water pollutants. Contract No. 6801-4646.

U.S. EPA. 1979. Nitrophenols: Ambient Water Quality Criteria. (Draft).

Wulff, L.M.B., et al. 1935. Some effects of alpha-dinitrophenol on pregnancy in the white rat. Proc. Soc. Exp. Biol. Med. 32: 678.

Yoshikawa, K., et al. 1976. Studies on the mutagenicity of hair-dye. Kokuritsu Eisei Shikenjo 94: 28.

No. 137

Nitrosamines

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

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DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

SPECIAL NOTATION

U.S. EPA's Carcinogen Assessment Group (CAG) has evaluated nitrosamines and has found sufficient evidence to indicate that this compound is carcinogenic.

NITROSAMINES

Summary

Nitrosamines and nitrosamides are widespread in the environment and can also be produced endogenously by nitrosation of constituents of food. Nitrosamines and nitrosamides are considered to be among the most potent of all carcinogenic, mutagenic, and teratogenic agents known. The livers of rats chronically exposed to nitrosamines exhibit pathological changes.

Toxicity data examining the effects of nitrosamines on aquatic organisms is scant. For freshwater life forms, acute toxicity levels of 5,850 to 7,760 µg/l were reported, while for marine fish an acute value of nearly 3,300,000 µg/l was reported (both values for N-nitrosodiphenylamine). N-nitrosodimethylamine has been shown to induce hepatocellular carcinoma in rainbow trout.

NITROSAMINES

I. INTRODUCTION

This profile is based on the Ambient Water Quality Criteria Document for Nitrosamines (U.S. EPA, 1979).

The nitrosamines (and nitrosamides) belong to a large group of chemicals generally called N-nitroso compounds. Because they frequently coexist with N-nitrosamines in the environment and are structurally related to nitrosamines, nitrosamides are also included in the U.S. EPA (1979) document and in this profile.

The nitrosamines vary widely in their physical properties and may exist as solids, liquids or gases. Nitrosamines of low molecular weight are volatile at room temperature, while those of high molecular weight are steam volatile. Nitrosamines are soluble in water and organic solvents (U.S. EPA, 1976).

Synthetic production of nitrosamines is limited to small quantities. The only nitrosamine produced in quantities greater than 450 kg per year is N-nitrosodiphenylamine, which is used in rubber processing and in the manufacture of pesticides. Other N-nitroso compounds are produced primarily as research chemicals (U.S. EPA, 1976).

Nitrosamines are rapidly decomposed by sunlight and thus do not persist in ambient air or water illuminated by sunlight (U.S. EPA, 1979; Fine, et al. 1977a). Some nitrosamines have been found to persist for extended periods of time in the aquatic environment (Fine, et al. 1977a; Tate and Alexander, 1975).

II. EXPOSURE

Nitrosamines are widespread in the environment. The most probable source of environmental nitrosamines is nitrosation of amine and amide precursors which are ubiquitous in the environment (Bogovski, et al. 1972).

It has been estimated that air, diet, and smoking all play a roughly equivalent role in human exposure to preformed nitrosamines, contributing a few micrograms per day; intake from drinking water is probably much less than 1 ug per day (U.S. EPA, 1976).

A. Water

Significant concentrations of nitrosamines have been reported for a limited number of samples of ocean water, river water, and waste treatment plant effluent (3 to 4 μg dimethylnitrosamine/l) adjacent to or receiving wastewater from industries using nitrosamines or secondary amines in production operations (Fine, et al. 1977b). Well water with high nitrate levels and coliform counts had nitrosamine concentrations of less than 0.015 μg/l (U.S. EPA, 1977). Non-volatile nitrosamines have been tentatively identified in New Orleans drinking water at levels of 0.1 to 0.5 μg/l (Fine, et al. 1976).

Contamination of water can occur both from industrial wastewater and from agricultural runoff.

B. Food

Nitrosamines have been found in foods, particularly in meats such as sausages, ham, and bacon which have been cured with nitrite. N-nitrosodimethylamine was present in a variety of foods in the 1 to 10 μg/kg range and occasionally at levels up to 100 μg/kg (Montesano and Bartsch, 1976). N-nitrosopyrrolidine has been consistently found in cooked bacon in the range of 10-50 μg/kg (Fine, et al. 1977a).

Many food constituents can either be converted directly to N-nitroso compounds or give rise to nitrosatable products after a metabolic intermediate step which can be involved directly or indirectly in such reactions.

Constituents include nitrate, nitrite, some amino acids, choline, phospholipids, purines, pyrimidines, some vitamins, caffeine, and some pesticides (Walters, 1977; Elsperu and Lijinsky, 1973).

Nitrate and nitrite are well supplied in the diet. Eighty-six percent of the nitrate ingested comes from vegetables; 9 percent comes from cured meats. Only 2 percent of the nitrite ingested comes from vegetables, while 21 percent comes from cured meat (White, 1975).

The U.S. EPA (1979) has estimated the weighted average bioconcentration factor to be 500 for N-nitrosodiphenylamine in the edible portions of fish and shellfish consumed by Americans. This estimate is based on measured steady-state bioconcentration studies with bluegills. Based on the octanol/water partition coefficient for each compound, the U.S. EPA (1979) has estimated weighted average bioconcentration factors for the following compounds in the edible portions of fish and shellfish consumed by Americans: N-nitrosodimethylamine, 0.06; N-nitrosodiethylamine, 0.39; N-nitroso-di-n-butylamine, 4.9; and N-nitrosopyrrolidine, 0.12.

C. Inhalation

Due to the photolabile nature of nitrosamines, concentrations in ambient air are very low, except near sources of direct emissions of nitrosamines (i.e. chemical plants) (Fine, et al. 1977a). Nitrosamines were detected only twice at 40 collection points in New Jersey and New York City, and then only below the 0.01 $\mu g/m^3$ level.

Tobacco and tobacco smoke contain both secondary amines and nitrosamines (Hoffman, et al. 1974). The intake of nitrosamines from smoking 20 cigarettes per day has been estimated at approximately 6 µg/day (U.S. EPA, 1979).

III. PHARMACOKINETICS

A. Absorption

Pertinent data could not be located in the available literature.

B. Distribution

Following intravenous injection into rats, nitrosamides and nitrosamines are rapidly and fairly uniformly distributed throughout the body (Magee, 1972; Stewart, et al. 1974). Both nitrosamides and nitrosamines appear to cross the placenta since they induce neoplasms in offspring if administered maternally to rats in late pregnancy (Magee, et al. 1976).

C. Metabolism and Excretion

Nitrosamides are rapidly metabolized in animals and excreted in the urine within 24 hours (Magee, et al. 1976).

Nitrosamines are metabolized less rapidly and persist in the body unchanged for a longer period. The rate of metabolism depends upon the chemical structure (U.S. EPA, 1979).

After administration of ^{14}C-labeled dimethylnitrosamine, diethylnitrosamine, or nitrosomorpholine, the amount of isotope appearing as $^{14}CO_2$ within 12 hours is 60, 45, and 3 percent, respectively, while the corresponding urinary excretions are 4, 14, and 80 percent. Urinary metabolites include other nitroso compounds formed by oxidation of the alkyl groups to the alcohols and carboxylic acids (Magee, et al. 1976). Dimethylnitrosamine is excreted in the milk of female rats (Schoental, et al. 1974).

The liver appears to be the major site for metabolism of nitrosamines; kidney and lung also metabolize nitrosamines (Magee, et al. 1976). The metabolites of nitrosamines are thought to be the active teratogenic, mutagenic and carcinogenic forms (U.S. EPA, 1979).

IV. EFFECTS

A. Carcinogenicity

The epidemiological studies conducted to date have been inadequate to establish any correlation between exposure to N-nitroso compounds or their precursors and human cancer (U.S. EPA, 1979).

In animals, nitrosamines and nitrosamides are potent carcinogens, inducing tumors in essentially all vital organs via all routes of administration (Montesano and Bartsch, 1976; Druckrey, et al. 1967).

Many of the N-nitroso compounds which have been tested are carcinogenic. There is a strong relationship between chemical structure and type of tumors produced. Symmetrically substituted dialkylnitrosamines and some cyclic nitrosamines produced carcinomas of the liver. Asymmetrical dialkylnitrosamines produced carcinomas of the esophagus (Druckrey, et al. 1967). Apparently all N,N-dialkylnitrosamines containing a tert-butyl group are noncarcinogenic (Heath and Magee, 1962).

There are large differences in species response to carcinogenic nitrosamines and nitrosamides, both in type of tumor produced and in susceptibility, but all animal species tested are vulnerable. The late fetus and neonate appear to be highly susceptible (U.S. EPA, 1979). Exposure to nitrosamides during pregnancy may result in a risk not only to the immediate offspring, but also for at least two more generations of animals (Montesano and Bartsch, 1976). There is no evidence to indicate that nitrosamines pose a similar threat (U.S. EPA, 1979).

Daily oral doses of N-nitroso compounds of 2.5 percent of the LD_{50} values were sufficient to induce cancer in rats (Druckrey, et al. 1967).

B. Mutagenicity

The N-nitroso compounds include some of the most powerful mutagens known. Nitrosamides are mutagenic in almost all test systems, due to non-enzymic formation of active degradation products. Nitrosamines must be metabolically activated to be mutagenic in microbial assays (U.S. EPA, 1979).

Dimethylnitrosamine and diethylnitrosamine have been reported to induce forward and reverse mutations in S. typhimurium, E. coli, Neurospora crassa and other organisms; gene recombination and conversion in Saccharomyces cerevisiae; "recessive lethal mutations" in Drosophila; and chromosome aberrations in mammalian cells (Montesano and Bartsch, 1976). Negative results were obtained in the mouse dominant lethal test.

C. Teratogenicity

N-nitroso compounds can be potent teratogens (U.S. EPA, 1979). Nitrosamides are teratogenic over an extended period of gestation, whereas nitrosamines are active only when administered late in pregnancy (Druckrey, 1973) probably because of the inability of the embryonic tissue to metabolize nitrosamines during early pregnancy (Magee, 1973).

D. Other Reproductive Effects

Nitrosamines and nitrosamides are embryotoxic (Druckrey, 1973).

E. Chronic Toxicity

The livers of rats and other species chronically exposed to nitrosamines exhibit pathological changes including biliary hyperplasia, fibrosis, nodular parenchymal hyperplasia, and the formation of enlarged hepatic parenchymal cells with large nuclei (Magee, et al. 1976).

F. Other Relevant Information

Unlike nitrosamines, nitrosamides cause tissue injury at the site of contact (Magee, et al. 1976). This is thought to be due to the nonenzymatic decomposition of nitrosamides into active products upon contact with tissues.

Aminoacetonitrile, which inhibits the metabolism of dimethylnitrosamine, prevented the toxic and carcinogenic effects of dimethylnitrosamine in rat liver (Magee, et al. 1976).

Ferric oxide, cigarette smoke, volatile acids, aldehydes, methyl nitrite, and benzo(a)pyrene have been suggested to act in a cocarcinogenic manner with dimethylnitrosamine (Stenback, et al. 1973; Magee, et al. 1976).

V. AQUATIC TOXICITY

A. Acute Toxicity

The LC_{50} value of 5,850 µg/l for bluegill sunfish (Lepomis macrochirus) exposed to N-nitrosodiphenylamine represents the sole acute toxicity data for freshwater fish, while an LC_{50} value of 7,760 µg/l was obtained for the freshwater invertebrate, Daphnia magna (U.S. EPA, 1978). The marine mummichog (Fundulus heteroclitus) was relatively resistant to N-nitrosodimethylamine in a 96-hour static test, where an adjusted LC_{50} value of 3,300,000 µg/l was reported (Ferraro, et al. 1977). No additional data concerning marine organisms was presented in the Ambient Water Quality Criteria Document (U.S. EPA, 1979).

B. Chronic Toxicity

The chronic effects of N-nitrosodiphenyl amine have been examined in Daphnia magna, with no adverse effects being reported at a concentration of 48 µg/l. No chronic data concerning marine organisms were found in the available literature.

C. Plant Effects

Pertinent data could not be located in the available literature.

D. Residues

A bioconcentration factor of 217 was reported, as was a biological half-life of less than one day in the freshwater bluegill sunfish (U.S. EPA, 1978). No data on residues in marine life were found in the available literature.

E. Miscellaneous

Shasta strain rainbow trout (Salmo gairdneri) fed N-nitrosodimethylamine in their diet for 52 weeks developed a dose-response occurrence of hepatocellular carcinoma at doses of 200, 400, and 800 mg N-nitrosodimethylamine per kg body weight (Grieco, et al. 1978).

VI. EXISTING GUIDELINES AND STANDARDS

Neither the human health nor the aquatic criteria derived by U.S. EPA (1979), which are summarized below, have gone through the process of public review; therefore, there is a possibility that these criteria will be changed.

A. Human

Using the "one-hit" model, the U.S. EPA (1979) has estimated the following levels of nitrosamines in ambient water which will result in specified risk levels of human cancer.

The water concentration of dimethylnitrosamine corresponding to a lifetime cancer risk for humans of 10^{-5} is 0.026 µg/l, based on the induction of liver tumors in rats (Druckrey, 1967).

The water concentration of dibutylnitrosamine corresponding to a lifetime cancer risk for humans of 10^{-5} is 0.013 µg/l, based on induction of tumors of the bladder and esophagus in mice (Bertram and Craig, 1970).

The water concentration of N-nitroso-pyrrolidine corresponding to a lifetime cancer risk for humans of 10^{-5} is 0.11 μg/l, based on the induction of hepatocellular carcinomas in rats (Preussman, et al. 1977).

No other guidelines or standards are available.

B. Aquatic

No criteria for freshwater or marine life have been drafted (U.S. EPA, 1979).

NITROSAMINES

REFERENCES

Bertram, J.S., and A.W. Craig. 1970. Induction of bladder tumours in mice with dibutylnitrosamine. Br. Jour. Cancer 24: 352.

Bogovski, P., et al. 1972. N-nitroso compounds, analysis and formation. IARC Sci. Pub. No. 3. Int. Agency Res. Cancer, Lyon, France.

Druckrey, H., et al. 1967. Organotropic carcinogenic action of 65 different N-nitroso compounds in BD rats. Z. Krebsforsch. 69: 103.

Druckrey, H. 1973. Specific carcinogenic and teratogenic effects of "indirect" alkylating methyl and ethyl compounds, and their dependency on stages of oncogenic development. Xenobiotica 3: 271.

Elsperu, R., and W. Lijinsky. 1973. The formation of N-nitroso compounds from nitrite and some agricultural chemicals. Food Cosmet. Toxicol. 11: 807.

Ferraro, A.F., et al. 1977. Acute toxicity of water-borne dimethylnitrosamine (DMN) to Fundulus heteroclitus (L). Jour. Fish. Biol. 10: 203.

Fine, D.H., et al. 1976. N-Nitroso compounds in air and water. IARC Sci. Publ. No. 14. Int. Agency Res. Cancer, Lyon, France.

Fine, D.H., et al. 1977a. Human exposure to N-nitroso compounds in the environment. In: H.H. Hiatt, et al., eds. Origins of human cancer. Cold Spring Harbor Lab., Cold Spring Harbor, New York.

Fine, D.H., et al. 1977b. Determination of dimethylnitrosamine in air, water and soil by thermal energy analysis: measurements in Baltimore, Md. Environ. Sci. Technol. 11: 581.

Grieco, M.P., et al. 1978. Carcinogenicity and acute toxicity of dimethylnitrosamine in rainbow trout (Salmo gairdneri). Jour. Natl. Cancer Inst. 60: 1127.

Heath, D.F., and P.N. Magee. 1962. Toxic properties of dialkylnitrosamines and some related compounds. Br. Jour. Ind. Med. 19: 276.

NITROSAMINES

REFERENCES

Bertram, J.S., and A.W. Craig. 1970. Induction of bladder tumours in mice with dibutylnitrosamine. Br. Jour. Cancer 24: 352.

Bogovski, P., et al. 1972. N-nitroso compounds, analysis and formation. IARC Sci. Pub. No. 3. Int. Agency Res. Cancer, Lyon, France.

Druckrey, H., et al. 1967. Organotropic carcinogenic action of 65 different N-nitroso compounds in BD rats. Z. Krebsforsch. 69: 103.

Druckrey, H. 1973. Specific carcinogenic and teratogenic effects of "indirect" alkylating methyl and ethyl compounds, and their dependency on stages of oncogenic development. Xenobiotica 3: 271.

Elsperu, R., and W. Lijinsky. 1973. The formation of N-nitroso compounds from nitrite and some agricultural chemicals. Food Cosmet. Toxicol. 11: 807.

Ferraro, A.F., et al. 1977. Acute toxicity of water-borne dimethylnitrosamine (DMN) to Fundulus heteroclitus (L). Jour. Fish. Biol. 10: 203.

Fine, D.H., et al. 1976. N-Nitroso compounds in air and water. IARC Sci. Publ. No. 14. Int. Agency Res. Cancer, Lyon, France.

Fine, D.H., et al. 1977a. Human exposure to N-nitroso compounds in the environment. In: H.H. Hiatt, et al., eds. Origins of human cancer. Cold Spring Harbor Lab., Cold Spring Harbor, New York.

Fine, D.H., et al. 1977b. Determination of dimethylnitrosamine in air, water and soil by thermal energy analysis: measurements in Baltimore, Md. Environ. Sci. Technol. 11: 581.

Grieco, M.P., et al. 1978. Carcinogenicity and acute toxicity of dimethylnitrosamine in rainbow trout (Salmo gairdneri). Jour. Natl. Cancer Inst. 60: 1127.

Heath, D.F., and P.N. Magee. 1962. Toxic properties of dialkylnitrosamines and some related compounds. Br. Jour. Ind. Med. 19: 276.

Hoffman, D., et al. 1974. Chemical studies on tobacco smoke. XXVI. On the isolation and identification of volatile and non-volatile N-nitrosamines and hydrazines in cigarette smoke. In: N-Nitroso compounds in the environment. IARC Sci. Pub. No. 9. Int. Agency Res. Cancer, Lyon, France.

Magee, P.N. 1972. Possible mechanisms of carcinogenesis and mutagenesis by nitrosamines. In: W. Nakahara, et al., eds. Topics in chemical carcinogenesis. University of Tokyo Press, Tokyo.

Magee, P.N. 1973. Mechanisms of transplacental carcinogenesis by nitroso compounds. In: L. Tomatis and U. Mohr, eds. Transplacental carcinogenesis. IARC Sci. Pub. No. 4. Int. Agency Res. Cancer, Lyon, France.

Magee, P.N., et al. 1976. N-Nitroso compounds and related carcinogens. In: C.S. Searle, ed. Chemical Carcinogens. ACS Monograph No. 173. Am. Chem. Soc., Washington, D.C.

Montesano, R., and H. Bartsch. 1976. Mutagenic and carcinogenic N-nitroso compounds: Possible environmental hazards. Mutat. Res. 32: 179.

Preussmann, R., et al. 1977. Carcinogenicity of N-nitrosopyrrolidine: Dose-response study in rats. Z. Krebsforsch. 90: 161.

Schoental, R., et al. 1974. Carcinogens in milk: Transfer of ingested diethylnitrosamine into milk by lactating rats. Br. Jour. Cancer 30: 238.

Stenback, F., et al. 1973. Synergistic effect of ferric oxide on dimethylnitrosamine carcinogenesis in the Syrian golden hamster. Z. Krebsforsch. 79: 31.

Stewart, B.W., et al. 1974. Cellular injury and carcinogenesis. Evidence for the alkylation of rat liver nucleic acids in vivo by N-nitrosomorpholine. Z. Krebsforsch. 82: 1.

Tate, R.L., and M. Alexander. 1975. Stability of nitrosamines in samples of lake water, soil and sewage. Jour. Natl. Cancer Inst. 54: 327.

U.S. EPA. 1976. Assessment of scientific information on nitrosamines. A report of an ad hoc study group of the U.S. Environ. Prot. Agency Sci. Advis. Board Executive Comm. Washington, D.C.

U.S. EPA. 1977. Scientific and assessment report on nitrosamines. EPA 600/6-77-001. Off. Res. Dev. U.S. Environ. Prot. Agency, Washington, D.C.

U.S. EPA. 1978. In-depth studies on health and environmental impacts of selected water pollutants. Contract No. 68-01-4646. U.S. Environ. Prot. Agency.

U.S. EPA. 1979. Nitrosamines: Ambient Water Quality Criteria (Draft).

Walters, C.L. 1977. Nitrosamines - environmental carcinogens? Chem. Br. 13: 140.

White, J.W., Jr. 1975. Relative significance of dietary sources of nitrate and nitrite. Jour. Agric. Food Chem. 23: 886.

No. 138

N-Nitrosodiphenylamine

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

-1633-

DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

N-NITROSODIPHENYLAMINE

SUMMARY

Formation of N-nitrosodiphenylamine (NDPhA) has been shown experimentally in the stomachs of individuals receiving nitrite and diphenylamine. N-nitrosodiphenylamine undergoes photochemical decomposition in solution or in the atmosphere in the presence of sunlight. Bacterial degradation of NDPhA has been demonstrated in soil.

Prior to the release of recent findings from the NCI bioassay program, NDPhA was considered a non-carcinogenic nitrosamine. In the NCI lifetime rat feeding study, however, NDPhA was found to induce a significant incidence of urinary bladder tumors in both males and females. Few urinary bladder tumors were observed in mice in a similar experiment, although there was a high incidence of non-neoplastic bladder lesions.

N-nitrosodiphenylamine has consistently been found negative in a variety of mutagenicity assays.

I. INTRODUCTION

This document is based on the Ambient Water Quality Criteria Document on Nitrosamines (U.S. EPA, 1979b), the Scientific and Technical Assessment Report on Nitrosamines (U.S. EPA, 1977), and other selected references. The term "N-nitrosodiphenylamine" (NDPhA) in this report refers specifically to that compound; the term "nitrosamine" when used in this report refers to nitrosamines in general.

N-nitrosodiphenylamine (NDPhA; molecular weight 198.23; molecular formula $C_{12}H_{10}N_2O$) is a yellow to brown or orange powder or flakes. It has the following physical/chemical properties (Hawley, 1977):

Melting Point:	64-66°C
Solubility:	insoluble in water; soluble in organic solvents.

NDPhA is used as a vulcanization retarder in the rubber industry (Hawley, 1977).

A review of the production range (includes importation) statistics for N-nitrosodiphenylamine (CAS No. 86-30-6) which is listed in the initial TSCA Inventory (1979a) has shown that between 400,000 and 900,000 pounds of this chemical were produced/imported in 1977.*/

II. EXPOSURE

A. Formation

The chemistry of formation of nitrosamines is quite complex, however, they are in general formed by the combination of amines (R_1R_2N-) with some nitrosating agent. Formation has been shown to occur with primary, secondary, and tertiary amines, as well as

*/ This production range information does not include any production/importation data claimed as confidential by the person(s) reporting for the TSCA Inventory, nor does it include any information which would compromise Confidential Business Information. The data submitted for the TSCA Inventory, including production range information, are subject to the limitations contained in the Inventory Reporting Regulations (40 CFR 710).

other amino compounds. The nitrosating agent can be derived from nitric oxides (NO, NO_2, N_2O_3, or N_2O_4) or inorganic nitrite (U.S. EPA, 1977).

The *in vivo* formation of nitrosamines following ingestion of precursors has been demonstrated in human and animal studies (U.S. EPA, 1977) Sander and Seif (1969) showed the formation of NDPhA in the stomachs of humans given nitrite and diphenylamine.

B. Environmental Fate

In the absence of light, nitrosamines are quite stable and will decompose hydrolytically only following prolonged contact with strong acid. There is no evidence of thermal instability of nitrosamines in the gas phase; however, they do undergo photochemical decomposition in solution or in the atmosphere in the presence of sunlight or ultra-violet light (U.S. EPA, 1977).

Transnitrosation reactions involving direct transfer of the nitroso group from NDPhA to other amines have been demonstrated (Challis and Osborn, 1972). Such a reaction yields a new N-nitroso compound and diphenylamine.

In unamended soil, 70% of added NDPhA was lost within 30 days. In soil amended with bacteria, added NDPhA had disappeared completely at the end of day 10 (Mallik, 1979).

C. Bioconcentration

See Section V.C.

III. PHARMACOKINETICS

Intestinal bacteria common in the gastrointestinal tract of many animals and humans have been shown capable of degrading NDPhA (Rowland and Grasso, 1975).

IV. HEALTH EFFECTS IN MAMMALS

A. Carcinogenicity

In a one-year study, Argus and Hoch-Ligeti (1961) administered NDPhA by gavage to 25 male rats for 45 weeks (total dose 244 mg/rat). No tumors were observed. In other studies (Boyland et al., 1968) no tumors were seen when 20 rats were given the test compound in the diet for 100 weeks at daily doses of 120 mg/kg, or when 24 male rats were administered DNPhA by intraperitoneal injection once per week for 6 months at a dose of 2.5 mg/week. Both tests were terminated after 2 years. When two groups of mice (18 male and 18 female per group) were administered NDPhA by gavage daily for 3 weeks at 1,000 mg/kg, then in diet at 3,769 ppm for 18 months, no significant incidences of tumors were observed. However, in another assay reticulum cell sarcomas were observed in the mice when the chemical was injected subcutaneously (NCI, 1968; Innes et al., 1969). Druckrey et al. (1967) reported a lack of tumorigenicity in rats administered 120 mg/kg/day of NDPhA for 700 days, for a total dose of 65 g/kg. Taken together, these studies were viewed as a demonstration of the non-carcinogenicity of NDPhA.

Recent results from the NCI bioassay program, however, have demonstrated that NDPhA is a carcinogen in rats (NCI, 1979; Cardy

et al., 1979). In these studies NDPhA was administered in the diet to rats and mice at two doses, the "maximum tolerated dose" for each species and one-half that amount. Groups of 50 animals of each sex were tested at each dose for approximately 100 weeks. The study found that dietary exposure to NDPhA gave rise to a significant incidence of urinary bladder tumors in both male (40%) and female (90%) rats. Few urinary bladder tumors were observed in the mice, although there was a high incidence of non-neoplastic bladder lesions. The authors (Cardy et al., 1979) ascribed the strong carcinogenic effect seen in rats in this study to the higher doses used; they estimated that the maximum daily intake of NDPhA was 320 mg/kg in females and 240 mg/kg in males. These levels are somewhat higher than those used by Druckrey et al. (1967) in the only other known chronic feeding study done in rats.

B. Mutagenicity

NDPhA has consistently been reported negative in a variety of mutagenicity assays: S. typhimurium (Ames test), with and without activation (Yahagi et al., 1977; Bartsch et al., 1976; Simmon, 1979a; Rosenkranz and Poirier, 1979); E. coli, with activation (Nakajima et al., 1974); (Pol A^-) E. coli (Rosenkranz and Poirier, 1979); N. crassa (Marquardt et al., 1963); Chinese hamster V79 (lung) cell line, with and without activation (Kuroki et al., 1977); Saccharomyces cerevisiae D3, with activation (Simmon, 1979b); host mediated assay (tester strains: S. typhimurium and S. cerevisiae D3) (Simmon et al., 1979); in vivo mouse testicular DNA synthesis assay (Friedman and Staub, 1976).

C. Other Toxicity

The oral LD_{50} in rats is 1650 mg/kg; in mice the oral LD_{50} is 3,850 mg/kg (NIOSH, 1978).

V. AQUATIC EFFECTS

A. Acute

The 96-hour LC_{50} for NDPhA in bluegill sunfish under static test conditions is 5.9 mg/l (nominal concentration). The 48-hour EC_{50} (static conditions) in Daphnia magna is 7.7 mg/l (nominal concentration). The adjusted 96-hour LC_{50} for the mummichog (a marine fish) under static conditions is 3,300 mg/l (nominal concentration) (U.S. EPA, 1979b).

B. Chronic

No adverse effects were reported at any test concentration in a chronic toxicity study in Daphnia magna at concentrations below 0.048 mg/l (U.S. EPA, 1979b).

C. Other

Bioconcentration of NDPhA by bluegill sunfish reached equilibrium within 14 days; the bioconcentration factor was 217. The half-life of the compound in bluegill sunfish was less than one day (U.S. EPA, 1979b).

VI. EXISTING GUIDELINES

Criteria for the protection of aquatic species from excess NDPhA exposure have not been established (U.S. EPA, 1979b).

REFERENCES

Argus, M.F., and Hoch-Ligeti, C. 1961. Comparative study of the carcinogenic activity of nitrosamines. J. Natl. Cancer Inst. 27, 695.

Bartsch, H., C. Malaveille, and R. Montesano. 1976. The predictive value of tissue-mediated mutagenicity assays to assess the carcinogenic risk of chemicals. IARC Scientific Publications (Lyon), No. 12, 467.

Boyland, E., R.L. Carter, J.W. Gorrod, and F.J.C. Roe. 1968. Carcinogenic properties of certain rubber additives. Europ. J. Cancer 4, 233. (as cited in NCI, 1979).

Cardy, R.H., W. Lijinsky, P.K. Hilderbrandt. 1979. Neoplastic and non-plastic urinary bladder lesions induced in Fischer 344 rats and B6C3F, hybrid mice by N-nitrosodiphenylamine. Ectotoxicol. Env. Safety, 3(1), 29.

Challis, B.C. and M.R. Osborn. 1972. Chemistry of nitroso compounds. The reaction of N-nitrosodiphenylamine with N-methylaniline--a direct transnitrosation. Chem. Comm. 518

Druckrey, H., R. Preussmann, S. Ivankovic, and D. Schmahl. 1967. Organotrope carcinogene Wirkungen bei 65 verschiedenen N-Nitroso-Verbindungen an BD-Ratten. Z. Krebsforsch. 69, 103. (as cited in NCI, 1979 and Cardy et al., 1979).

Friedman, M.A., J. Staub. 1976. Inhibition of mouse testicular DNA synthesis by mutagens and carcinogens as a potential simple mammalian assay for mutagenesis. Mutat. Res., 37(1), 67-76.

Hawley, G.G. 1977. The Condensed Chemical Dictionary, 9th ed., Van Nostrand Reinhold Co.

Innes, J.R.M., B.M. Ulland, M.G. Valerio, L. Petrucelli, L. Fishbein, E.R. Hart, A.J. Pallotta. R.R. Bates, H.L. Falk, J.J. Gart, M. Klein, I. Mitchell, and J. Peters. 1969. Bioassay of pesticides and industrial chemicals for tumorigenicity in mice: a preliminary note. J. Natl. Cancer Inst. 42(6), 1101-1106. (as cited in NCI, 1979).

Kuroki, T., C. Drevon, and R. Montesano. 1977. Microsome-mediated mutagenesis in V79 Chinese hamster cells by various nitrosamines. Cancer Res. 37, 1044-1050.

Mallik, M.A. 1979. Microbial contribution to nitrosamine formation in soil. Smithsonian Scientific Information Exchange No. GY 70884 2.

Marquardt, H., R. Schwaier, and F. Zimmerman. 1963. Nicht-Mutagenitat von Nitrosamininen bei Neurospora Crassa. Naturwissenschaften 50, 135. (as cited in Cardy et al., 1979).

Nakajima, T., A. Tanaka, and K.I. Tojyo. 1974. The effect of metabolic activation with rat liver preparations on the mutagenicity of several N-nitrosamines on a streptomycin-dependent strain of Escherichia coli. Mutat. Res. 26, 361-366.

National Cancer Institute. 1968. Evaluation of Carcinogenic, Teratogenic, and Mutagenic Activities of Selected Pesticides and Industrial Chemicals. Vol. I. Carcinogenic Study. (as cited in NCI, 1979).

National Cancer Institute. 1979. Bioassay of N-Nitrosodiphenylamine for Possible Carcinogenicity. NIH Publication No. 79-1720.

National Institute for Occupational Safety and Health. 1978. Registry of Toxic Effects of Chemical Substances.

Rosenkranz, H.S. and L.A. Poirier. 1979. Evaluation of the mutagenicity and DNA-modifying activity of carcinogens and noncarcinogens in microbial systems. J. Natl. Cancer Inst. 62, 873-892.

Rowland, I.R. and P. Grasso. 1975. Degradation of N-nitrosamines by intestinal bacteria. Appl. Microbiol. 29(1), 7-12. (Abstract only).

Sander, J. and F. Seif. 1969. Bakterielle reduction von nitrat in Magen des Menschen als Ursoche einer nitrosaminbildung. Arnz.-Forsch 19, 1091. (as cited in U.S. EPA, 1977).

Simmon, V.F. 1979a. In vitro mutagenicity assays of chemical carcinogens and related compounds with Salmonella typhimurium. J. Natl. Cancer Inst. 62, 893-899.

Simmon, V.F. 1979b. In vitro assays for recombinogenic activity of chemical carcinogens and related compounds with Saccharomyces cerevisiae D3. J. Natl. Cancer Inst. 62, 901-909.

Simmon, V.F., H.S. Rosenkranz, E. Zeiger et al. 1979. Mutagenic activity of chemical carcinogens and related compounds in the intraperitoneal host-mediated assay. J. Natl. Cancer Inst. 62, 911-918.

U.S. EPA. 1977. Scientific and Technical Assessment Report on Nitrosamines, EPA-600/6-77-001.

U.S. EPA. 1979a. Toxic Substances Control Act Chemical Substances Inventory, Production Statistics for Chemicals on the Non-Confidential Initial TSCA Inventory.

U.S. EPA. 1979b. Ambient Water Quality Criteria: Nitrosamines. PB 292 438.

Yahagi, T., M. Nagao, Y. Seino, T. Matsushima, T. Sugimura, and M. Okada. 1977. Mutagenicities of N-nitrosamines on Salmonella. Mutat. Res. 48, 121.

No. 139

N-Nitrosodi-n-propylamine

Health and Environmental Effects

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WASHINGTON, D.C. 20460

APRIL 30, 1980

-1643-

DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

SPECIAL NOTATION

U.S. EPA's Carcinogen Assessment Group (CAG) has evaluated n-nitrosodi-n-propylamine and has found sufficient evidence to indicate that this compound is carcinogenic.

N-NITROSODI-n-PROPYLAMINE

SUMMARY

The International Agency for Research on Cancer has concluded that "N-nitrosodi-n-propylamine should be regarded for practical purposes as if it were carcinogenic in humans." The conclusion is based on positive findings in several long-term animal studies with the compound. It has also been found mutagenic in several test systems with activation.

The chemistry of formation of nitrosamines is quite complex, however, they are formed in general by the combination of amines with some nitrosating agent. Nitrates, nitrites, and amines (primary, secondary, and tertiary), the precursors in the formation of nitrosamines, are ubiquitous in the environment. Significant quantities of the precursors are also produced through human activities.

The *in vivo* formation of nitrosamines following ingestion of precursors has been demonstrated in humans and animals.

Nitrosamines degrade in the presence of sunlight; however, in the dark they are quite stable. Microorganisms can function both in the formation and degradation of nitrosamines. The half-life of aliphatic nitrosamines in the environment ranges from one hour in the atmosphere in sunlight to more than 40 days in soils and water (in the absence of light).

I. INTRODUCTION

This document is based on the Ambient Water Quality Criteria Document for Nitrosamines (U.S. EPA, 1979a), Volume 17 of the

IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans (IARC, 1978), the Scientific and Technical Assessment Report on Nitrosamines (U.S. EPA, 1977), and other selected references. The term "N-nitrosodi-n-propylamine" (NDPA) in this report refers specifically to that compound; the term "nitrosamine" when used in this report refers in general to simple aliphatic nitrosamines.

N-nitrosodi-n-propylamine (NDPA; $C_6H_{14}N_2O$; molecular weight 130.2) is a yellow liquid having the following physical chemical properties (IARC, 1978).

Boiling Point:	81°C
Density:	d_4^{20} 0.9160
Solubility:	soluble in water, organic solvents, and lipids.
Volatility:	can be steam distilled quantitatively.

A review of the production range (includes importation) statistics for NDPA (CAS No. 621-64-7) which is listed in the initial TSCA Inventory (1979b) has shown that between zero and 900 pounds of this chemical were intentionally produced/imported in 1977.*/

*/ This production range information does not include any production/importation data claimed as confidential by the person(s) reporting for the TSCA Inventory, nor does it include any information which would compromise Confidential Business Information. The data submitted for the TSCA Inventory, including production range information, are subject to the limitations contained in the Inventory Reporting Regulations (40 CFR 710).

No information on the commercial uses of NDPA was located, however, it appears likely that most, if not all, of that produced is used solely in the laboratory.

II. EXPOSURE

Nitrates, nitrites, and amines (in this case the propylamines), which are precursors in the formation of nitrosamines, are ubiquitous in the environment and occur in food, water, soil, and air. The natural occurrence of nitrates, nitrites, and secondary and tertiary amines results from their formation during the nitrogen cycle. In addition to the naturally formed precursors, significant quantities are produced through human activities (U.S. EPA, 1977). Some of the major man-made sources of the precursors are listed in Table 1.

A. Formation

The chemistry of formation of nitrosamines is quite complex, however, they are formed in general by the combination of amines (R_1R_2N-) with some nitrosating agent. Formation has been shown to occur with primary, secondary, and tertiary amines, as well as other amino compounds. The nitrosating agent can be derived from nitric oxides (NO, NO_2, N_2O_3, or N_2O_4) or inorganic nitrite. Certain factors (catalysts) can affect the rate of nitrosation. Depending on the reactants and catalysts that are present, nitrosation can occur under acidic, neutral, or alkaline conditions. Nitrosation of amines can also occur by transnitrosation involving other, more labile N-nitroso compounds (U.S. EPA, 1977; Mirvish, 1977).

Table 1. Man-Made Sources of Nitrosamine Precursors (U.S. EPA, 1977)

Nitric Oxides	Amines
Transportation	Feedlots
Motor vehicles	Rendering plants
Aircraft	Antioxidants
Railroads	Vulcanization accelerators
Fuel combustion in stationary sources	Pharmaceuticals
Coal	Self-polishing waxes
Fuel Oil	Synthetic detergents
Natural gas	Pesticides
Wood	Solvents
Industrial processes	Corrosion inhibitors
Solid waste disposal	Animal glues
Miscellaneous	Photographic products
Forest fires	Leather tanning
Structural fires	Primary amine production
Coal refuse	
Agricultural	

The *in vivo* formation of nitrosamines following the ingestion of precursors has been demonstrated in human and animal studies (U.S. EPA, 1976,).

Nitrosamines can be formed in soil, water, and sewage under appropriate conditions (Ayanaba *et al*., 1973a, b; Ayanaba and Alexander, 1974; Kohl *et al*., 1971). Microorganisms in soil and water can participate in the formation of nitrosamines (Ayanaba *et al*., 1973b; Mills and Alexander, 1976), although microbial involvement in such formation reactions is not essential (Mills, 1976; Mills and Alexander, 1976).

B. Environmental Fate

In the absence of light, nitrosamines are quite stable and will decompose hydrolytically only following prolonged contact with strong acid. There is no evidence of thermal instability of nitrosamines in the gas phase; however, they do undergo photo-

chemical decomposition in solution or in the atmosphere in the presence of sunlight or ultra-violet light. There are very few quantitative studies on the rate of photochemical degradation of nitrosamines or on the rate effects of other factors (U.S. EPA, 1977; IARC, 1978). Nonetheless, it has been shown that N-nitrosodimethylamine has an atmospheric half-life (during ambient atmospheric conditions) of between 30 minutes and one hour in sunlight (Hanst et al., 1977). The atmospheric half-life of NDPA should be similar (U.S. EPA, 1979a).

N-nitrosodi-n-propylamine appears to be fairly resistant to microbial attack under environmental conditions. The soil half-life of NDPA under varying conditions has been reported as ranging between 10 and 40 days (Tate and Alexander, 1975; Saunders et al., 1979; Oliver et al., 1978). In lake water under laboratory conditions, NDPA persisted for more than 4 months (Tate and Alexander, 1975).

A laboratory soil leaching study (Saunders et al., 1979) has indicated that NDPA (which is about 1% soluble in water) will leach under heavy simulated rainfall conditions. In a field study, however, NDPA did not leach below a depth of 20 cm. The authors suggest that under field conditions, NDPA is dissipated due to volatilization and degradation.

C. Bioconcentration

No information on the bioaccumulation potential of NDPA was located, although it should be fairly low.

D. Environmental Occurrence

NDPA has been detected in food, alcoholic beverages, and several pesticides (IARC, 1978). It has also been detected in

the waste-water from several chemical plants (Cohen and Bachman, 1978).

III. PHARMACOKINETICS

A. Absorption

In goats, one hour after oral administration, NDPA was found in milk and blood, indicating fairly rapid uptake. Only traces were found in the milk after 24 hours (Juszkiewicz and Kowalski, 1974).

B. Distribution

No information was located on the distribution of NDPA; however, simple aliphatic nitrosamines tend to distribute rapidly and fairly uniformly in the body (U.S. EPA, 1979a).

C. Metabolism

Available evidence suggests that NDPA must be metabolically activated to exert its toxic and carcinogenic effects. Urine collected during the 48 hours after oral administration of an LD_{50} dose of NDPA to rats contained the following compounds: N-nitroso-3-hydroxy-n-propyl-n-propylamine, N-nitroso-2-carboxy-ethyl-n-propylamine, and to a lesser extent, N-nitrosocarboxy-methyl-n-propylamine, and N-nitroso-2-hydroxy-n-propyl-n-propylamine (Blattman and Preussmann, 1973). The last named metabolite, N-nitroso-2-hydroxy-n-propyl-n-propylamine, has been found carcinogenic in rats (Reznik *et al.*, 1975) and hamsters (Pour *et al.*, 1974a,b), thus it may be the active carcinogenic metabolite (proximate and/or ultimate carcinogen) of NDPA.

IV. HUMAN HEALTH EFFECTS

A. Carcinogenicity

Groups of rats were given NDPA in the drinking water at doses of 4, 8, 15, or 30 mg/kg day. Of the 48 animals on test, 45 developed liver carcinomas, 8 developed papillomas or carcinomas of the esophagus, and 6 showed carcinomas of the tongue (Druckrey et al., 1967).

Groups of rats were injected subcutaneously with 1/5, 1/10, or 1/20 the LD_{50} of NDPA (LD_{50}: 487 mg/kg) once weekly for life. The average total dose of NDPA ranged between 0.93 and 2.7 g/kg. A high incidence of neoplasms was observed in the nasal cavities. In addition, tumors of the liver, lung, kidney, and esophagus were observed (Althoff et al., 1973a; Reznik et al., 1975).

Groups of Syrian golden hamsters were injected subcutaneously with 1.2% NDPA in olive oil once weekly for life at 5 dose levels (highest dose was 60 mg/kg). Tumors were observed in the nasal cavities, laryngobronchial tract, lungs, and a variety of other organs (Althoff et al., 1973b; Pour et al., 1973).

The International Agency for Research on Cancer (1978) has concluded:

> There is sufficient evidence of a carcinogenic effect of N-nitrosodi-n-propylamine in two experimental animal species. Although no epidemiological data were available...N-nitrosodi-n-propylamine should be regarded for practical purposes as if it were carcinogenic to humans.

B. Mutagenicity

NDPA was positive in the Ames test (S. typhimurium strains TA 1530, TA 1535, and TA 100) with activation (Barstch et al.,

1976; Camus et al., 1976; Olajos and Cornish, 1976; Sugimura et al., 1976). NDPA was also mutagenic in E. coli (Nakajima et al., 1974) and in Chinese hamster V79 cells (Kuroki et al., 1977), in both cases with activation.

C. Other Toxic Effects

The acute oral LD_{50} of NDPA was 480 mg/kg in rats (Druckrey et al., 1967); the subcutaneous LD_{50} was 487 mg/kg in rats and 600 mg/kg in hamsters (Pour et al., 1973; Reznik et al., 1975).

V. AQUATIC EFFECTS

No data on the aquatic effects of NDPA were located.

VI. EXISTING GUIDELINES

The class of compounds "nitrosamines" was included in the American Conference of Governmental Industrial Hygienists (1977) list of "Industrial Substances Suspected of Carcinogenic Potential for Man." No threshold limit value (TLV) was given.

As noted in Section IV.A, the International Agency for Research on Cancer (1978) has concluded that "N-nitrosodi-n-propylamine should be regarded for practical purposes as if it were carcinogenic to humans."

REFERENCES

Althoff, J., F.W. Kruger, J. Hilfrich, D. Schmahl, and U. Mohr. 1973a. Carcinogenicity of B-hydroxylated dipropylnitrosamine. Naturwissenschaften, 60, 55 (as cited in IARC, 1978).

Althoff, J., F.W. Kruger, and U. Mohr. 1973b. Carcinogenic effect of dipropylnitrosamine and compounds related by B-oxidation. J. Nat. Cancer Inst., 51, 287-288 (as cited in IARC, 1978).

American Conference of Governmental Industrial Hygienists, Threshold Limit Values for Chemical Substances and Physical Agents in the Workroom Environment, 1977.

Ayanaba, A., W. Verstraete, and M. Alexander. 1973a. Formation of dimethylnitrosamine, a carcinogen and mutagen in soils treated with nitrogen compounds. Soil Sci. Soc. Amer. Proc. 37, 565-568. (as cited in U.S. EPA, 1977).

Ayanaba, A., W. Verstraete, and M. Alexander. 1973b. Possible microbial contribution to nitrosamine formation in sewage and soils. J. Nat. Cancer Inst. 50, 811-813. (as cited in U.S. EPA, 1977).

Ayanaba, A. and M. Alexander. Transformation of methylamines and formation of a hazardous product, dimethylnitrosamine, in samples of treated sewage and lake water. J. Environ. Qual. 3, 83-89. (as cited in U.S. EPA, 1979).

Bartsch, H., C. Malaveille, and R. Montesano. 1976. The predictive value of tissue-mediated mutagenicity assays to assess the carcinogenic risk of chemicals. In: Montesano, R., Bartsch, H. and Tomatis, L., eds. Screening Tests in Chemical Carcinogenesis, Lyon (IARC Scientific Publications No. 12), pp. 467-491. (as cited in IARC, 1978).

Blattman, L. and R. Preussmann. 1973. Struktur von metaboliten carcinogener dialkylnitrosamine im rattenurin. Z. Krebsforsch., 79, 3-5. (as cited in IARC, 1978).

Camus, A., B. Bertram, Kruger, F.W., C. Malaveille, and H. Bartsch. 1976. Mutagenicity of B-oxidized N,N-di-n-propylnitrosamine derivatives in S. typhimurium mediated by rat and hamster tissues. Z. Krebsforsch., 86, 293-302 (as cited in IARC, 1978).

Cohen, J.B. and J.D. Bachman. 1978. Measurement of environmental nitrosamines. In: Walker, E.A., Castegnaro, M., Gricuite, L. and Lyle, R.E., eds., Environmental Aspects of N-Nitroso Compounds, Lyon (IARC Scientific Publications No. 19). (as cited in IARC, 1978).

Druckrey, H., R. Preussmann, S. Ivankovic, D. Schmahl. 1967. Organotrope carcinogene Wirkungen bei 65 verschiedenen N-nitrosoverbindungen an BD-ratten. Z. Krebsforsch., 69, 103-201. (as cited in IARC, 1978).

Hanst, P.L., J.W. Spence, and M. Miller. 1977. Atmospheric chemistry of N-nitroso dimethylamine. Env. Sci. Tech., 11(4), 403.

Juskiewicz, T. and B. Kowalski, 1974. Passage of nitrosamines from rumen into milk in goats. In: Bogavski, P. and E.A. Walker, eds., N-Nitroso Compounds in the Environment, Lyon (as cited in IARC, 1978).

International Agency for Research on Cancer. 1978. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans, Vol. 17.

Juskiewicz, T. and B. Kowalski, 1974. Passage of nitrosomines from rumen into milk in goats. In: bogaski, P. and E. A. Walker, eds., n-Nitroso Compounds in the Environment, Lyon (as cited in IARC, 1978).

Kuroki, T., C. Drevon, and R. Montesano. 1977. Microsome-mediated mutagenesis in V79 Chinese hamster cells by various nitrosamines. Cancer Res., 37, 1044-1050. (as cited in IARC, 1978).

Mills, A.L. 1976. Nitrosation of secondary amines by axenic cultures of microorganisms and in samples of natural ecosystems. Ph.D. Thesis. Cornell University, Ithaca, New York. 95 pp. (as cited in U.S. EPA, 1977).

Mills, A.L. and M. Alexander. 1976. Factors affecting dimethylnitrosamine formation in samples of soil and water. J. Environ. Qual., 5(4), 437.

Mirvish, S.S. 1977. N-Nitroso compounds: Their chemical and *in vivo* formation and possible importance as environmental carcinogens. J. Toxicol. Env. Hlth., 2, 1267.

Nakajima, T., A. Tanaka, and K.I. Tojyo. 1974. The effect of metabolic activation with rat liver preparations on the mutagenicity of several N-nitrosamines on a streptomycin-dependent strain of *Escherichia coli*. Mutat. Res., 26, 361-366. (as cited in IARC, 1978).

Olajos, E.J. and H.H. Cornish. 1976. Mutagenicity of dialkylnitrosamines: metabolites and derivatives (Abstract No. 43). Toxicol. Appl. Pharmacol., 37, 109-110. (as cited in IARC, 1978).

Oliver, J.E., P.C. Kearney, and A. Kontson. 1978. Abstract presented at the 175th National Meeting of the American Chemical Society, Paper No. 80, Pesticide Division. (as cited by Saunders *et al.*, 1979).

Pour, P., F.W. Kruger, A. Cardesa, J. Althoff, and U. Mohr. 1973. Carcinogenic effect of di-n-propylnitrosamine in Syrian golden hamsters. J. Nat. Cancer Inst., 51, 1019-1027. (as cited in IARC, 1978).

Pour, P., F.W. Kruger, A. Cardesa, J. Althoff, and U. Mohr. 1974a. Effect of beta-oxidized nitrosamines on Syrian golden hamsters. I. 2-Hydroxypropyl-n-propylnitrosamine. J. Nat. Cancer Inst., 52, 1245-1249. (as cited in IARC, 1978).

Pour, P., J. Althoff, A. Cardesa, F.W. Kruger, and U. Mohr. 1974b. Effect of beta-oxidized nitrosamines on Syrian golden hamsters. II. 2-Oxopropyl-n-propylnitrosamine. J. Nat. Cancer Inst., 52, 1869-1874. (as cited in IARC, 1978).

Reznik, G., U. Mohr, F.W. Kruger. 1975. Carcinogenic effect of di-n-propylnitrosamine, B-hydroxypropyl-n-proylnitrosamine, and methyl-n-propylnitrosamine on Sprague-Dawley rats. J. Nat. Cancer Inst., 54, 937-943. (as cited in IARC, 1978).

Saunders, D.G., J.W. Mosier, J.E. Gray, and A. Loh. 1979. Distribution and movement of N-nitrosodipropylamine in soil. J. Agric. Fd. Chem., 27(3), 584.

Sugimura, T., T. Yahagi, M. Nagao, M. Takeuchi, T,. Kawachi, K. Hara, E. Yamakaki, T. Matsushim Y. Hashimoto, and M. Okada. 1976. Validity of mutagenicity tests using microbes as a rapid screening method for environmental carcinogens. In: Montesano, R., Bartsch, H. and Tomatis, L., eds., Screening Tests in Chemical Carcinogenesis, Lyon (IARC Scientific Publication No. 12), pp. 81-101. (as cited in IARC, 1978).

Tate, R.L. and M. Alexander. 1975. Stability of N-nitrosamines in samples of lake water, soil, an sewage. J. Nat. Cancer Inst. 54, 327-330. (as cited in U.S. EPA, 1977).

U.S. EPA. 1977. Scientific and T hnical Assessment Report on Nitrosamines. EPA-600/6-77-001.

U.S. EPA. 1979a. Ambient Water Quality Criteria: Nitrosamines. PB 292 438.

U.S. EPA. 1979b. Toxic Substances Control Act Chemical Substances Inventory, Production Statistics for Chemicals on the Non-Confidential Initial TSCA Inventory.

No. 140

Paraldehyde

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

-1657-

DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

PARALDEHYDE

Summary

There is no evidence in the available literature to indicate that paraldehyde, a central nervous system depressant, is carcinogenic, mutagenic, or teratogenic.

In low doses (4-8 ml) paraldehyde has a hypnotic effect on the central nervous system. Following chronic and acute exposures at higher concentrations, paraldehyde affects the respiratory and circulatory systems.

Data concerning the effects of paraldehyde on aquatic organisms were not found in the available literature.

Guidelines or standards concerning air or water exposures were not found in the available literature.

PARALDEHYDE

I. INTRODUCTION

Paraldehyde, 2,4,6-trimethyl-1,3,5-trioxane, also known as paraacetaldehyde, is a colorless liquid with a molecular weight of 132.2. This compound melts at 13°C and boils at 125°C. It has a specific gravity of 0.994 at 20°C, and its solubility in water is 120,000 mg/l at 13°C and 58,000 mg/l at 100°C (Verschueren, 1977). The odor of paraldehyde is not pungent or unpleasant, but it is characterized by a disagreeable taste (Wilson, et al. 1977).

Paraldehyde was introduced into medicine by Ceruello in 1882 as the second synthetic organic compound to be used as a sedative hypnotic (Wilson, et al. 1977). It is used frequently in delirium tremens and in treatment of psychiatric states characterized by excitement when drugs must be given over a long period of time (Wilson, et al. 1977). It also is administered for intractable pain which does not respond to opiates and for basal and obstetrical anaesthesia (Goodman and Gilman, 1970). It is effective against experimentally induced convulsions and has been used in emergency therapy of tetanus, eclampsia, status epilepticus, and poisoning by convulsant drugs (Goodman and Gilman, 1970).

It is used primarily in medicine, and therefore, the chance of accidental human exposure or environmental contamination is low. However, paraldehyde decomposes to acetaldehyde and acetic acid (Gosselin, et al. 1976); these compounds have been found to be toxic. In this sense, occupational exposure or environmental contamination is possible. Since paraldehyde is prepared from acetaldehyde by polymerization in the presence of an acid catalyst, there exists a potential for adverse effects, although none have been reported in the available literature.

II. EXPOSURE

No monitoring data are available to indicate ambient air or water levels of the compound. Human exposure to paraldehyde from ingestion cannot be assessed, due to a lack of monitoring data. No data on dermal exposure of humans were found in the available literature.

III. PHARMACOKINETICS

Paraldehyde is rapidly absorbed from the gastrointestinal tract and parenteral sites. Following oral administration to rats, the maximum concentration in the brain is reached within 30 minutes (Figot, et al. 1953). A significant percentage is excreted unchanged through the lungs. Lang, et al. (1969) reported that human subjects given unspecified oral doses exhaled 7 percent of the administered dose within 4 hours. Only traces are observed in the urine; the rest is metabolized by the liver. There is indirect evidence that paraldehyde is depolymerized to acetaldehyde in the liver, then oxidized by aldehyde dehydrogenase to acetic acid which, in turn, is ultimately metabolized to carbon dioxide and water in mice (Hitchcock and Nelson, 1943).

No data on bioaccumulation of paraldehyde were found in the available literature. Based on the evidence of metabolism above, however, significant bioaccumulation would appear unlikely.

IV. EFFECTS

A. Carcinogenicity

Paraldehyde has been designated a "suspect carcinogen" (NIOSH, 1978), although no increase in neoplasms was observed in the mouse-skin painting study (Row and Salaman, 1955), which was cited by NIOSH.

B. Mutagenicity, Teratogenicity and Other Reproductive Effects.

Pertinent data could not be located in the available literature.

C. Chronic Toxicity

In low doses (4-8 ml), paraldehyde has found use as a therapeutic agent. However, if used for a prolonged period of time, intoxication results in tolerance and dependence. Paraldehyde addiction resembles alcoholism; withdrawal may result in delirium tremens and vivid hallucinations (Goodman and Gilman, 1970).

Acidosis, bleeding gastritis, muscular irritability, azotemia, oliguria, albuminuria, leukocytosis, fatty changes in the liver and kidney with toxic hepatitis and nephrosis, pulmonary hemorrhages, edema, and dilation of the right heart have all been observed in cases of chronic paraldehyde poisoning. Metabolic acidosis is a manifestation of paraldehyde intoxication in the paraldehyde addict. The etiology of the acidosis is uncertain (Beier, et al. 1963).

D. Acute Toxicity

Figot, et al. (1953) reported an oral LD_{50} of 1.65 g/kg for paraldehyde in rats. These investigators reported that the level of paraldehyde in the brain was predictive of the degree of toxicity. The median brain concentration lethal to rats was 47 mg percent.

In humans, therapeutic oral doses of 4-8 ml induce sleep. At this dose, little effect on respiration or blood pressure is seen. There appears to be little margin of safety, and slight increases in dosage may result in poisoning. The poisoned patient commonly exhibits very rapid, labored respiratory movements (Goodman and Gilman, 1970). Accompanying the rapid respiration is a marked depression of blood pressure which persists for several hours. Degenerative changes in the kidney and liver have also been observed (Kirk and Othmer, 1979). Unfortunately, it is not absolutely certain whether these effects are due to paraldehyde or to its decomposition products, acetaldehyde and acetic acid.

Toxic doses of unspecified amounts, given intravenously, cause diffuse, massive pulmonary hemorrhages and edema, as well as dilation of the right heart. Adverse effects, as seen in cases of severe acute paraldehyde intoxication, resemble those seen in chronically exposed individuals, e.g., addicts.

Metabolic acidosis is also found in the severe acute cases. Hayward and Boshell (1957) produced metabolic acidosis and other toxic effects, including pulmonary edema in dogs, by administering unspecified amounts of deteriorated paraldehyde through gastric tubes over a period of 18 hours. In this case it is uncertain whether the paraldehyde or the deteriorated product was the cause of the observed effects. The same is true in another study where a deteriorated product (40 percent acetic acid) produced sudden death with intense corrosion of buccal mucosa and upper air passages. Rectal administration (a common route in therapeutic settings) in another poisoning victim caused great pain and sloughing of rectal mucosa (Gosselin, et al. 1976).

High concentrations (unspecified) depressed cholinergic junctions in frogs, apparently by reducing the amount of acetylcholine liberated from nerve endings (Nicholls and Quillam, 1956; Quillam, 1959).

The lethal dose in humans is disputable. Less than one ounce by mouth has been shown to be lethal in some cases, while others have tolerated four ounces. Death results from respiratory failure preceded by prolonged and profound coma (Goodman and Gilman, 1970).

Paraldehyde has been used in obstetrics; however, it readily crosses the placental barrier and appears in the fetal circulation. Undesirable effects, including delay in respiratory movements, have been

observed in neonates following administration to the mother during labor (Goodman and Gilman, 1970). Consequently, paraldehyde finds little or no use in obstetrics today.

The lowest dose of paraldehyde reported to produce any toxic effect (unspecified) in humans is 121 mg/kg. Oral LD_{50} values have been reported for the following species: rats, 1530 mg/kg; rabbits, 3304 mg/kg; and dogs, 3500 mg/kg. NIOSH (1978) has reported the lowest lethal inhalation concentration to be 2000 ppm.

V. AQUATIC TOXICITY

Data concerning the effects of paraldehyde on aquatic organisms were not found in the available literature.

VI. EXISTING GUIDELINES AND STANDARDS

No exposure limits or standards were found in the available literature to exist for air or water.

References

Beier, L., et al. 1963. Metabolic acidosis occurring during paraldehyde intoxication. Chem. Abst. 59: 1022.

Figot, P., et al. 1953. Estimation and significance of paraldehyde levels in blood and brain. Chem. Abst. 47: 660.

Goodman, L. and A. Gilman. 1970. The Pharmacological Basis of Therapeutics. 4th ed. MacMillan Co., New York.

Gosselin, R.E., et al. 1976. Clinical Toxicology of Commercial Products. Williams and Wilkins Co., Baltimore, Maryland.

Hayward, J. and B. Boshell. 1957. Paraldehyde intoxication with metabolic acidosis. Am. Jour. Med. 23: 965.

Hitchcock, P. and E. Nelson. 1943. The metabolism of paraldehyde: II. Jour. Pharmac. Exp. Ther. 79: 286.

Kirk, R.E. and D.F. Othmer. 1979. Encyclopedia of Chemical Technology. John Wiley and Sons, New York.

Lang, D., et al. 1969. Data of pulmonary excretion of paraldehyde in man. Chem. Abst. 71: 202.

Nicholls, J. and J. Quillam. 1956. Mechanism of action of paraldehyde and methylpentynol on neuromuscular transmission in the frog. Chem. Abst. 50: 13295.

National Institute for Occupational Safety and Health. 1978. Suspected Carcinogens. A Subfile on the Registry of Toxic Effects of Chemical Substance. U.S. Department of Health, Education and Welfare, Cincinnati, Ohio.

Quillam, J. 1959. Paraldehyde and methylpentynol and ganglionic transmission. Chem. Abst. 53: 20562.

Row, .F.J.C. and M.H. Salaman. 1955. Further studies on incomplete carcinogenesis: Triethylene melamine (TEM), 1,2-benzanthracene, and β-propiolactone as initiators of skin tumor formation in the mouse. Brit. Jour. Cancer (London). 9: 177.

Verschueren, K. 1977. Handbook of Environmental Data on Organic Chemicals. Van Nostrand Reinhold Company, New York.

Wilson, C., et al. (ed.) 1977. Textbook of Organic Medicinal and Pharmaceutical Chemistry. J.B. Lippincott Co., Philadelphia, Pa.

No. 141

Pentachlorobenzene

Health and Environmental Effects

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WASHINGTON, D.C. 20460

APRIL 30, 1980

-1666-

DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

PENTACHLOROBENZENE

Summary

Oral feeding of pentachlorobenzene to pregnant rats has produced developmental effects and decreased body weights in fetuses. No adverse reproductive or developmental effects were seen in mice following maternal administration of the compound orally.

There is no information available on the mutagenic effects of pentachlorobenzene.

A single study has alluded to carcinogenic effects of pentachlorobenzene in mice and lack of carcinogenic effects in dogs and rats. The details of this study were not available for evaluation.

Reported 96-hour LC_{50} values for the bluegill, mysid shrimp, and sheepshead minnow range from 250 to 830 µg/l. Daphnia is considerably less sensitive. Studies with algae, with 96-hour EC_{50} values based on chlorophyll a concentration, have reported values ranging from 2,000 to 7,000 µg/l. The steady-state bioconcentration factor for the bluegill is 1,800.

I. INTRODUCTION

Pentachlorobenzene, CAS registry number 608-93-5, is a colorless crystalline solid with a pleasant aroma. It is produced mainly as a byproduct of other chlorobenzenes and has the following physical and chemical properties (Windholz, 1976; Weast, 1972; Hawley, 1971):

Formula:	C_6HCl_5
Molecular Weight:	250.34
Melting Point:	86^oC
Boiling Point:	277^oC
Density:	$1.8342^{16.5}$
Solubility:	Soluble in carbon disulfide, chloroform, and hot alcohol, insoluble in water

Pentachlorobenzene is used primarily as a precursor in the synthesis of the fungicide pentachloronitrobenzene, and as a flame retardant.

II. EXPOSURE

A. Water

Burlingame (1977) has identified pentachlorobenzene in the effluent from a wastewater treatment plant in southern California. Access to water can occur by industrial discharge or from the degradation of other organochlorine compounds.

B. Food

Pentachlorobenzene has been detected in plants (Balba and Saha, 1974; Kohli, et al. 1976a) and in animal fat (Stijve, 1971; Saha and Burrage, 1976; Greve, 1973), and was shown to arise from the metabolic breakdown of lindane or other organochlorine compounds. The U.S. EPA (1979) has estimated the weighted average bioconcentration factor for pentachlorobenzene to be 7,800 for the edible portions of fish and shellfish consumed by Americans. This estimate is based on steady-state bioconcentration studies in bluegills.

C. Inhalation

The primary site for inhalation exposure could be the workplace in industries utilizing or producing pentachlorobenzene.

D. Dermal

Pertinent data could not be located in the available literature.

III. PHARMACOKINETICS

A. Absorption

From studies with rabbits it would appear that pentachlorobenzene is very poorly absorbed from the gastrointestinal tract (Parke and Williams, 1960).

B. Distribution

The distribution of pentachlorobenzene favors retention in the fat (Parke and Williams, 1960). Khera and Villeneuve (1975) have found widespread tissue distribution of the compound following oral administration to pregnant rats and accumulation in fetal tissues.

C. Metabolism

There appear to be some qualitative and quantitative differences between species in the metabolism of pentachlorobenzene. In the rat and rabbit, pentachlorobenzene was shown to be metabolized to a variety of isomers of tetrachlorophenol, with the amount of unchanged pentachlorobenzene excreted in the urine of the rabbit being one percent (Kohli, et al. 1976b), and in the rat being nine percent (Koss and Koransky, 1977). Kohli and coworkers (1976b) suggest that the dechlorination hydroxylation step to the tetrachlorophenol derivative proceeds through an arene oxide intermediate.

D. Excretion

In rats and rabbits urinary excretion of metabolites or unchanged pentachlorobenzene predominated. Rozman, et al. (1978) found the biological half-life of pentachlorobenzene to be two to three months in rhesus monkeys.

After 40 days, ten percent of the total dose was secreted in the urine; of this, 58 percent was pentachlorophenol. After the same period, about 40 percent of the dose was excreted in the feces, 99 percent as pentachlorobenzene. The authors suggest that biliary excretion was occurring.

IV. EFFECTS

A. Carcinogenicity

There is one report, which could not be critically evaluated, which alludes to pentachlorobenzene being carcinogenic in mice but not in rats or dogs (Preussman, 1975).

B. Mutagenicity

Pertinent data could not be located in the available literature.

C. Teratogenicity

Rats receiving 50, 100, and 200 mg/kg pentachlorobenzene on days 6 to 15 of gestation had pups with increased suprauni ribs at all doses (Khera and Villeneuve, 1975). The high dose also produced sternal defects consisting of unossified or nonaligned sternabrae with cartilagenous precursors present. The authors did not consider these defects to be teratogenic.

D. Other Reproductive Effects

Oral administration of pentachlorobenzene (50 or 100 mg/kg) to pregnant mice on days 6 to 15 of gestation produced no teratogenic or adverse reproductive effects (Courtney, et al. 1977).

E. Chronic Toxicity

Pertinent data could not be located in the available literature.

V. AQUATIC TOXICITY

A. Acute

The U.S. EPA (1978) reported 96-hour LC_{50} values for the bluegill (Lepomis macrochirus) exposed to pentachlorobenzene to be 250 µg/l.

The 48-hour EC_{50} value reported for Daphnia magna is 5,280 µg/l (U.S. EPA, 1978). For the saltwater species, sheepshead minnow (Cyprinodon variegatus) and mysid shrimp (Mysidopsis bahia), the determined 96-hour LC_{50} values are 830 and 160 µg/l, respectively.

B. Chronic

Pertinent data could not be located in the available literature.

C. Plant Effects

The reported 96-hour EC_{50} value for Selenastrum capricornatum based on chlorophyll a concentration is 6,780 µg/l (U.S. EPA, 1978). For the marine alga Skeletonema costatum, a 96-hour EC_{50} value on the same basis is 1,980 ug/l (U.S. EPA, 1978).

D. Residue

After a 28-day exposure, the steady-state bioconcentration factor for the bluegill for pentachlorobenzene is 1,800. The half-life is greater than seven days (U.S. EPA, 1978).

VI. EXISTING GUIDELINES AND STANDARDS

A. Human

The U.S. EPA (1979) has drafted a criterion of 0.5 µg/l for the protection of human health.

B. Aquatic

No criteria have been developed or proposed to protect aquatic organisms from pentachlorobenzene toxicity due to the lack of pertinent data.

REFERENCES

Balba, M.H. and J.G. Saha. 1974. Metabolism of Lindane--^{14}C by wheat plants grown from treated seed. Environ. Let. 7: 181.

Burlingame, A.L. 1977. Assessment of the trace organic molecular composition of industrial and municipal wastewater effluents by capillary gas chromatography/real time high resolution mass spectrometry: a preliminary report. Ecotoxicol. Environ. Saf. 1: 111.

Courtney, K.D., et al. 1977. Teratology study of pentachlorobenzene in mice: no teratogenic effect at 50 or 100 mg/kg/day from day 6 to day 15 of gestation. IRCS Med. Sci. 5: 587.

Greve, P.A. 1973. Pentachlorobenzene as a contaminant of animal feed. Meded. Fac. Lanbouwwet Rijksuniv Gent. 38: 775.

Hawley, G.G. (ed.) 1971. The Condensed Chemical Dictionary. 8th ed., Van Nostrand Reinhold Co., New York.

Khera, K.S. and D.C. Villeneuve. 1975. Teratogenicity studies on halogenated benzenes (pentachloro-, pentachloronitro-, and hexabromo-) in rats. Toxicology. 5: 117.

Kohli, J., et al. 1976a. Balance of conversion of carbon-14 labeled lindanes in lettuce in hydroponic culture. Pestic. Biochem. Physiol. 6: 91.

Kohli, J., et al. 1976b. The metabolism of higher chlorinated benzene isomers. Can Jour. Biochem. 54: 203.

Koss, G. and W. Koransky. 1977. Pentachlorophenol in different species of vertebrates after administration of hexachlorobenzene and pentachlorobenzene. Pentachlorophenol, K.R. Rao, (ed.), Plenum Press, New York. p. 131.

Parke, D.V. and R.T. Williams. 1960. Studies in detoxification LXXXI. Metabolism of halobenzenes: (a) Penta- and hexachlorobenzene: (b) Further observations of 1,3,5-trichlorobenzene. Biochem. Jour. 74: 1.

Preussman, R. 1975. Chemical carcinogens in the human environment. Hand. Allg. Pathol. 6: 421.

Rozman, K., et al. 1978. Metabolism and body distribution of pentachlorobenzene after single oral dose in rhesus monkeys. Toxicol. Appl. Pharmacol. 45: 283.

Saha, J.G. and R.H. Burrage. 1976. Residues of lindane and its metabolites in eggs, chicks and body tissues of hen pheasants after ingestion of Lindane carbon-14 via treated wheat seed or gelatin capsules. Jour. Environ. Sci. Health Bull. 67.

Stijve, T. 1971. Determination and occurrence of hexachlorobenzene residues. Mitt. Geb. Lebenmittelunters. Hyg. 62: 406.

U.S. EPA. 1978. In-depth studies on health and environmental impacts of selected water pollutants. Contract No. 68-01-4646, U.S. Environ. Prot. Agency.

U.S. EPA. 1979. Chlorinated Benzenes: Ambient Water Quality Criteria. (Draft)

Weast, R.C. 1971. Handbook of Chemistry and Physics. 53rd ed., Chemical Rubber Company, Cleveland, Ohio.

Windholz, M. (ed.) 1976. The Merck Index. 9th ed., Merck and Co., Inc., Rahway, New Jersey.

No. 142

Pentachloronitrobenzene

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

-1675-

DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

SPECIAL NOTATION

U.S. EPA's Carcinogen Assessment Group (CAG) has evaluated pentachloronitrobenzene and has found sufficient evidence to indicate that this compound is carcinogenic.

DISCLAIMER

The mention of company trade names or products does not constitute endorsement by the U.S. EPA or the Federal government.

PENTACHLORONITROBENZENE

Summary

Increased incidence of hepatoma formation was reported in hybrid mice treated with pentachlorobenzene (PCNB). PCNB was found to be mutagenic in the hcr-strain of Escherichia coli ochre, but not in another E. coli strain.

PCNB containing a number of contaminants produced renal agenesis and cleft palate in C57Bl/6 mice, cleft palate in CD-1 mice, but was not teratogenic in CD rats. Purified PCNB (less than 20 ppm hexachlorobenzene) resulted in fewer cleft palates in the fetuses. No significant teratogenic effects in rats were detected at dosages as high as 1,563 ppm. In a three generation study using doses as high as 500 ppm, PCNB had no significant effects on the reproduction of rats.

Acute toxicity data for fish were: a 96-hour LC_{50} in bluegill from 0.29 to 0.38 ppm and a 96-hour LC_{50} of 0.31 ppm in rainbow trout.

I. INTRODUCTION

This profile is based on the Initial Scientific Review of Pentachloronitrobenzene, PCNB, plus relevant scientific research articles published subsequent to that document (U.S. EPA, 1976).

Pentachloronitrobenzene (molecular weight, 295.34) is a pale yellow-to-white solid, depending on purity, that melts between 142° and 146°C, has a boiling point of 328°C at 760 mm Hg, and a density of 1.718 g/cm^3 at 25°C. Reported vapor pressure values for PCNB are: 1.16×10^{-5} mm Hg at 10°C, 5.0×10^{-5} mm Hg at 20°C, and 11.3×10^{-5} mm Hg at 25°C (U.S. EPA, 1976). PCNB has a relative vapor density (air = 1) of 10.2 (Verschueren, 1977). Water solubility of PCNB is 0.44 mg/l at 20°C and 2 mg PCNB will dissolve in one liter ethanol at 25°C. PCNB is freely soluble in carbon disulfide, benzene, chloroform, ketones, and aromatic and chlorinated hydrocarbons, and slightly soluble in alkanols (U.S. EPA, 1976).

PNCB is primarily registered as a soil fungicide for a wide variety of crops and is also used as a seed-treatment fungicide. It is effective against bunt of wheat, Botrytis, Rhizoctonia, and Sclerotinia spp. There are no current nonagricultural uses of PCNB (U.S. EPA, 1976). PCNB is manufactured domestically under the trade name Terraclor® with an estimated annual production in 1971 of 3 million pounds (U.S. EPA, 1972). According to the Olin Corporation (1974), 60 to 70 percent of the PCNB produced will be used in the United States. The United States has imported from 20,000 to 132,000 lbs. between 1966 and 1969 (U.S. EPA, 1976). PCNB manufactured in Europe is marketed under the common name Quintozene (Dejonckheere, et al.

1976). It may be worth noting that commercial PCNB fungicides contain impurities such as hexachlorobenzene, pentachlorobenzene and tetrachloronitrobenzene, which may be more hazardous than PCNB itself (Dunn, et al. 1978; Simon, et al. 1979).

No data are available for the disassociation of PCNB in aqueous systems. Crosby and Hamadmad (1971) studied the photoreduction of PCNB. The compound remained unchanged in sunlight, probably excluding photolysis as a major route of environmental degradation. At temperatures above 328°C, some decomposition of PCNB has been noted (U.S. EPA, 1976).

PCNB can be biodegraded by pure cultures of actinomycetes and filamentous fungi during their active growth phase (Chacko, et al. 1966).

II. EXPOSURE

PCNB is prepared by either chlorination or nitration reactions. The reaction temperature for the chlorination process is 60 to 70°C. Although this reaction is well below the boiling point of PCNB, atmospheric emissions are possible because of PCNB's relatively high vapor pressure. Furthermore, there exists a potential for environmental release via wastewater effluents at the manufacturing sites. No monitoring data are available for ambient air or water levels of the compound. The major source of environmental contamination is through its application as a fungicide. In the United States, PCNB is used primarily on cotton and peanut crops. Geographic use distribution is mainly concentrated west of the Mississippi River (U.S. EPA, 1976). Carey, et al. (1979) in their study of pesticide residues in the soil detected PCNB in only three of the 1,483 sample sites. The detected residue concentration was from 0.22 to 2.61 ppm. It should be noted, however, that their study was primarily confined to the eastern United States.

Routes of human exposure to PCNB include water, air, contaminated foods, and fish. Casanova and Dubroca (1973) studied the residues of PCNB found in lettuce grown in soil treated with the fungicide. Residue values were 0.73 ppm (15 kg PCNB/ha) and 1.56 ppm (45 kg PCNB/ha). Goursaud, et al. (1972) detected PCNB contamination in endive roots. Since the main objective of their study was the uptake of hexachlorobenzene, actual PCNB concentrations were not noted. However, in a subsequent experiment Goursaud, et al. (1972) fed cows endive roots containing 2.16 ppm PCNB. PCNB residues found in the cows' milk were negligible. Bioaccumulation of PCNB in White Leghorn cockerels (Dunn, et al. 1978) was also found to be negligible (accumulation ratio 0.001 = tissue concentration/dietary concentration). Broiler chickens (Reed, et al. 1977) did not accumulate PCNB or its metabolites to any appreciable extent (0.002 ppm). No additional information on the levels of PCNB in foods is available.

Bioaccumulation data on PCNB were not found in the literature for aquatic organisms. Ko and Lockwood (1968) reported that the mycelium of fungi had accumulated a concentration of PCNB seven times that of the surrounding soil.

III. PHARMACOKINETICS

A. Absorption

Absorption data on PCNB were restricted to oral administration involving three test species. Betts, et al. (1955) reported that 60 percent of the oral dosage was not absorbed from the gastrointestinal tract in rabbits. Two subsequent studies, however, report that PCNB is readily absorbed from the gastrointestinal tract and/or metabolized by gut flora to another compound and then almost fully absorbed. Kögel, et al. (1979) found that PCNB was readily and almost completely absorbed from the gastrointestinal

tract of Rhesus monkeys. After a single dose of 2 mg/kg given in methyl cellulose suspension, only 7.4 percent of the administered amount was excreted as unmetabolized PCNB in the feces. When 91 mg/kg PCNB was given in sesame oil, only 4.3 percent of the dose was excreted unmetabolized. Uptake occurs mainly by the portal venous route, with little involvement of the lymphatic system, bringing the absorbed PCNB directly to the liver where biotransformation can begin. Studies of Comet Red and White Leghorn chickens yielded similar results. Chickens fed 300 ppm PCNB in laying mash for sixteen weeks excreted only 1.1 ppm PCNB (Simon, et al. 1979).

B. Distribution

Several studies have been conducted on the distribution and storage of ingested PCNB. Due to rapid metabolism and elimination, this compound shows very little accumulation in body tissues. Betts, et al. (1955) used rabbits and Borzelleca, et al. (1971) employed beagles and rats. In neither experiment was PCNB detected in liver, kidney, muscle, or adipose tissue. Other studies have indicated very low concentrations of PCNB in various tissues. Simon, et al. (1979) found PCNB at concentrations of 0.85 ppm in fat and 0.005 ppm in egg whites of chickens fed 300 ppm PCNB for sixteen weeks. Other tissues examined contained no detectable levels of PCNB. Dunn, et al. (1978) found the highest tissue residues of PCNB in adipose tissue (1.14 and 1.87 ppm) and the gizzard (1.60 and 0.84 ppm) in chickens given 100 ppm and 1,000 ppm PCNB in feed, respectively. Leg and breast muscles and heart, kidney, and liver contained very low (0.16 to 0.07 ppm) or trace amounts of PCNB.

Concentrations of PCNB in various organs of Rhesus monkeys after chronic feeding of 2 ppm PCNB in the daily diet were (in ppm): blood, 0.07; muscle, 0.01; brain, 0.03; liver, 0.19; kidney, 0.14; adrenal cortex, 0.08;

thymus, 0.20; lymph nodes (large intestine), 0.12; bone marrow, 0.13; and omental fat, 0.21 (Mueller, et al. 1978). Kögel, et al. (1979) found the highest concentration of PCNB and/or its metabolites occurring in bile (7.73 ± 0.2 ppm in males and 3.72 ± 0.05 in females) after feeding of 2 ppm PCNB for 70 days.

C. Metabolism

PCNB metabolism has been studied in rats, dogs, cows, and rabbits. Pentachloroaniline and methyl pentachlorophenyl sulfide are the major metabolites. Tissue retention of these compounds is found primarily in body fat with minimal concentrations found in muscle (U.S. EPA, 1976). Two major pathways for the biotransformation of PCNB in Rhesus monkeys are: 1) the reduction of the nitro-moeity to the corresponding aniline, and 2) the cleavage of the C-N bond, presumably via conjugation with sulfur-containing amino acids (Kögel, et al. 1979).

D. Excretion

PCNB and its metabolites are excreted mainly in the urine and feces. Mueller, et al. (1978) reported that Rhesus monkeys excreted almost 80 percent of the ingested PCNB within 5 days; of the excreted radioactivity, 91.2 percent was in the form of metabolites.

IV. EFFECTS

A. Carcinogenicity

Very little information on possible carcinogenic effects of PCNB was found in the available literature. Courtney, et al. (1976) cite one study which found PCNB to be carcinogenic in a hybrid mouse with an increased incidence of hepatoma formation. Levels of exposure were not given.

B. Mutagenicity

PCNB was found to be mutagenic in the hcr-strain of Escherichia coli B/r ochre, but not in another E. coli strain. In the host-mediated assay in mice, no significant increase in mutation rates in Salmonella typhimurium and Serratia morcescens was observed after subcutaneous injection of PCNB. The compound also gave negative results in spot tests (U.S. EPA, 1976).

C. Teratogenicity and Other Reproductive Effects

PCNB was administered to pregnant rats by intubation on days 6 and 15 of gestation at dosages from 100 to 1,563 ppm. Fetuses were examined for gross malformations. No significant effects on the number of corpora lutae, the position and numbers of dead or resorbed fetuses, or the fetal weights and sex ratios were observed at any dose level. No significant skeletal or soft tissue anomalies were reported in the fetuses (U.S. EPA, 1976).

A three-generation study with groups of rats fed diets containing 0, 5, 50 or 500 ppm (Olin technical PCNB) showed no significant effects on fertility, gestation, viability, lactation, rats born per litter, or rats weaned per litter or their average weaning weights (U.S. EPA, 1976).

PCNB containing a number of contaminants, however, produced renal agenesis and cleft palate in C56Bl/6 mice and cleft palate in CD-1 mice, but was not teratogenic in CD rats. Purified PCNB (less than 20 ppm hexachlorobenzene) resulted in few cleft palates in fetuses (Courtney, et al. 1976).

D. Chronic Toxicity

PCNB does not appear to be chronically toxic when administered in feeding studies. Rhesus monkeys given 2 ppm or 91 ppm PCNB in their diet for 70 days were monitored for clinical chemistry and hematology parameters throughout the study. These parameters remained unchanged, indicating that

organ function and hematopoiesis was not affected by PCNB or its metabolites (Kögel, et al. 1979).

White Leghorn chickens fed PCNB at concentrations up to 1,000 ppm for the first 8 weeks of life did not develop tissue lesions and hens fed up to 1,000 ppm for 35 weeks failed to develop histopathological changes (Dunn, et al. 1978).

Kögel, et al. (1979) cite studies which report that the toxic effect of Terraclor^R in rats and dogs is limited to liver enlargement due to hepatocellular hypertrophy. Also, cats had increased methemoglobin levels after moderate and high doses of Terraclor^R and dogs fed a very high dose (5,000 ppm) of PCNB of undetermined purity for two years were found to have reduced hematopoiesis. These effects, however, may be due to the presence of hexachlorobenzene as a contaminant (Kögel, et al. 1979).

E. Acute Toxicity

Cholakis, under contract with the U.S. EPA, administered single doses of pentachloronitrobenzene by gavage to several species of microtine rodents (voles) (U.S. EPA, 1978). The acute oral LD_{50} values in male and female M. montanus were 4,194 mg/kg and 3,717 mg/kg, respectively. In M. ochrogaster, M. canicaudus, and M. pennsylvanicus, values were greater than 5,000 mg/kg for both sexes. Toxicologic signs observed were some piloerection, loss of righting reflex and lachrymation. Most signs disappeared after 24 hours. Most deaths occurred within two to six days of dosing.

V. AQUATIC TOXICITY

A. Acute Toxicity

In static, acute toxicity bioassays using various PCNB formulations, bluegill (Lepomis macrochirus) had 96-hour median lethal concentration (LC_{50}) values ranging from 0.29 to 0.38 ppm. Rainbow trout (Salmo

gairdneri) had a 96-hour LC_{50} value of 0.31 ppm (U.S. EPA, 1976).

B. Chronic Toxicity, Plant Effects and Residues

Pertinent data could not be located in the available literature.

VI. EXISTING GUIDELINES AND STANDARDS

No guidelines or standards were located in the available literature for humans or aquatic life.

REFERENCES

Betts, J.J., et al. 1955. The metabolism of PCNB and 2,3,4,6-tetrachloronitrobenzene and the formulation of meriapturic acids in rabbit. Biochem. Jour. 61: 611.

Borzelleca, J.F., et al. 1971. Toxicologic and metabolic studies on PCNB. Toxicol. Appl. Pharmacol. 18: 522.

Carey, A.E., et al. 1979. Pesticide residue levels in soils and crops from 37 states, 1972. Pest. Monit. Jour. 12: 209.

Casanova, M. and J. Dubroca. 1973. Etude des residues de divers fongicides utilises dans le traitement des cultures de laitures en serre. Ann. Phytopathol. 5: 65.

Chacko, C.I., et al. 1966. Chlorinated hydrocarbon pesticides: degradation by mirobes. Science 154: 893.

Courtney, K.D., et al. 1976. The effects of pentachloronitrobenzene, hexachlorobenzene, and related compounds on fetal development. Toxicol. Appl. Pharmacol. 35: 239.

Crosby, D.G. and N. Hamadmad. 1971. The photoreduction of pentachlorobenzenes. Jour. Agr. Food Chem. 19: 1171.

Dejonckheere, W., et al. 1976. Residues of Quinotozene. Pest. Monit. Jour. 10: 68.

Dunn, J.S., et al. 1978. The accumulation and elimination of tissue residues after feeding PCNB to White Leghorn cockerels. Poultry Sci. 57: 1533.

Goursaud, J., et al. 1972. Sur la pollution du lait par les residues HCB. Industries Alimientoires et Agr. 89: 31.

Ko, W.H. and J.L. Lockwood. 1968. Accumulation and concentration of chlorinated hydrocarbon pesticides by microorganisms in soil. Can. Jour. Microbiol. 14: 1075.

Kögel, W., et al. 1979. Biotransformation of PCNB - ^{14}C in Rhesus monkeys after single and chronic oral administration. Chemosphere 8: 97.

Mueller, W.F., et al. 1978. Comparative metabolism of HCB and PCNB in plants, rats, and Rhesus monkeys. Ecotoxicol. Environ. Safety. 2: 437.

Olin Corporation. 1974. Agricultural Products Division, Little Rock, Ark. Personal communication to Econ. Branch, Criteria and Evaluation Division, Office of Pesticide Programs, U.S. EPA.

Reed, E.L., et al. 1977. Tissue residues from feeding PCNB to broiler chickens. Toxicol. Appl. Pharmacol. 42: 433.

Simon, G.S., et al. 1979. Distribution and clearance of pentachloronitrobenzene in chickens. Toxicol. Appl. Pharmacol. 50: 401.

U.S. EPA. 1972. The pollution potential in pesticide manufacturing. Midwest Research Institute. EPA Rep. No. OWP-TS-00-72-04. NTIS PB-213 782.

U.S. EPA. 1976. Initial Scientific Review of PCNB. Office of Pesticide Programs, Washington, D.C. EPA-540/1-75-016.

U.S. EPA. 1978. Study of the chemical and behavioral toxicology of substitute chemicals in microtine rodents. EPA-600/3-78-082. Midwest Research Institute, Kansas City, MO.

Verschueren, K. 1977. Handbook of Environmental Data on Organic Chemicals. Van Nostrand Reinhold Co., New York.

No. 143

Pentachlorophenol

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

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-1690-

DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

PENTACHLOROPHENOL

SUMMARY

Pentachlorophenol has shown no evidence of carcinogenicity. Evidence for mutagenicity is equivocal. Pentachlorophenol is teratogenic in experimental animals at levels which produce maternal or fetal toxicity. Adverse health effects have been minimal in workers chronically exposed to pentachlorophenol. Relatively high levels of continous exposure produce muscle weakness, headache, anorexia, abdominal pain, weight loss, and irritation of skin, eyes, and respiratory tract. Pentachlorophenol is a strong uncoupler of oxidative phosphorylation.

Pentachlorophenol has been demonstrated to be acutely toxic to freshwater salmonids at levels as low as 37 µg/l. Comparable levels of toxicity were observed for marine fish. Freshwater plants were also highly susceptible to the action of this chemical with effective concentrations as low as 7.5 µg/l.

PENTACHLOROPHENOL

I. INTRODUCTION

This profile is based on the Ambient Water Quality Criteria Document for Pentachlorophenol (U.S. EPA, 1979).

Pentachlorophenol (PCP; C_6Cl_5OH; molecular weight 266.35) has the following physical and chemical properties (Stecher, 1968; Natl. Fire Prot. Assoc., 1973; Sax, 1975; Spector, 1956; Weast, 1975-76):

Melting Point Range	190 - 191° C
Boiling Point Range	309 - 310° (decomposes)
Vapor Pressure	0.12 mm Hg at 100° C
Solubility	Water: 14 mg/l at 20° C

Commercial preparations of pentachlorophenol contain "caustic insolubles" or "nonphenolic neutral impurities" such as octachlorodibenzofurans and tetra-, penta-, hexa-, hepta-, and octachlorodibenzo-p-dioxins (Johnson, et al. 1973; Schwetz, et al. 1974). In addition, commercial pentachlorophenol contains three to ten percent tetrachlorophenol (Goldstein, et al. 1977; Schwetz, et al. 1978).

Pentachlorophenol is a commercially produced bactericide, fungicide, and slimicide used primarily for the preservation of wood, wood products, and other materials. As a chlorinated hydrocarbon, PCP is also used as a herbicide, insecticide, and molluscicide (U.S. EPA, 1979).

Pentachlorophenol and its sodium salt are widely disseminated in the environment (U.S. EPA, 1979). Pentachlorophenol undergoes photochemical degradation in solution in the presence of sunlight (Mitchell, 1961; Hanadmad, 1967; Wong and Crosby, 1977) and is reported to persist in warm moist soils for a period

of 12 months (Harvey and Crafts, 1952). In laboratory experiments, some microorganisms have been reported to metabolize pentachlorophenol and its sodium salt (Watanabe, 1973; Suzuki and Nose, 1971; Cserjesi, 1967; Reiner, et al. 1977).

II. EXPOSURE

Residues of pentachlorophenol have been found in food, water and human tissues. Pentachlorophenol levels of 0.06 µg/l in finished drinking water prepared from untreated water containing 0.17 µg/l have been reported (Buhler, et al. 1973). Pentachlorophenol has been detected in 13 of 240 food composites at levels of 0.01 to 0.04 mg/kg (Johnson and Manske, 1977). The calculated daily dietary exposure is one to six µg/person/day (Duggan and Corneliusen, 1972).

The U.S. EPA (1979) has estimated the weighted average bioconcentration factor of pentachlorophenol at 58 for the edible portion of fish and shellfish consumed by Americans. This estimate is based on measured steady-state bioconcentration studies in goldfish (*Carassius auratus*), bluegill (*Lepomis macrochirus*), eastern oyster (*Crassostrea virginica*), and sheepshead minnow (*Cyprinodon variegatus*).

Inhalation and dermal exposure data for the general population are not available (U.S. EPA, 1979). These routes of exposure are more likely to occur occupationally.

Total body exposures, based on reported urine levels of pentachlorophenol, appear to be in the range of 10-17 µg/person/day for the general population and 1500-4400 µg/person/day for occupational exposures (U.S. EPA, 1979). These values may be

due not only to direct exposure to pentachlorophenol, but also to exposure to hexachlorobenzene (pesticide, fungicide) and lindane (pesticide), which are degraded in part to pentachlorophenol (Yang, et al. 1975; Lui and Sweeney, 1975; Mehendale, et al. 1975; Koss and Koransky, 1978; Karapally, et al. 1973; Engst, et al. 1976).

III. PHARMACOKINETICS

A. Absorption

The half-life for absorption in humans after oral ingestion of pentachlorophenol is 1.3 ± 0.4 hr. In humans, a peak plasma concentration of 0.248 mg/l was observed four hours after ingestion of a 0.1 mg/kg dose (Braun, et al. 1978). Absorption in rats is similar to that found in humans (Braun, et al. 1977).

Pentachlorophenol is readily absorbed through the skin as indicated by its lethality after dermal exposure (Deichmann, et al. 1942; Armstrong, et al. 1969).

B. Distribution

In humans (fatal pentachlorophenol intoxication) and in rats (non-lethal exposure), the highest levels of pentachlorophenol are found in liver, kidney, and blood, with the lowest levels in brain, spleen, and fat (Cretney, 1976; Armstrong, et al. 1969; Braun, et al. 1977; Larsen, et al. 1975).

C. Metabolism

In four male volunteers ingesting 0.1 mg pentachlorophenol/kg, approximately 74 percent of the dose was eliminated in the urine as pentachlorophenol (PCP) and 12 percent as PCP glucuronide; four percent was eliminated in feces as pentachloro-

phenol and PCP glucuronide (Braun, et al. 1978). Rats excrete 75 percent of administered pentachlorophenol as the unchanged PCP, 16 percent as tetrachlorohydroquinone, and nine percent as PCP glucuronide (Braun, et al. 1977). In another study (Ahlborg, 1978), trichloro-p-hydroquinone was found as an additional metabolite of pentachlorophenol in rats. Mice also metabolize pentachlorophenol to tetrachlorohydroquinone (Jakobson and Yllner, 1971).

D. Excretion

In humans and in experimental animals, the primary mode of excretion for pentachlorophenol is in the urine (Diechmann, et al. 1942; Braun, et al. 1977, 1978; Larsen, et al. 1975; Jakobson and Yllner, 1971).

In humans, the plasma pentachlorophenol half-life is 30.2 ± 4.0 hours. The half-lives for elimination of pentachlorophenol and PCP glucuronide from urine are 33.1 ± 4.5 and 12.7 ± 5.4 hours, respectively (Braun, et al. 1978). Elimination of pentachlorophenol by the rat is similar to elimination by humans (Braun, et al. 1977).

The available literature indicates that pentachlorophenol does not accumulate in body tissues to any significant extent (U.S. EPA, 1979). Long term, low level tissue binding has not been adequately studied.

IV. EFFECTS

A. Carcinogenicity

Pentachlorophenol has not shown evidence of carcinogenicity. Pentachlorophenol did not promote papillomas or carcinomas when applied repeatedly to the skin at high concentra-

tions after initiation with dimethylbenzanthracene (Boutwell and Bosch, 1959). Mice receiving commercial pentachlorophenol in the diet throughout their lifespans (about 18 months) did not have a significant incidence of tumors (Innes, et al. 1969). Pentachlorophenol, with low levels of nonphenolic contaminants, was non-carcinogenic when fed to rats for 22 to 24 months (Schwetz, et al. 1978).

B. Mutagenicity

Pentachlorophenol has been shown to be mutagenic in a few test systems. Recrystallized pentachlorophenol increased the frequency of mutations and mitotic gene conversion in Saccharomyces cerevisiae when used at a level (400 mg/l) which resulted in a 59 percent survival rate of test organisms (Fahrig, et al. 1978). Four of the 473 offspring of female mice injected with a single high dose of pure pentachlorophenol during gestation were reported to have changes in hair coat color (spots) of genetic significance (Fahrig, et al. 1978).

No mutagenic activity was detected in male germ cells of Drosophila (Vogel and Chandler, 1974), in the mouse host-mediated assay, in in vitro spot tests (Buselmaier, et al. 1973), or in histidine-required mutants of Salmonella typhimurium (Anderson, et al. 1972).

C. Teratogenicity

Information suggesting pentachlorophenol is a human teratogen was not encountered. Pentachlorophenol of both commercial and purified grades produced fetal anomalies in rats at levels considered to be toxic either to the maternal rat or

to the fetus (Larsen, et al. 1975; Schwetz, et al. 1974; 1978). Abnormalities included subcutaneous edema, dilated ureters, delayed ossification of the skull, skeletal anomalies, dwarfism, exencephaly, macropthalmia, and taillessness.

D. Other Reproductive Effects

In a study in which male and female rats were fed 3 or 30 mg/kg pentachlorophenol continuously starting 62 days before mating, no adverse effects were observed at the 3 mg/kg level. At 30 mg/kg, the following indices were decreased: maternal body weight; percent liveborn pups; 7, 14, 21 day survival; 1, 7, 14, 21 day body weight-pups; 7, 14, 21 day litter size. Selected abnormalities were also seen at this dose.(Schwetz, et al. 1978).

E. Chronic Toxicity

Adverse health effects have been minimal in workers chronically exposed to pentachlorophenol (Klemmer, 1972; Takahashi, et al. 1976). Increased levels of serum enzymes SGOT, SGPT, and LDH, and elevated levels of total bilirubin and creatine phosphokinase were noted, but all levels were still within normal limits. A significantly higher prevalence of gamma mobility C-reactive protein (CRP) was detected in the sera of chronically exposed workers. CRP levels are often elevated in acute states of various inflammatory disorders or tissue damage (Takahashi, et al. 1976). A chronic health effect which has been associated with human exposure to certain types of commercial PCP is chloracne (Baader and Bauer, 1951; Nomura, 1953). Chloracne could have resulted from impurities in the pentachlorophenol; commercial PCP containing high levels of chlorodioxins produced chloracne in the rabbit ear test, while pure pentachlorophenol or penta-

chlorophenol with reduced dioxin content did not (Johnson, et al. 1973).

Chronic intoxication in humans results from relatively high levels of continuous exposure. Symptoms include muscle weakness, headache, anorexia, abdominal pain, and weight loss in addition to skin, eye, and respiratory tract irritation (U.S. EPA, 1979).

Rats fed pentachlorophenol containing low levels of nonphenolic contaminants at daily levels of 1 to 30 mg/kg for eight months (Goldstein, et al. 1977) and 22 to 24 months (Schwetz, et al. 1978) had decreased body weight gains at dosage levels of 30 and 10 mg/kg, respectively. In the 22 to 24 month study, the 30 mg/kg dose resulted in increased serum enzyme SGPT levels and increased specific gravity of the urine.

F. Other Relevant Information

Pentachlorophenol is a strong uncoupler of oxidative phosphorylation (Weinbach and Garbus, 1965; Mitsuda, et al. 1963).

V. AQUATIC TOXICITY

A. Acute Toxicity

The results of 38 freshwater flow-through bioassays reveal a range of 96-hour LC_{50} values of from 63 µg/l for the sockeye salmon (Oncorhynchus nerka) (Webb and Brett, 1973) to 340 µg/l for the fathead minnow (Pimephales promelas) (Ruesink and Smith, 1975). In 19 static assays, LC_{50} values ranged from 37 µg/l for the coho salmon (O. kisutch) to 600 µg/l for the fathead minnow. Five species of salmonids were more sensitive than 4 other species of minnows or centrachids. Freshwater invertebrates displayed LC_{50} values ranging from 310 µg/l to 1,400

µg/l for the tubificid worm (Tubifex tubifex) and were affected by increasing the PH from 7.5 to 9.5. The acute toxicity of pentachlorophenol to saltwater fish ranged from 38 µg/l in a 96-hour static pinfish (prolarvae) (Lagodon rhomboides) assay (Borthwick and Schimmel, 1978) to 442 µg/l for juvenile sheepshead minnows (Cyprinodon variegatus) (Parrish, et al. 1978). For three marine invertebrate species tested, LC_{50} values ranged from 40 to 5,600 µg/l, with the eastern oyster (Crassostrea virginica) being the most sensitive marine invertebrate.

B. Chronic Toxicity

Freshwater chronic studies for fish or invertebrates were not available. A life-cycle chronic test of 151 days in the marine sheepshead minnow produced a chronic value of 64 µg/l (Parrish, et al. 1978). Data for marine invertebrates was not available (U.S. EPA, 1979).

C. Plant Effects

For freshwater plants, the lowest effective concentration was 7.5 µg/l, which resulted in the total destruction of chlorophyll in the alga Chlorella pyrenoidosa after 72 hours. A drastic decrease in cell numbers of the marine alga Monochrysis lutheri was observed after 12 days of exposure to 293 µg/l (Woelke, 1965), and 50 percent inactivation of photosynthesis was seen in kelp (Macrocystis pyrifera) exposed for 4 days to 300 µg/l (Clendenning and North, 1960).

D. Residues

Equilibrium levels of PCP in water and tissues of aquatic organisms are attainable within four days; and when previously exposed marine eastern oysters (Crassostrea virginica)

or freshwater bluegills (Lepomis macrochirus) were held in PCP-free water, a rapid loss of PCP from the organism occurred (Schimmel, et al. 1978; Pruitt, et al. 1977). Bioconcentration factors in marine organisms ranged from 0.26 for the juvenile brown shrimp (Penaeus aztecus) to 78 for the eastern oyster. In freshwater fish, bioconcentration factors of 1,000 for the whole body of the goldfish (Carassius auratus) and of 13 for the muscle tissue of the bluegill have been reported (Kobayashi and Akitake, 1975; Pruitt, et al. 1977).

VI. EXISTING GUIDELINES AND STANDARDS

A. Human

The U.S. EPA (1979) draft criterion for pentachlorophenol in ambient water is 680 ug/l.

The maximum air concentration established by the American Industrial Hygiene Association (1970) is 0.5 mg pentachlorophenol or 0.5 mg sodium pentachlorophenate/m^3 for an 8-hour exposure (TLV). The code of Federal Regulations 21, part 121, paraaph 121:2556 allows up to 50 ppm pentachlorophenol in treated wood which will come in contact with food.

A NOEL in drinking water of 0.021 mg pentachlorophenol/l is suggested by the National Research Council (1977), based on a NOEL of 3 mg/kg in 90 day and 8 month rat studies and an uncertainty factor of 1,000.

B. Aquatic

The draft criterion to protect marine life is 6.2 µg/l as a 24-hour average, not to exceed 14 µg/l at any time. The draft criterion to protect marine life is 3.7 µg/l for a 24-hour average, not to exceed 8.5 µg/l at any time (U.S. EPA, 1979).

PENTACHLOROPHENOL

REFERENCES

Ahlborg, U.D. 1978. Dechlorination of pentachlorophenol in vivo and in vitro. pp. 115-130. In: K.R. Rao (ed.), Pentachlorophenol: Chemistry, pharmacology and environmental toxicology. Plenum Press, New York.

American Industrial Hygiene Association. 1970. Hygienic Guide Series: Pentachlorophenol and sodium pentachlorophenate. Am. Ind. Assoc. Jour. 31: 521.

Anderson, K.J., et al. 1972. Evaluation of herbicides for possible mutagenic properties. Jour. Agri. Food Chem. 20: 649.

Armstrong, R.W., et al. 1969. Pentachlorophenol poisoning in a nursery for newborn infants. II. Epidemiologic and toxicologic studies. Jour. Pediatr. 75: 317.

Baader, E.W. and H.J. Bauer. 1951. Industrial intoxication due to pentachlorophenol. Industr. Med. & Surg. 20: 286.

Borthwick, P.W., and S.C. Schimmmel. 1978. Toxicity of pentachlorophenol and related compounds to early life stages of selected estuarine animals. Pages 141-146 In: K.R. Rao (ed.), Pentachlorophenol: Chemistry, pharmacology and environmental toxicology. Plenum Press, N.Y.

Boutwell, R.K. and K.K. Bosch. 1959. The tumor-promoting action of phenol and related compounds for mouse skin. Cancer Res. 19: 413.

Braun, W.H., et al. 1977. The pharmacokinetics and metabolism of pentachlorophenol in rats. Toxicol. Appl. Pharmacol. 41: 395.

Braun, W.H., et al. 1978. The metabolism/pharmacokinetics of pentachlorophenol in man, and a comparison with the rat and monkey model. Toxicol. Appl. Pharmacol. 45: 135.

Buhler, D.R., et al. 1973. Occurrence of hexachlorophene and pentachlorophenol in sewage and water. Environ. Sci. Technol. 7: 929.

Buselmaier, et al. 1973. Comparative investigations of the mutagenicity of pesticides in mammalian test systems. Mutat. Res. 21: 25.

Clendenning, K.A. and W.J. North. 1960. Effects of wastes on the giant kelp, Macrocystis pyrifera. Pages 82-91 In: Proc. 1st Conf. on waste disposal in the marine environment. Pergamon Press, New York

Cretney, M.J. 1976. Pentachlorophenol death. Bull. T.I.A.F.T. 12 10. In: T.J. Haley, 1977. Human poisoning with pentachlorophenol and its treatment. Ecotoxicol. Environ. Safety (In press).

Cserjesi, A.J. 1967. The adaptation of fungi to pentachlorophenol and its biodegradation. Can. Jour. Microbiol. 13: 1234.

Deichmann, W., et al. 1942. Acute and chronic effects of pentachlorophenol and sodium pentachlorophenate upon experimental animals. Jour. Pharm. Exp. Therap. 76: 104.

Duggan, R.E., and P.E. Corneliussen. 1972. Dietary intake of pesticide chemicals in the United States (III), June 1968-April 1970. Pestic. Monitor. Jour. 5: 331.

Engst, R., et al. 1976. The metabolism of lindane and its metabolites gamma-2,3,4,5,6-pentachlorocyclohexene, pentachlorobenzene and pentachlorophenol in rats and the pathways of lindane metabolism. Jour. Environ. Sci. Health 2: 95.

Fahrig, R., et al. 1978. Genetic activity of chlorophenols and chlorophenol impurities. Pages 325-338 In: K.R. Rao (ed.), Pentachlorophenol: Chemistry, pharmacology and environmental toxicology. Plenum Press, New York.

Goldstein, J.A., et al. 1977. Effects of pentachlorophenol on hepatic drug-metabolizing enzymes and porphyria related to contamination with chlorinated dibenxo-p-dioxins and dibenzofurans. Biochem. Pharmacol. 26: 1549.

Hanadmad, N. 1967. Photolysis of pentachloronitrobenzene, 2,3,5,6-tetrachloronitrobenzene and pentachlorophenol. Ph.D. dissertation. University of California, Davis.

Harvey, W.A. and A.S. Crafts. 1952. Toxicity of pentachlorophenol and its sodium salt in three yolo soils. Hilgardia 21: 487.

Innes, J.R.M., et al. 1969. Bioassay of pesticides and industrial chemicals for tumorigenicity in mice. A preliminary note. Jour. Natl. Cancer Inst. 42: 1101.

Jakobson, I. and S. Yllner. 1971. Metabolism of ^{14}C-pentachlorophenol in the mouse. Acta. Pharmacol. Toxicol. 29: 513.

Johnson, R.D. and D.D. Manske. 1977. Pesticides in food and feed: Pesticide and other chemical residues in total diet samples (XI). Pestic. Monitor. Jour. 11: 116.

Johnson, R.L., et al. 1973. Chlorinated dibenzodioxins and pentachlorophenol. Environ. Health Perspec. Exp. Issue 5: 171.

Karapally, J.C., et al. 1973. Metabolism of lindane-^{14}C in the rabbit: ether-soluble urinary metabolites. Jour. Agric. Food Chem. 21: 811

Klemmer, H.W. 1972. Human Health and Pesticides - community pesticide studies. Residue Rev. 41: 55.

Kobayashi, K. and H. Akitake. 1975. Studies on the metabolism of chlorophenols in fish. I. Absorption and excretion of PCP by goldfish. Bull. Jap. Soc. Sci. Fish. 41: 87.

Koss, G. and W. Koransky. 1978. Pentachlorophenol in different species of vertebrates after administration of hexachlorobenzene and pentachlorobenzene. Pages 131-137 In: K.R. Rao (ed.), Pentachlorophenol: Chemistry, pharmacology and environmental toxicology. Plenum Press, New York.

Larsen, R.V., et al. 1975. Placental transfer and teratology of pentachlorophenol in rats. Environ. Lett. 10: 121.

Lui, H., and C.D. Sweeney. 1975. Hepatic metabolism of hexachlorobenzene in rats. FEBS Lett. 51: 225.

Mehendale, H.M., et al. 1975. Metabolism and effects of hexachlorobenzene on hepatic microsomal enzymes in the rat. Agric. Food Chem. 23: 261.

Mitchell, L.C. 1961. Effect of ultraviolet light (2537A) on 141 pesticide chemicals by paper chromatography. Jour. Off. Anal. Chem. 44: 643.

Mitsuda, W., et al. 1963. Effect of chlorophenol analogues on the oxidative phosphorylation in rat liver mitochondria. Agric. Biol. Chem. 27: 366.

National Fire Protection Assoc. 1973. Fire protection guide on hazardous materials. 5th ed. Natl. Fire Prot. Assoc. Int., Boston.

National Research Council. 1977. Drinking water and health. Natl. Acad. of Sci. Washington, D.C.

Nomura, S. 1953. Studies on chlorophenol poisoning. Podo Kaguku Jour. Sci. Labor 29: 474.

Parrish, P.R., et al. 1978. Chronic toxicity of chlordane, trifluralin, and pentachlorophenol to sheepshead minnows, Cyprinoden variegatus. Report No. EPA 60013-78-010:1.

Pruitt, G.W., et al. 1977. Accumulation and eliminatrion of pentachlorophenol by the bluegill, Lepomis macrochirus. Trans. Am. Fish. Soc. 106: 462.

Reiner, E.A., et al. 1977. Microbial metabolism of pentachlorophenol. Proc. Symp. on Pentachlorophenol, June 27-29. U.S. Environ. Prot. Agency and Univ. West Florida.

Ruesink, R.G. and L.L. Smith, Jr. 1975. The relationship of the 96-hour LC_{50} to the lethal threshold concentration of hexavalent chromium, phenol, and sodium pentachlorophenate for fathead minnows, Pimephales promelas rafinesque. Trans. Am. Fish. Soc. 104: 567.

Sax, N.I. 1975. Dangerous properties of industrial materials. 4th ed. Van Nostrand Reinhold Co., New York.

Schimmel, S.C., et al. 1978. Effects of sodium pentachlorophenol on several estuarine animals: toxicity, uptake, and depuration. Pages 147-155 In: K.R. Rao (ed.), Pentachlorophenol: Chemistry, pharmacology and environmental toxicology. Plenum Press, N.Y.

Schwetz, B.A., et al. 1974. The effect of purified and commercial grade pentachlorophenol on rat embryonal and fetal development. Toxicol. Appl. Pharmacol. 28: 151.

Schwetz, B.A., et al. 1978. Results of two-year toxicity and reproduction studies on pentachlorophenol in rats. In: K.R. Rao (ed.), Pentachlorophenol: Chemistry, pharmacology and environmental toxicology. Plenum Press, New York.

Spector, U.S. 1956. Handbook of toxicology. W.B. Saunders Co., Philadelphia.

Stecher, P.G. (ed.). 1968. The Merck Index. 8th ed. Merck and Co., Inc., Rahway, N.J.

Suzuki, T. and K. Nose. 1971. Decomposition of PCP in farm soil. Part II. PCP metabolism by a microorganism isolated from soil. Moyaku Seisan Gijutsi (Japan) 26: 21.

Takahashi, W., et al. 1976. Acute phase proteins and pesticide exposure. Life Sci. 19: 1645.

U.S. EPA. 1979. Pentachlorophenol: Ambient Water Quality Criteria (Draft).

Vogel, E. and J.L.R. Chandler. 1974. Mutagenicity testing of cyclamate and some pesticides in Drosophila melanogaster. Experientia 30: 621.

Watanabe, I. 1973. Decomposition of pesticides by soil microorganisms. Jap. Agric. Res. Q. 7: 15.

Weast, R.C. (ed.). 1975-1976. Handbook of chemistry and physics. 5th ed. CRC Press, Cleveland, Ohio.

Webb, P.W. and J.R. Brett. 1973. Effects of sublethal concentrations of sodium pentachlorophenate on growth rate, food conversion efficiency, and swimming performance in underyearling sockeye salmon (Oncorhynchus nerka). Jour. Fish. Res. Board Can. 30: 499.

Weinbach, E.C. and J. Garbus. 1965. The interaction of uncoupling phenols with Mitochondria and with Mitochondrial protein. Jour. Biol. Chem. 240: 1811.

Woelke, C.E. 1965. Development of a bioassay method using the marine algae, Monochrysis lutheri. Wash. Dep. Fish. Shellfish Progress Rep. 9p.

Wong, A.S. and D.G. Crosby. 1977. Photodecomposition of pentachlorophenol (PCP). Proc. Symp. on Pentachlorophenol, June 27-29. U.S. Environ. Prot. Agency and Univ. West Florida.

Yang, R.S.H., et al. 1975. Chromatographic methods for the analysis of hexachlorobenzene and possible metabolites in monkey fecal samples. Jour. Assoc. of Anal. Chem. 58: 1197.

No. 144

Phenol

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

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DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

PHENOL

SUMMARY

Insufficient data exist to indicate that phenol is a carcinogenic agent. In skin painting studies, phenol appears to function primarily as a nonspecific irritant. Information on the mutagenicity of phenol is equivocal. Phenol does not appear to be teratogenic. Chronic exposure to phenol at relatively high levels causes liver damage in humans and animals, and kidney damage in animals. Exposure to acutely toxic levels of phenol causes CNS depression.

The toxic effects of phenol have been extensively examined in freshwater organisms by acute studies in 13 fish and 13 invertebrate species. Considerable interspecies and intraspecies variation were described, with acute values ranging from 5,020 to 780,000 µg/l. Only three marine species were examined in acute tests, and LC_{50} values ranged from 5,200 to 58,250 µg/l.

PHENOL

I. INTRODUCTION

This profile is based on the Ambient Water Quality Criteria Document for Phenol (U.S. EPA, 1979).

Phenol (C_6H_5OH; molecular weight 94.11) is a clear, colorless (light pink when impurities are present) hygroscopic, crystalline solid at 25° C with the following physical and chemical properties (Manufacturing Chemist Assoc., 1974; Kirk and Othmer, 1963; Weast, 1974).

Melting Point	43° C
Boiling Point	182° C at 760 mm Hg
Flash Point	open cup 85° C closed cup 79° C
Vapor Pressure	0.35 mm Hg at 25° C
Solubility	Water: 6.7 g/100 ml at 16° C and is soluble at all proportions at 66° C. Also soluble in ether, alcohol, acetic acid, glycerol, liquid sulfur dioxide, benzene, and oils.

Industrial capacity for production is 1.44 to 10^6 tons per year (Chem. Eng. News, 1975). About 90 percent of the phenol produced is used in the production of phenolic resins, caprolactam, bisphenol-A, alkylphenols, and adipic acid (Chemical Profiles, 1972).

Phenol may be biochemically hydroxylated to ortho- and para-dihydroxybenzenes and readily oxidized to the corresponding benzoquinones. These may in turn react with numerous components of industrial waters or sewage such as mercaptans, amines, or the -SH or -NH groups of proteins (Stom, 1975). When ambient water containing phenols is chlorinated, various chlorinated phenols may be produced in sufficient

quantities to produce an objectionable taste and odor (Aly, 1968; Barnhart and Campbell, 1972; Jolley, 1973; Jolley, et al. 1975).

II. EXPOSURE

A. Water

There have been no market basket surveys of free and conjugated phenols with which to estimate the average daily dietary intake of phenols. The National Organic Monitoring Survey (U.S. EPA, 1977) reported finding unspecified concentrations of phenol in 2 out of 110 raw water supplies. The Survey found no phenol in any finished water supplies. The National Commission on Water Quality (1975) reported an annual mean concentration of 1.5 μg phenol/l in raw water from the lower Mississippi River.

B. Food

Phenol is produced endogenously in the mammalian intestinal tract through microbial metabolism (Harborne, 1964) and free and conjugated phenol is a normal constituent of animal matter (U.S. EPA, 1979). Phenol concentrations of 7 mg/kg in smoked summer sausage and 28.6 mg/kg in smoked pork belly have been reported (Lustre and Issenberg, 1970). Several mouthwashes and lozenges contain phenol in amounts of up to 32.5 mg total phenol/lozenge.

The U.S. EPA (1979) has estimated the weighted average bioconcentration factor for phenol to be 2.3 in the edible portions of fish and shellfish consumed by Americans. This estimate is based on the octanol/water partition coefficient of phenol.

C. Inhalation

The inhalation of phenol vapor appears to be largely restricted to the occupational environment (U.S. EPA, 1979). Dermal exposures can be from a number of medicinal preparations for skin application (lotions, powders, ointments) containing up to 4.75 percent phenol, or from certain feminine hygiene products, and hemorrhoidal products (U.S. EPA, 1979).

III. PHARMACOKINETICS

A. Absorption

Phenol is readily absorbed by all routes. This is illustrated by the fact that acutely toxic doses of phenol can produce symptoms within minutes of administration regardless of the route of entry (U.S. EPA, 1979). Sixty to 80 percent of inhaled phenol is retained in the lungs. Piotrowski (1971) found that phenol vapor could be readily absorbed by intact human skin. The rate of dermal absorption for phenol vapor can be represented by the formula A=(0.35)C, when A is the amount of phenol absorbed in mg/hour and C is the phenol concentration in mg/m^3 (Piotrowski, 1971; recalculation of data of Ohtsuji and Ikeda, 1972 by U.S. EPA, 1979).

B. Distribution

Free and conjugated phenol appear to be normal trace constituents in humans and other mammals (Harborne, 1964). Values reported for free and conjugated phenol in normal human blood vary greatly due in part to the specificity of the analytical methods used in and in part to the

amount of the dietary protein which increases urinary phenol excretion. Recent values in normal human blood are between 0.04 to 0.56 mg/l for the free phenol and 1.06 to 5.18 mg/l for conjugated phenols (Dirmikis and Darbre, 1974). For the total phenol (free and conjugated) a range between 2 and 18 mg/l has been reported (Van Haaften and Sie, 1965).

Upon absorption, phenol is rapidly distributed to all organ systems, followed by relatively rapid metabolism and excretion. Within 15 minutes of an oral dose, the highest concentrations are found in the liver, followed by heart, kidneys, lungs, brain and blood (Deichmann, 1944).

C. Metabolism

The major metabolites of phenol are sulfate and glucuronic acid conjugates of phenol and 1,4-dihydroxybenzene. There are, however, species differences in the excretion pattern of these metabolites (Capel, et al. 1972). The cat, which is sensitive to phenol, in addition to sulfate conjugated phenols, excretes also, as a major metabolite, 1,4-dihydroxybenzene (Miller, et al. 1976). The metabolic pattern is also dose dependent. Other agents, which are normally metabolized to phenol, such as benzene or phenylsalicylate, produce increased urinary excretion of phenol metabolites (Kociba, et al. 1976).

D. Excretion

In humans and in all mammals that have been tested, nearly all of the phenol and its metabolites are excreted in the urine within 24 hours (U.S. EPA, 1979; Piotrowski, 1971; Deichmann and Keplinger, 1963). Reported normal background

values for human urinary phenol range from 1.5 to 5 mg/l (Fishbeck, et al. 1975; U.S. EPA, 1979). Urinary excretion levels of phenol metabolites in workers exposed to phenylsalicylate ranged from 150 to 1,371 mg/l. Upon ingestion of eight chloraseptic lozenges at the recommended dosing schedule, the total phenol and the free phenol concentrations in the urine peaked at 270 and 10 mg/l, respectively. When dogs were fed 125 mg phenylsalicylate/kg/day for 41 days, the peak urinary phenol concentration was 6,144 mg/l and the treatment was not associated with ill effects (Kociba, et al. 1976). The half-life of phenol in man is approximately 3.5 hours (U.S. EPA, 1979).

IV. EFFECTS

A. Carcinogenicity

There is no convincing evidence that phenol acts as a carcinogen, particularly at concentrations within normal physiologic limits. Phenol appears to function primarily as a nonspecific irritant (NIOSH, 1976). Only one case of human cancer associated with exposure to phenol was found in the literature. A 72-year old man who had applied a salve of phenol and ergot to his back daily for 20 years developed an invasive squammous cell epithelioma (Stevens and Callaway, 1940).

Phenol produced papillomas but not carcinomas when applied to the skin of some strains of mice. Phenol has carcinogenic activity when applied repeatedly to the skin of a specially bred strain of Sutter mice at concentrations which produce repeated skin damage (Boutwell and Bosch, 1959; Sala-

man and Glendenning, 1956). Phenol promotes skin cancer in mice when repeatedly applied after initiation with known carcinogens (Boutwell and Bosch, 1959; Salaman and Glendenning, 1956; Van Duuren, et al. 1971). Tumorigenesis is highest at dose levels of phenol which have some sclerosing activity. Phenol has no cocarcinogenic activity when applied simultaneously and repeatedly with benzo(a)pyrene to mouse skin (Van Duuren, et al. 1973).

B. Mutagenicity

Phenol was found to be mutagenic in Drosphila (Hadorn and Niggli, 1946) and also reported to be nonmutagenic for Neurospora (Dickey, et al. 1949). Phenol produced back mutations in E. coli from streptomycin dependence to non-dependence at phenol concentrations high enough that the survival of bacteria was only 0.5 to 1.7 percent (Demerec, et al. 1951).

C. Teratogenicity

Studies dealing directly with teratogenicity were not reported in the U.S. EPA (1979) or NIOSH (1976) documents. In a study, not designed specifically as a teratogenicity study, rats were given phenol at concentrations of 100 to 12,000 mg/l in their drinking water over three to five generations. Specific teratogenic effects were not noted (Heller and Pursell, 1938).

D. Other Reproductive Effects

In the study mentioned under teratogenicity, higher concentrations of phenol in the drinking water (7,000 mg/l) produced stunted growth in the young, death of the offspring

at birth (10,000 mg/l), and failure to reproduce (12,000 mg/l) (Heller and Pursell, 1938).

E. Chronic Toxicity

Repeated exposures to phenol at high concentrations have resulted in chronic liver damage in humans (Merliss, 1972). In unpublished studies by Dow Chemical Company (1976), rats received 135 doses of 100 mg phenol/kg or 50 mg phenol/kg by gavage over a six month period. The growth of the rats was comparable to that of controls. Very slight liver changes and slight to moderate kidney damage were seen at the higher dose of phenol. The lower dose of phenol produced only slight kidney damage.

Rats given phenol in their drinking water at 800, 1,200, 1,600, 2,000, and 2,400 mg/l had corresponding average intakes of 21, 30, 49, 56, and 55 mg phenol per rat per day based on actual water consumption data. The rats at the three lower dosage levels showed no overt symptoms of toxicity. The weight gain of the rats at the two highest dose levels was depressed (Deichmann and Oesper, 1940).

F. Other Relevant Information

The primary effect of exposure to acutely toxic levels of phenol is CNS depression. Significant evidence could not be found to support the occurrence of synergistic or antagonistic actions of phenol with other compounds in mammals (U.S. EPA, 1979).

V. AQUATIC TOXICITY

A. Acute Toxicity

Acute toxicity data for phenol display a wide range of interspecific variability and intraspecific sensitivity. The range of LC_{50} values for 13 species of freshwater fish is 5,020 µg/l for the rainbow trout (Salmo gairdneri) to 200,000 µg/l for the goldfish (Carassius auratus) (Cairns, et al. 1978). Several studies have indicated an inverse relationship between survival time and temperature for rainbow trout, golden shiner (Notemigonius crysoleueus) (U.S. EPA, 1979). Similar intraspecific sensitivity and interspecific variability was demonstrated by bioassays with freshwater invertebrates as test organisms. The cladocerans, Daphnia magna and D. longispina, displayed the greatest sensitivity to phenol with LC_{50} values as low as 7,000 µg/l reported. The freshwater clam, Sphaerium corneum, was the most resistant species with an LC_{50} value of 780,000 µg/l (U.S. EPA, 1979).

Data for the acute toxicity of phenol to marine organisms is not nearly as extensive as that for freshwater species. For marine fish, LC_{50} values of 5,200 and 6,014 µg/l were obtained for rainbow trout in saline waters and mountain bass (Kuhlia sandvicensis), respectively (U.S. EPA, 1979). Eastern oyster embryos (Crassostrea virginica) and hardclam embryos (Mercenaria mercenaria) were much more resistant with LC_{50} values of 58,250 and 52,630 µg/l, respectively (Davis and Hidu, 1969).

B. Chronic

Data for the chronic effects of phenol on freshwater fish are not available. In a life cycle chronic test, a chronic value of 3,074 µg/l was obtained for the freshwater cladoceran, Daphnia magna (U.S. EPA, 1978). Chronic data for marine organisms were not available.

C. Plant Effects

Plants are relatively insensitive to phenol exposure with effective concentrations ranging from 20,000 to 1,504,000 µg/l for three species of algae, one species of diatom, and duckweed. Marine plants species have not been examined for toxic effects of phenol.

D. Residues

Measured bioconcentration factors of 1.2 to 2.3 have been determined for goldfish (Kobayashi, et al. 1976; Kobayashi and Akitake, 1975). Bioconcentration factors have not been determined for freshwater invertebrates or plants, or for any marine species.

VI. EXISTING GUIDELINES AND STANDARDS

Neither the human health nor the aquatic criteria derived by U.S. EPA (1979), which are summarized below, have gone through the process of public review; therefore, there is a possibility that these criteria will be changed.

A. Human

On the basis of chronic toxicity data for rats and an uncertainity factor of 500, the U.S. EPA (1979) has derived a draft criterion of 3.4 mg/l for phenol in ambient water corresponding to the calculated acceptable daily intake

of 0.7 mg. The draft criterion for phenol is 1.0 µg/l in those instances where chlorination of phenol may take place during water purification processes.

The 1974 Federal standard and the ACGIH (1977) recommendation for phenol in air in the workplace is 19 mg/m^3 (5 ppm) as a time-weighted average.

The NIOSH (1976) criterion for a recommended standard for occupational exposure to phenol is 20 mg/m^3 in air as a time weighted average for up to a 10-hour work day and a 40-hour work week, with a ceiling concentration of 60 mg/m^3 for any 15-minute sampling period.

The U.S. EPA interim drinking water limit for phenol is 1 µg/l, which is largely an organoleptic standard based on the objectionable taste and odor produced by chlorinated phenols. In response to a phenol spill in southern Wisconsin, the U.S. EPA proposed on November 26, 1974 an emergency standard of 0.1 mg phenol/l as being temporarily acceptable for human consumption.

B. Aquatic

The draft criterion for protecting freshwater organisms is 600 µg/l, not to exceed 3,400 µg/l. No criterion for marine organisms was derived (U.S. EPA, 1979).

PHENOL

REFERENCES

Aly, O.M. 1968. Separation of phenols in waters by thin-layer chromatography. Water Res. 2: 287.

American Council for Governmental Industrial Hygienists. 1977. Threshold limit values for chemical substances and physical agents in workroom environment with intended changes for 1977.

Barnhart, E.L. and G.R. Campbell. 1972. The effect of chlorination on selected organic chemicals. U.S. Environ. Prot. Agency.

Boutwell, R.K. and D.K. Bosch. 1959. The tumor-promoting action of phenol and related compounds. Cancer Res. 19: 413.

Cairns, J., Jr., et al. 1978. Effects of temperature on aquatic organisms sensitivity to selected chemicals. Project B-084-VA. Bull. 106. Virginia Polytechnic Inst. State University.

Capel, I.D., et al. 1972. Species variations in the metabolism of phenol. Biochem. Jour. 127: 25.

Chemical and Engineering News. July 28, 1975.

Chemical Profiles. 1972. Phenol. Schnell Publishing Co., New York.

Davis, H.C. and H. Hidu. 1969. Effects of pesticides on embryonic development of clams and oysters and on survival and growth of the larvae. Fish Wildl. Fish. Bull. 67: 393. U.S. Dep. Inter.

Deichmann, W.B. 1944. Phenol studies. V. The distribution, detoxification, and excretion of phenol in the mammalian body. Arch. Biochem. 3: 345.

Deichmann, W.B. and M.L. Keplinger. 1963. Phenols and phenolic compounds. Page 1363 In: F.A. Patty (Ed.), Industrial hygiene and toxicology. Interscience Publishers, New York.

Deichmann, W.B. and P. Oesper. 1940. Ingestion of phenol -- Effects on the albino rat. Ind. Med. 9: 296.

Demerec, M., et al. 1951. A survey of chemicals for mutagenic action on E. coli. Am. Natur. 85: 119.

Dickey, F.H., et al. 1949. The role of organic peroxides in the induction of mutations. Proc. Natl. Acad. Sci. 35: 581.

Dirmikis, S.M. and A. Darbre. 1974. Gas-liquid chromatography of simple phenols for urinalysis. Jour. Chromatogr. 94: 169.

Dow Chemical Co. 1976. References and literature review pertaining to toxicological properties of phenol. Toxicol. Res. Lab. Unpubl. Manuscript.

Fishbeck, W.A., et al. 1975. Elevated urinary phenol levels not related to benzene exposure. Am. Ind. Hyg. Jour. 36: 820.

Hadorn, E. and H. Niggli. 1946. Mutations in Drosophila after chemical treatment of gonads in vitro. Nature 157: 162.

Harborne, J.B. 1964. Biochemistry of phenolic compounds. Academic Press, New York.

Heller, V.G. and L. Pursell. 1938. Phenol-contaminated waters and their physiological action. Jour. Pharmacol. Exp. Ther. 63: 99.

Jolley, R.L. 1973. Chlorination effects on organic constituents in effluents from domestic sanitary sewage treatment plants. Ph.D. dissertation, University of Tennessee, Knoxville.

Jolley, R.L., et al. 1975. Chlorination of cooling water: a source of envi- ronmentally significant chlorine-containing organic compounds. Proc. 4th Natl. Symp. Radioecology. Corvallis, Ore.

Kirk, R.E. and D.F. Othmer. 1963. Kirk-Othmer encyclopedia of chemical technology. 2nd ed. John Wiley and Sons, Inc., New York.

Kobayashi, K. and H. Akitake. 1975. Metabolism of chlorophenols in fish. IV. Absorption and excretion of phenol by goldfish. Nippon Suisan Gakkaishi. 41: 1271.

Kobayashi, K., et al. 1976. Studies on the metabolism of chlorophenols in fish. VI. Turnover of absorbed phenol in goldfish. Bull. Jap. Soc. Sci. Fish. 42: 45.

Kociba, R.J., et al. 1976. Elevated urinary phenol levels in beagle dogs treated with salol. Am. Ind. Hyg. Jour. 37: 183.

Lustre, A.O. and P. Issenberg. 1970. Phenolic components of smoked meat products. Jour. Agric. Food Chem. 18: 1056.

Manufacturing Chemists Assoc. 1974. Chemical safety data sheet SD-4; Phenol. Washington, D.C.

Merliss, R.R. 1972. Phenol moras. Mus. Jour. Occup. Med. 14: 55.

Miller, J.J., et al. 1976. The toxicity of dimethylphenol and related compounds on the cat. Toxicol. Appl. Pharmacol. 38: 47.

National Commission on Water Quality. 1975. Water quality and environmental assessment and predictions to 1985 for the lower Mississippi River and Barataria Bay. Vol. 1. Contract WQ5AC062.

National Institute for Occupational Safety and Health. 1976. Criteria for a recommended standard...Occupational exposure to phenol. NIOSH 76-196.

Ohtsuji, J. and M. Ikeda. 1972. Quantitative relationship between atmospheric phenol vapor and phenol in the urine of workers in bakelite factories. Br. Jour. Ind. Med. 29: 70.

Piotrowski, J.K. 1971. Evaluation of exposure to phenol: absorption of phenol vapour in the lungs and through the skin and excretion of phenol in urine. Br. Jour. Ind. Med. 28: 172.

Salaman, M.H. and O.M. Glendenning. 1956. Tumor promotion in mouse skin by sclerosing agents. Br. Jour. Cancer 11: 434.

Stevens, J.B. and J.L. Callaway. 1940. Mixed epithelioma of the back arising from daily applicaton of a phenl and ergot ointment. Am. Jour. Cancer. 38: 364.

Stom, D.J. 1975. Use of thin-layer and paper chromatography for detection of ortho- and para- quinones formed in the course of phenol oxidation. Acata Hydrochim. Hydrobiol. 3: 39.

U.S. EPA. 1977. National Organic Monitoring Survey. General review of results and methodology: phases I-III. Water Supply Res. Div.

U.S. EPA. 1978. In-depth studies on health and environmental impacts of selected water pollutants. Contract No. 68-01-4646.

U.S. EPA. 1979. Phenol: Ambient Water Quality Criteria. (Draft)

Van Duuren, B.L., et al. 1971. Cocarcinogenesis studies on mouse skin and inhibition of tumor production. Jour. Natl. Cancer Inst. 46: 1039.

Van Duuren, B.L., et al. 1973. Cocarcinogenic agents in tobacco carcinogenesis. Jour. Natl. Cancer Inst. 51: 703.

Van Haaften, A.B. and S.T. Sie. 1965. The measurement of phenol in urine by gas chromatography as a check on benzene exposure. Am. Ind. Hyg. Assoc. Jour. 26: 52.

Weast, R.C. (Ed.) 1974. Handbook of chemistry and physics. 55th ed. CRC Press, Cleveland, Ohio.

No. 145

Phorate

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

-1722-

DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

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PHORATE

Summary

Phorate is an organophosphorous insecticide used on a variety of crops, mainly in south-central states. Phorate is readily absorbed through inhalation and skin contact and is highly toxic to humans and other animals. Primarily, it affects the central and peripheral nervous systems by inhibiting cholinesterase activity. Information concerning carcinogenic and mutagenic effects was not located in the available literature. The threshold limit value for phorate is 50 $\mu g/m^3$, based on dermal contact. Additionally, phorate has been classified for restrictive use by the U.S. EPA.

Although phorate is highly toxic to certain aquatic organisms, no apparent adverse effects have been observed in the aquatic environment.

I. INTRODUCTION

Phorate is a highly toxic organophosphorous insecticide used on a variety of agricultural crops. It was introduced in 1954 by the American Cyanamid Co. under the trade name Thimet® (Martin and Worthing, 1974). Phorate is prepared by the reaction of phosphorous pentasulfide with ethanol, formaldehyde, and ethyl mercapton. Production in the U.S. totaled 3400 tonnes in 1977 (NAS, 1977). Virtually all of the phorate is used on root and field cropsoils to control sucking insects and nematodes (NAS, 1975). Phorate is slightly soluble in water and hydrolyzes in moisture. It has an overall degradation rate constant of 0.02/day and a bioconcentration factor of 5.2. Other properties are listed in Table 1.

II. EXPOSURE

A. Water

Phorate is produced in the United States by the American Cyanamid Co. at Hannibal, Mo. (SRI, 1977). Available information on an annual U.S. production shows that 1900 tonnes were produced in 1971, 3600 tonnes in 1974, and 3400 tonnes in 1977 (NAS, 1975, 1977). Berg, et al. (1972) noted an application rate of 1 pound of actual material per acre (1.1 kg/ha; in this case, to control corn borers). Application rates vary according to use.

Phorate has found increasing use on croplands in the south-central states to protect cotton, hops, alfalfa, barley, sorghum, peanuts, sugar beets, sugar cane, potatoes, rice, and tomatoes. Only small amounts are used in the southeastern and northeastern U.S. American Cyanamid Co. reported that phorate may fill the void left by the removal from the market of chlorinated hydrocarbons and projected a strong demand for phorate in the corn rootworm market (Berg, et al. 1977).

TABLE 1. PHYSICAL AND CHEMICAL PROPERTIES OF PHORATE

Synonyms: O,O-diethyl-S-(ethylthiomethyl)phosphorodithioate;
O,O-diethyl-S-ethylmercaptomethyl dithiophosphate;
THIMET American Cyanamid (3911): timet (USSR);
CAS Registry No. (298-02-2); Dranutox; Rampart; Vergfru

Structural Formula: $(C_2H_5O)_2(P{=}S)SCH_2SC_2H_5$

Molecular Weight: 260.4

Description: Clear liquid
Miscible with: CCl_4, dioxan, vegetable oils, xylene, alcohols, ethers, esters

Soil Attenuation: K_d approx. 5×10^2; $K_{oc} = 3199$

Specific Gravity and/or Density: $d^{25} = 1.167$

Melting and/or Boiling Points: bp 118 to 120°C at 0.8 mm
mp less than -15°C

Stability: Stable at room temperature
Hydrolyzed in the presence of moisture
Overall degradation rate constant (0.02/day)

Soil half-life: 1-4 weeks
Bacterial/Hydrolysis: constant = $8 \times 10^{-4} hr^{-1}$

Solubility (water): 50 ppm at room temp.
$\frac{\text{sediment}}{H_2O} : \frac{4.5}{1}$

Vapor Pressure: 8.4×10^{-4} mm Hg at 20°C

Bioconcentration Factor (BCF) and/or
Octanol/water partition coefficient (K_{ow}): $K_{ow} = 18$
BCF = 5.2

Source: Martin and Worthing, 1974; Fairchild, 1977; Windholz, 1976; U.S. EPA, 1980

Little information was found on phorate production processes. Lawless, et al. (1977) noted that in the production, crude phorate was washed and filtered. No information was given on the treatment of the waste water or filter cake associated with this process. No information on waste sludge or landfill disposal was found in the available literature.

Phorate can enter water by runoff or by ground water drainage after application. Phorate is relatively stable in ground water. Only 10 percent decomposition was estimated in a river environment in 5 days (50 to 250 mile transport; 80-400 km). Also, estimates show that less than 90 percent decomposition per year occurs in a lake environment (U.S. EPA, 1980). There are no estimates on the amount of phorate entering the environment or on the levels of phorate in ambient water. Menzie (1974) noted that phorate decomposes to phorate sulfoxide and phorate sulfone and the sulfoxide and sulfone of the oxygen analog.

Walter-Echols and Lichtenstein (1977) showed that some oxidation products of phorate (phorate sulfoxide) reduce to phorate in lake mud under certain conditions. Using a flooded phorate sulfoxide-treated loam soil, they noticed the production of only small amounts of phorate. After lake mud was added, the reduction of phorate sulfoxide to phorate increased dramatically and, after two weeks' incubation, accounted for 44 percent of the recovered residues. They related the reduction process to the activity of microorganisms in an environment of organic nutrients.

B. Food

Information available in the open literature does not quantify the amount of phorate detected on foods. In a study reported by Menzie (1974), phorate was applied to bermuda grass and corn at the rate of 2 pounds per

acre (2.2 kg/ha). Fourteen days after treatment, less than 1 ppm phorate residue was noted on the corn; after 21 days less than 1 ppm was found on bermuda grass.

C. Inhalation and Dermal

Data are not available indicating the number of people subject to inhalation or dermal exposure to phorate. The primary human exposure would appear to occur during production and application. The U.S. EPA (1976) listed by occupational group the frequency of illness caused by exposure to organophosphorous pesticides. Of 1157 reported cases, most illnesses occurred among ground applicators (229) and mixer/loaders (142); the lack of, or refusal to use, safety equipment was a major factor of this contamination. Other groups affected were gardeners (101), field workers exposed to pesticide residues (117), nursery and greenhouse workers (75), soil fumigators in agriculture (29), equipment cleaners and mechanics (28), tractor drivers and irrigators (23), workers exposed to pesticide drift (22), pilots (crop dusters) (17), and flaggers for aerial application (6). Most illnesses were a result of carelessness, lack of knowledge of the hazards, and/or lack of safety equipment. Under dry, hot conditions, workers tended not to wear protective clothing. Such conditions also tended to increase pesticide levels and dust on the workers.

III. PHARMACOKINETICS

A. Absorption

Newell and Dilley (1978) exposed four different groups of rats to phorate via four routes of administration. They compared LD_{50} and LC_{50} values and found that inhalation was the most toxic route, followed, in decreasing order, by intravenous, oral, and dermal routes. The phorate aero-

sol generated in the laboratory had a particle size range of 0.3-3.0 μm diameter, a size small enough to enter the gas exchange regions of the lung.

Young, et al. (1979) reported on two occupational exposure incidents that suggested absorption in the lungs was the most effective route of entry. In both cases, the individuals wore protective clothing, goggles, and respirators while working in the dust house where technical grade phorate was produced. Gas chromatographic analyses of air samples from the dust house showed phorate levels ranging from 0.7 to 14.6 mg/m^3. No estimate of particle size was reported by the authors.

B. Distribution

Phorate would be expected to distribute in the body like organophosphorous pesticides of similar solubility. A report by Pugh and Forest (1975) described the distribution in calves exposed to phorate in a manger containing 1200 ppm. Phorate concentrations in the liver ranged from 0.004-0.26 ppm; in the kidney, 0.002-0.021 ppm; and in the brain, 0.025-0.19 ppm.

C. Metabolism

The major phorate metabolites found in blood after oral administration to rats are phorate sulfoxide, phorate sulfone, and phoratoxon sulfone (NAS, 1977). Bowman and Casida (1958) showed that phorate hydrolyzes in rats to produce urinary diethylphosphorodithioic acid, diethylphosphorothioic acid, and diethylphosphoric acid. Oxidative metabolites are not found as components of excretory products of animals treated with phorate (NAS, 1977). However, DuBois, et al. (1950) showed that in rat liver slices, phorate was converted to its oxidative products.

D. Excretion

The previous section notes that phorate is eliminated primarily through the urinary system.

IV. EFFECTS

A. Carcinogenicity and Mutagenicity

Pertinent data could not be located in the available literature on the carcinogenicity or mutagenicity of phorate. Formaldehyde, a suspected carcinogen, and other contaminants may be present in technical grade phorate.

B. Teratogenicity

In a study described in the absorption section of this report, Newell and Dilley (1978) did not find dose-related teratogenesis in rats exposed to phorate via inhalation, intravenous, dermal, or oral routes. In the chick embryo test, Richert and Prahlad (1972) injected 1.5 or 2.0 ppm in a peanut oil medium into eggs on the tenth day of incubation. Controls received only peanut oil. Hatchability of the eggs decreased in a dose-dependent manner. Malformations were produced, but these did not seem to be dose-related. The relevance of these studies to mammalian teratology is unclear (NAS, 1977).

C. Other Reproductive Effects

In a study in which CFI mice were fed diets containing 98.7 percent phorate at 0.6, 1.5, and 3.0 ppm, the no-adverse-effect level for reproductive performance was 1.5 ppm (NAS, 1977).

D. Chronic Toxicity and Other Relevant Information

Pertinent data on chronic toxicity could not be located in the available literature. Several subchronic studies have been reported. In subchronic feeding studies of 1, 5, and 25 ppm phorate for 28 days, cholinesterase in the 1 ppm group was not decreased (Tusing, 1955). In a second rat study, Tusing (1956) fed groups of 50 males and females 92 percent phorate for 13 weeks at 0.22, 0.66, 2.0, 6.0, 12.0, and 18.0 ppm. He noted a no-adverse-effect dosage at 0.66 ppm.

Tusing (1956) fed three dogs 92 percent phorate at 0.01, 0.05, 0.25 and 1.24 mg/kg 6 days per week for 13-15 weeks. The no-adverse-effect dosage was judged to be 0.01 mg/kg; even at this level, a very slight decrease in plasma cholinesterase resulted. Higher dosages caused significant depression of cholinesterase, culminating in death at the two highest dosages.

Rat feeding studies showed higher subchronic toxicities on phorate oxidative metabolites than on phorate, according to Rombunski, et al. (1958). Others have also noted that phorate metabolites are more potent cholinesterase inhibitors than phorate (Curry, et al. 1961).

Young, et al. (1979) reported on acute exposures to high levels of phorate (up to 14.6 mg/m^3) in a production facility (see absorption section). The symptoms accompanying the exposures were confusion, dizziness, nausea, vomiting, pupil constriction, respiratory distress, cardiac arrhythmia, and unconsciousness. Treatment involved a regime of PAM and atropine. According to Gleason (1969), the symptoms produced by a sublethal dose are typical of central and peripheral nervous system toxicity. EPA's accident files contain reports of 21 episodes of poisoning involving phorate for 1971-1973. Eleven were agriculturally related. There are no controlled studies in humans from which no-adverse-effect dosages could be derived.

For humans, the lowest published lethal (LD_{LO}) value is estimated to be 5 mg/kg. The following studies list acute phorate toxicity levels for human and nonhuman species, reported by Fairchild (1977):

Species	Exposure	LD_{50} (mg/kg)
Rat	Oral	1.1
Rat	Skin	2.5
Rat	Intravenous	1.2
Mouse	Oral	11
Guinea pig	Oral	20
Guinea pig	Skin	20
Duck	Oral	2.55
Duck	Skin	203
Wild Bird	Oral	1

V. AQUATIC TOXICITY

A. Acute and Chronic Toxicity

Phorate is highly toxic to certain species of fish, crustaceans, and terrestrial wildlife (NAS, 1977). NAS noted that there were no reported killings of these species in the environment.

B. Plant Effects and Residues

Pertinent data could not be located in the available literature.

VI. EXISTING GUIDELINES

A. Human

The threshold limit value for phorate is 50 $\mu g/m^3$, based on skin contact (Fairchild, 1977). An 8-hour time-weighted average of 50 mg/m^3 was adapted for phorate by the Tennessee Department of Health (Young, et al. 1979). In addition, phorate is classified for restrictive use by the U.S. EPA for liquid formulations containing 65 percent and greater active ingredients. The restriction was influenced by the acute dermal toxicity of phorate and by residue effects on avian species (applicable to foliar applications only).

B. Aquatic

Pertinent data could not be located in the available literature.

REFERENCES

Berg, G.L., et al. (ed.) 1977. Farm Chemicals Handbook. Meister Publishing Company, Willoughby, Ohio.

Bowman, J.S. and J.E. Casida. 1958. Further studies on the metabolism of Thimet by plants, insects and mammals. Jour. Econ. Entomol. 51: 838.

Curry, A.N., et al. 1961. Determination of residue of phorate and its insecticidally active metabolites by cholinesterase inhibition. Jour. Agric. Food Chem. 9: 469.

DuBois, K.P., et al. 1950. Studies on toxicity and pharmacological action of octamethyl pyrophosphoramide. Jour. Pharmacol. Exp. Ther. 99: 376.

Fairchild, E.J. (ed.) 1977. Agricultural Chemicals and Pesticides. A Subfile of the NIOSH Registry of Toxic Effects of Chemical Substances. U.S. DHEW.

Gleason, M.N., et al. 1969. Clinical Toxicology of Commercial Products. Acute Poisoning. 3rd ed.

Lawless, E.W., et al. 1972. The Pollution Potential in Pesticide Manufacturing. U.S. EPA, Office of Water Programs, Technical Studies Report TS-00-72-04.

Martin, H. and C.R. Worthing (eds.) 1974. Pesticide Manual. 4th ed.

Menzie, C.M. 1974. Metabolism of Pesticides: An Update. U.S. Dept. of the Interior Special Scientific Report - Wildlife No. 184, Washington, D.C.

National Academy of Sciences. 1975. Pest Control: An Assessment of Present and Alternative Technologies, Vol. I.

National Academy of Sciences. 1977. Drinking Water and Health. Natl. Acad. Sci., Washington, D.C.

Newell, G.W. and J.V. Dilley. 1978. Teratology and Acute Toxicology of Selected Chemical Pesticides Administered by Inhalation. U.S. NTIS, PB Rep. PB-277077, 66 pp.

Pugh, W.S. and O.N.T. Forest. 1975. Outbreak of organophosphate poisoning (Thimet) in cattle. Can. Vet. Jour. 16: 56.

Richert, E.P. and K.V. Prahlad. 1972. The effect of the organophosphate O,O diethyl S-[(ethylthio)methyl]phosphorodithioate on the chick. Poultry Sci. 51: 613.

Rombunski, et al. 1958. Cited in National Academy of Sciences, 1977.

Stanford Research Institute. 1977. Directory of Chemical Producers. Stanford Research Institute, Menlo Park, California.

Tusing, T.W. 1955. Unpublished report of American Cyanamid. Cited in U.S. EPA Initial Scientific and Minieconomic Review of Phorate, 1974.

Tusing, T.W. 1956. Unpublished report of American Cyanamid. Cited in U.S. EPA Initial Scientific and Minieconomic Review of Phorate, 1974.

U.S. Environmental Protection Agency. 1976. Organophosphate Exposure from Agricultural Usage, EPA 600/1-76-025.

U.S. Environmental Protection Agency. 1980. Aquatic Fate and Transport Estimates for Hazardous Chemical Exposure Assessments. Environmental Research Laboratory, Athens, Georgia.

Walter-Echols, G. and E.P. Lichtenstein. 1977. Microbial reduction of phorate sulfoxide to phorate in a soil-lake mud-water microcosm. Jour. Econ. Entomol. 70: 505.

Windholz, M. (ed.) 1976. The Merck Index, 9th ed. Merck Co., Inc., Rahway, New Jersey.

Young, R.J., et al. 1979. Phorate intoxication at an insecticide formulating plant. Am. Ind. Hyg. Assoc. Jour. 40: 1013.

No. 146

Phthalate Esters

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

-1737-

DISCLAIMER

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PHTHALATE ESTERS

Summary

Certain phthalates (dimethyl phthalate, diethyl phthalate, mono-2-ethyl-hexyl phthalate and dimethoxyethyl phthalate), have shown mutagenic effects in both bacterial systems and the dominant lethal assay.

All eight phthalates tested by injection in pregnant rats produced teratogenic effects. These effects were not noted when DEHP or dibutyl phthalate were administered orally to pregnant rats. Additional reproductive effects produced include impaired implantation, parturition and decreased fertility in rats. Testicular damage has been reported following intraperitoneal (i.p.) or oral administration of DEHP, or oral administration of dibutyl phthalate. No evidence of carcinogenic effects produced by phthalates is available.

Chronic toxicity includes toxic polyneuritis in workers exposed primarily to dibutyl phthalate. DEHP animal studies show induced liver and kidney changes while dimethyl phthalate induced only kidney effects. Following injection dibutoxyethyl phthalate, di-(2-methoxyethyl) phthalate, and octylisodecyl phthalate have caused damage to the developing chick embryo nervous system.

Toxicity of the phthalate esters to aquatic organisms varies within this group of chemicals. Freshwater organisms have appeared somewhat more sensitive than marine species. The data is insufficient to allow for the drafting of criteria to protect aquatic life for any of the phthalates.

PHTHALATE ESTERS

I. INTRODUCTION

This profile is based primarily on the draft Ambient Water Quality Criteria Document for Phthalate Esters (U.S. EPA, 1979).

The phthalate esters are esters of the benzenedicarboxylic acid ortho form. Esters of the parent compound meta and para forms will not be reviewed in this profile. The phthalate esters are colorless liquids of low volatility, poorly soluble in water and soluble in organic solvents and oils. Some physical and chemical properties of the phthalate esters are indicated in Table 1 on the following page (U.S. EPA, 1979).

The phthalate esters are widely used as placticizers, and through this application are incorporated into wire and cable covering, floor tiles, swimming pool liners, upholstery and seat covers, footwear, and in food and medical packaging materials. Non-plasticizer uses include incorporation into pesticide carriers, cosmetics, fragrances, munitions, industrial oils, and insect repellants (U.S. Int. Trade Commission, 1978). The most current production figure is 6 $\times 10^5$ tons/year in 1977 (U.S. EPA, 1979).

Phthalate esters are ubiquitous. Monitoring surveys have detected phthalates in soil, air, water, animal and human tissues, and certain vegetation. Some plants and animal tissues may synthesize phthalic acid esters (Peakall, 1975). From <u>in vitro</u> studies indications, certain bacterial flora may be capable of metabolizing phthalates to the monoester form (Englehardt, et al. 1975).

II. EXPOSURE

Phthalate esters appear in all areas of the environment. Environmental release of the phthalates may occur through leaching of plasticizers from polyvinyl chloride (PVC) materials, volatilization of phthalates from PVC

materials, and the incineration of PVC items. Human exposure to phthalates includes contaminated foods and fish, dermal application of phthalates in cosmetics and insect repellants, and parenteral administration by use of PVC blood bags, tubings, and infusion devices (U.S. EPA, 1979).

TABLE 1

PHYSICAL AND CHEMICAL PROPERTIES OF PHTHALATE ESTERS

Phthalate Compounds	Molecular Weight	Specific Gravity	Bp, °C	Percent Solubility in H_2O, g/100 ml
Dimethyl	194.18	1.189 (25/25)	282	0.5
Diethyl	222.23	1.123 (25/4)	296.1	Insoluble
Diallyl	246.27	1.120 (20/20)	290	0.01
Diisobutyl	278.30	1.040	327	Insoluble
Dibutyl	278.34	1.047 (21)	340	0.45 (25°C)
Dimethoxyethyl	282.00	1.171 (20)	190-210	0.85
Dicyclohex	330.00	1.200 (25/25)	220-228	Insoluble
Butyl octyl	334.00	--	340	--
Dihexyl	334.00	0.990	--	Insoluble
Butylphthayl butyl glycolate	336.37	1.097 (25/25)	219/5 mm	0.012
Dibutoxyethyl ethyl	366.00	1.063	210	0.03
Di-2-ethylhexyl	391.00	0.985 (20/20)	386.9/5 mm	Insoluble
Diisooctyl	391.00	0.981	239/5 mm	Insoluble
Di-n-octyl	391.00	0.978	220/5 mm	Insoluble
Dinonyl	419.00	0.965	413	Insoluble

Source: U.S. EPA, 1979

Monitoring studies have indicated that most water phthalate concentrations are in the ppm range, approximately 1-2 ug/l (U.S. EPA, 1979). Air levels of phthalates in closed PVC tiled rooms have been reported to be from 0.15 to 0.26 mg/m^3 (Peakall, 1975), while industrial monitoring has measured air levels of phthalates from 1.7 to 66 mg/m^3 (Milkov, et al. 1973). Phthalate levels in various foods have ranged from non-detectable to 82 ppm (Tomita, et al. 1977). Cheeses, milk, fish and shellfish present potential sources of high phthalate intake (U.S. EPA, 1979). Estimates of patient parenteral exposure to di-2-ethylhexyl phthalate (DEHP) during use of PVC medical appliances have indicated approximately 150 mg DEHP exposure from a single hemodialysis course. Through application of certain cosmetics and insect repellants dermal exposure to phthalates is possible (U.S. EPA, 1979).

Using average human fish and shellfish consumption data, the U.S. ERA (1979) has derived the following bioconcentration factors for the edible portions of fish and shellfish consumed by Americans - diethyl phthalate, 270; dibutylphthalate, 1500; DEHP, 95; dimethyl phthalate, 130. DMP, DEP and BBP are based on the steady-state bioconcentrations in bluegills and in fathead minnows for DEHP. A weighted average bioconcentration factor of 26 was calculated for dibutyl phthalate utilizing the octanol water partition coefficient (U.S. EPA, 1979).

III. PHARMACOKINETICS

A. Absorption

The phthalic acid esters and/or their metabolites are readily absorbed from the intestinal tract, the peritoneal cavity, and the lungs (U.S. EPA, 1979). Daniel and Bratt (1974) found that seven days following administration of radiolabelled-DEHP, 42 percent of the dose is recovered in the urine and 57 percent recovered in the feces of rats. Biliary excretion of

orally administered DEHP has been noted by Wallin, et al. (1974). Limited human studies indicate that 2 to 4.5 percent of orally administered DEHP is recovered in the urine within 24 hours (Shaffer, et al. 1945). Lake, et al. (1975) suggest orally administered phthalates are absorbed after metabolic conversion to the monoester form in the gut.

Dermal absorption of DEHP in rabbits has been reported at 16 to 20 percent of the initial dose within three days following administration (Autian, 1973).

B. Distribution

Studies in rats injected with radiolabelled-DEHP have shown that from 60 to 70 percent of the administered dose was detected in the liver and lungs within 2 hours after injection (Daniel and Bratt, 1974). Wadell, et al. (1977) have reported rapid accumulation of radiolabelled-DEHP in the kidney and liver of rats after intravenous (i.v.) injection, followed by rapid excretion into the urine, bile, and intestine. Seven days after i.v. administration of radiolabelled-DEHP to mice, levels of the compound were found preferentially in the lungs and to a lesser extent in the brain, fat, heart, and blood (Autian, 1973).

An examination of tissue samples from two deceased patients, recipients of large volumes of transfused blood, detected DEHP in the spleen, liver, lungs, and abdominal fat (Jaeger and Rubin, 1970). Daniel and Bratt (1974) have suggested phthalates achieve a steady-state concentration, after which the compounds or metabolites are rapidly eliminated by various routes.

Injection of radiolabelled-DEHP and diethyl phthalate in pregnant rats has shown the phthalates may cross the placental barrier (Singh, et al. 1975).

C. Metabolism

Various metabolites of DEHP have been identified following oral feeding of rats (Albro, et al. 1973). These results indicate that DEHP is initially converted from the diester to the monoester, followed by the oxidation of the monoester side chain forming two different alcohols. The alcohols are then oxidized to the corresponding carboxylic acid or ketone. Enzymatic clearance of phthalates to the monoester form may take place in the liver or in the gut (Lake, et al. 1977). This enzymatic conversion has been observed in stored whole blood indicating widespread distribution of this metabolic activity (Rock, et al. 1978).

D. Excretion

Elimination of orally administratered DEHP is virtually completed within four days in the rat (Lake, et al. 1975). Major excretion is through the urine and feces, with biliary excretion increasing the content of DEHP (or metabolites) in the intestine (U.S. EPA, 1979). Schulz and Rubin (1973) have noted a progressive increase in total water soluble metabolites in the first 24 hours following injection of radiolabelled DEHP to rats. Within one hour, eight percent of the DEHP was found in the liver, intestine and urine. After 24 hours, 54.6 percent DEHP was recovered in the intestinal tract, excreted feces and urine, and only 20.5 percent DEHP was recovered in organic extractable form.

The half-life of phthalate elimination from the tissues and total body is short (U.S. EPA, 1979). Biphasic elimination of DEHP from the blood of rats showed half-life values of 9 minutes and 22 minutes, respectively (Schulz and Rubin, 1973).

IV. EFFECTS

A. Carcinogenicity

Pertinent data could not be found in the available literature.

B. Mutagenicity

Testing of several phthalates in the Ames Salmonella assay has shown that diethyl phthalate has some mutagenic activity (Rubin, et al. 1979). Dibutyl, mono-2-ethylhexyl, di-(2-ethylhexyl) and butylbenzyl phthalate all produced negative effects in this test system. Yagi, et al. (1978) have reported mutagenic effects of mono-2-ethylhexyl phthalate in a Bacillus subtillus recombinant assay system.

Results of a dominant lethal assay in mice have indicated DEHP and dimethoxyethyl phthalate showed some mutagenic activity (Singh, et al. 1974).

C. Teratogenicity

The teratogenic effects of a number of phthalate esters (DEHP, dimethyl, dimethoxyethyl, diethyl, diisobutyl, butylcarbobutoxymethyl, and dioctyl phthalates) have been reported in rats (Singh, et al. 1972). Teratogenic effects were not seen following oral administration of DEHP and dibutyl phthalate to rats (Nikonorow, et al. 1973). Damage to the nervous system or developing chick embryos has been produced by injection of dibutoxyethyl phthalate, di-(2-methoxy-ethyl) phthalate, and octyl-isodecyl phthalate (Bower, et al. 1970).

D. Other Reproductive Effects

Effects on implantation and parturition have been observed in pregnant rats injected intraparenteneally with DEHP, dibutyl phthalate, and dimethyl phthalate (Peters and Cook, 1973). A three generation rat reproduction study has indicated decreased fertility following maternal DEHP treatment (Industrial Bio-Test, 1978).

Testicular damage has been reported in rats administered DEHP intraparenteneally or orally. Seth, et al. (1976) found degeneration of the seminiferous tubules and changes in spermatagonia; testicular atrophy and morphological damage was noted in rats fed DEHP or dibutyl phthalate (Carter, et al. 1977).

E. Chronic Toxicity

An increase in toxic polyneuritis has been reported by Milkov, et al. (1973) in workers exposed primarily to dibutyl phthalate. Lesser levels of exposure to dioctyl, diisooctyl, benzylbutyl phthalates, and tricresyl phosphate were also noted. Neurological symptoms have been observed in several phthalate plasticizer workers (Gilioli, 1978). Animal studies have shown central nervous system degeneration and encephalopathy in rats administered large oral or intraperitoneal doses of butylbenzyl phthalate (Mallette and Von Hamm, 1952).

Oral DEHP feeding has produced liver and kidney weight increases in several animal studies (U.S. EPA, 1979). Chronic exposure to transfused blood containing DEHP has produced liver damage in monkeys (Kevy, et al. 1978). Lake, et al. (1975) have produced liver damage in rats by administration of mono-2-ethylhexyl phthalate.

Two-year feeding studies with female rats have shown some kidney effects produced by dimethyl phthalate (Draize, et al. 1948).

F. Other Relevant Information

Several animal studies have demonstrated that DEHP pretreatment of rats resulted in increased hexobarbital sleeping times (Daniel and Bratt, 1974; Rubin and Jaeger, 1973; Swinyard, et al. 1976).

V. AQUATIC TOXICITY

A. Acute Toxicity

Acute values for freshwater fish were derived from eight 96-hour bioassays for four phthalate esters. LC_{50} values ranged from 730 µg/l for di-n-butyl phthalate in the bluegill sunfish (Lepomis macrochirus) (Mayer and Sanders, 1973) to 98,200 µg/l in diethyl phthalate for the bluegill, Lepomis macrochirus. Butylbenzyl and dimethyl phthalates were intermediate in their toxicity in bluegill assays with LC_{50} values of 43,300 to 49,500 µg/l respectively (U.S. EPA, 1978). The scud, Gammarus pseudolimnaeus, was the most sensitive of freshwater species tested, producing a static 48-hour adjusted LC_{50} value of 765 µg/l (Mayer and Sanders, 1973). In 48-hour static Daphnia magna assays, the adjusted LC_{50} values for butylbenzyl, diethyl dimethyl, and di-n-ethylhexyl phthalates were 92,300, 52,100, 33,000, and 11,100 µg/l, respectively. Among marine fish, juvenile sheepshead minnows, Cyprinodon variegatus, were most susceptible to diethyl phthalate, producing a static 96-hour LC_{50} value of 29,600 µg/l. In similar assays, the LC_{50} values for butylbenzyl and dimethyl phthalate were 445,000 µg/l and 58,000 µg/l respectively. The marine mysid shrimp, Mysidopsis bahia, was tested with diethyl phthalate, and produced a 96-hour LC_{50} value of 7,590 µg/l. LC_{50} values of 9,630 and 73,700 µg/l were reported for butylbenzyl and dimethyl phthalates, respectively, in mysid shrimp assays.

B. Chronic Toxicity

The only chronic studies available are for one species of freshwater fish and one species of freshwater invertebrate (Mehrle and Mayer, 1976; Mayer and Sanders, 1973). A chronic value of 4.2 µg/l was obtained in a rainbow trout, Salmo gairdneri, embryo-larval study of di-(2-ethylhexyl)

phthalate. In Daphnia magna significant reproductive impairment was observed for di-2(-ethylhexyl) phthalate at 3.0 µg/l, the lowest concentration tested. Chronic marine data was not available.

C. Plant Effects

In the freshwater algae, Selenastrum capricornutum, effective concentration ranges of 110 to 130 µg/l; 85,600 to 90,300 µg/l and 39,800 to 42,700 µg/l were obtained for butylbenzyl, diethyl and dimethyl phthalates respectively. Effective concentrations were based on chlorophyll a content and cell number.

D. Residues

Bioconcentration factors have been obtained for five of the phthalates. In the scud, bioconcentration factors of 1400 were reported for di-n-butyl phthalate, and 54,2680 for di-(2-ethylhexyl) phthalate. In the bluegill, bioconcentration factors of 57, 117, and 663 were obtained for dimethyl, diethyl, and butylbenzyl phthalates, respectively. For di-(2-ethylhexyl) phthalate bioconcentration factors were reported from 24 to 150 for the sowbug, Ascellus brevicaudus, 42 to 113 for the rainbow trout, and 155 to 886 for the fathead minnow.

VI. EXISTING GUIDELINES AND STANDARDS

Neither the human health nor the aquatic criteria derived by U.S. EPA (1979), which are summarized below, have gone through the process of public review; therefore, there is a possibility that these criteria will be changed.

A. Human

Based on "no effect" levels observed in chronic feeding studies of rats or dogs, the U.S. EPA calculated acceptable daily intake (ADI) levels for several phthalates, and established recommended water quality criteria

levels to protect human health for dimethyl phthalate, diethyl phthalate, dibutyl phthalate, and DEHP. These levels are listed in Table 2 (U.S. EPA, 1979)

B. Aquatic

Data are insufficient to derive draft criteria for any of the phthalate esters in either freshwater or marine environments (U.S. EPA, 1979).

TABLE 2

CALCULATED ALLOWABLE DAILY INTAKE IN WATER AND FISH FOR VARIOUS PHTHALATE ESTERS (U.S. EPA, 1979)

Ester	No Effect Dose (mg/kg/day)	Species	Days	ADI** (mg/day)	F***	Recommended Criteria (mg/l)
Dimethyl	1000	Rat	104	700	130	160
Diethyl	625	Dog	52	438	270	60
Dibutyl	18	Dog	52	12.6	26	5
Dicyclohexyl	14	Dog	52	9.8	Not Established	
Methyl phthayl ethyl glycolate	750	Rat	104	525	Not Established	
Ethyl phthayl ethyl glycolate	250	Rat	104	175	Not Established	
Butyl phthayl ethyl glycolate	140	Dog	104	98	Not Established	
Di-2-ethyhexyl	60	Dog	52	42	95	10

**Allowable Daily Intake for 70 kg person (100 safety factor)
***F = Biomagnification factor

PHTHALATE ESTERS

REFERENCES

Albro, P.W., et al. 1973. Metabolism of diethhexyll phthalate by rats. Isolation and characterization of the urinary metabolies. Jour. Chromatogr. 76: 321.

Autian, J. 1973. Toxicity and health threats of phthalate esters: Review of the literature. Environ. Health Perspect. June 3.

Bower, R.K., et al. 1970. Teratogenic effects in the chick embryo caused by esters of phthalic acid. Jour. Pharmacol. Exp. Therap. 171: 314.

Carter, B.R., et al. 1977. Studies on dibutyl phthalate-induced testicular atrophy in the rat: Effect on zinc metabolism. Toxicol. Appl. Pharmacol. 41: 609.

Daniel, J.W., and H. Bratt. 1974. The absorption, metabolism and tissue distribution of di(2-ethylhexyl) phthalate in rats. Toxicology 2: 51.

Draize, J.H., et al. 1948. Toxicological investigations of compounds proposed for use as insect repellents. Jour. Pharmacol. Exp. Ther. 93: 26.

Engelhardt, G. et al. 1975. The microbial metabolism of di-n-butyl phthalate and related dialkyl phthalates. Bull. Environ. Contam. Toxicol. 13: 342.

Gilioli, R. et al. 1978. A neurological electromyographic and electroneurographic study in subjects working at the production of phthalate plasticizers: Preliminary results. Med. Law. 69: 631.

Industrial Bio-Test. 1978. Three generation reproduction study with di-2-ethyl hexyl phthalate in albino rats. Plastic Industry News, 24, 201-203.

Jaeger, R.J., and R.J. Rubin. 1970. Plasticizers from plastic devices: Extraction, metabolism, and accumulation by biological systems. Science 170: 460.

Kevy, S.V., et al. 1978. Toxicology of plastic devices having contact with blood. Rep. NO1 HB 5-2906, Natl. Heart, Lung and Blood Inst. Bethesda, Md.

Lake, B.G., et al. 1975. Studies on the hepatic effects of orally administered di-(2-ethylhexyl) phthalate in the rat. Toxicol. Appl. Pharmacol. 32: 355.

Lake, B.G., et al. 1977. The in vitro hydrolysis of some phthalate diesters by hepatic and intestinal preparations from various species. Toxicol. Appl. Pharmacol. 39: 239.

Mallette, F.S., and E. Von Haam. 1952. The toxicity and skin effects of compounds used in the rubber and plastics industries. II. Plasticizers. Arch. Ind. Hyg. Occup. Med. 6: 231.

Mayer, F.L. Jr., and H.O. Sanders. 1973. Toxicology of phthalic acid esters in aquatic organisms. Environ. Health Perspect. 3: 153.

Mehrle, P.M., and F.L. Mayer. 1976. Di-2-ethylhexylphthalate: Residue dynamics and biological effects in rainbow trout and fathead minnows. Pages 519-524. In Trace substances in environmental health. University of Missouri Press, Columbia.

Milkov, L.E., et al. 1973. Health status of workers exposed to phthalate plasticizers in the manufacture of artificial leather and films based on PVC resins. Environ. Health Perspect. Jan. 175.

Nikonorow, M., et al. 1973. Effect of orally administered plasticizers and polyvinyl chloride stabilizers in the rat. Toxicol. Appl. Pharmacol. 26: 253.

Peakall, D.B. 1975. Phthalate esters: Occurrence and biological effects. Residue Rev. 54: 1.

Peters, J.W., and R.M. Cook. 1973. Effects of phthalate esters on reproduction of rats. Environ. Health Perspect. Jan. 91.

Rock, G. et al. 1978. The accumulation of mono-2-ethyl hexyl phthalate (MEHP) during storage of whole blood and plasm. Transfusion 18 553.

Rubin, R.J., and R.J. Jaeger. 1973. Some pharmacologic and toxicologic effects of di-2-ethylhexyl phthalate (DEHP) and other plasticizers. Environ. Health Perspect. Jan. 53.

Rubin, R.J., et al. 1979. Ames mutagenic assay of a series of phthalic acid esters: positive response of the dimethyl and diethyl esters in TA 100. Abstract. Soc. Toxicol. Annu. Meet. New Orleans, March 11.

Schulz, C.O., and R.J. Rubin. 1973. Distribution, metabolism and excretion of di-2-ethylhexyl phthalate in the rat. Environ. Health Perspect. Jan. 123.

Seth, P.K., et al. 1976. Biochemical changes induced by di-2-ethylhexyl phthalate in rat liver. Page 423 in Environmental biology. Interprint Publications, New Delhi, India.

Shaffer, C.B., et al. 1945. Acute and subacute toxicity of di(2-ethyhexyl) phthalate with note upon its metabolism. Jour. Ind. Hyg. Toxicol. 27: 130.

Singh, A. et al. 1972. Teratogenicity of phthalate esters in rats. J. Pharm. Sci. 61, 51 (1972).

Singh, A.R., et al. 1974. Mutagenic and antifertility sensitivities of mice to di-2-ethylhexyl phthalate (DEHP) and dimethoxyethyl phthalate (DMEP). Toxicol. Appl. Pharmacol. 29: 35.

Singh, A.R., et al. 1975. Maternal-fetal transfer of ^{14}C-di-2-ethylhexyl phthalate and ^{14}C-diethyl phthalate in rats. Jour. Pharm. Sci. 64: 1347.

Swinyard, E.A., et al. 1976. Nonspecific effect of bis(2-ethylhexyl) phthalate on hexobarbital sleep time. J. Pharm. Sci. 65: 733.

Tomita, I., et al. 1977. Phthalic acid esters in various foodstuffs anmd biological materials. Ecotoxicology and Environmental Safety. 1: 275.

U.S. EPA. 1978. In-depth studies on health and environmental impacts of selected water pollutants. U.S. Environ. Prot. Agency, Contract No. 68-01-4646.

U.S. EPA. 1979. Phthalate Esters: Ambient Water Quality Criteria Document. (Draft).

U.S. International Trade Commission. 1978. Synthetic organic chemicals, U.S. production and sales. Washington, D.C.

Waddell, W.M., et al. 1977. The distribution in mice of intravenously administered ^{14}C-di-2-ethylhexyl phthalate determined by whole-body autoradiography. Toxicol. Appl. Pharmacol. 39: 339.

Wallin, R.F., et al. 1974. Di(2-ethylhexyl) phthalate (DEHP) metabolism in animals and post-transfusion tissue levels in man. Bull. Parenteral Drug Assoc. 28: 278.

Yagi, Y. et al. 1978. Embryotoxicity of phthalate esters in mouse. In: Proceedings of the First International Congress on Toxicology. Plaa, G. and Duncan. W. (eds.)

No. 147

Phthalic Anhydride

Health and Environmental Effects

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WASHINGTON, D.C. 20460

APRIL 30, 1980

-1753-

DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

PHTHALIC ANHYDRIDE

Summary

Phthalic anhydride failed to produce carcinogenic effects in rats or mice in a long term National Cancer Institute (NCI) feeding study (7,500 ppm; 15,000 ppm).

Information on the mutagenic effects of phthalic anhydride was not found in the available literature.

The hydrolysis product of phthalic anhydride, phthalic acid, has shown teratogenic effects in the developing chick embryo, but not in any mammalian tests. Phthalic anhydride inhalation at high levels may produce reproductive impairment in male rats.

Chronic occupational exposure to phthalic anhydride has been reported to produce progressive respiratory damage in workers, including marked fibrosis of the lungs.

Data concerning the effects of phthalic anhydride to aquatic organisms was not found in the available literature.

PHTHALIC ANHYDRIDE

I. INTRODUCTION

This profile is based on the Preliminary Environmental Hazard Assessment of Chlorinated Naphthalenes, Silicones, Fluorocarbons, Benzenepolycarboxylates, and Chlorophenols (U.S. EPA, 1973).

Phthalic anhydride (molecular weight - 148.1) is a white, crystalline solid that melts (sublimes) at 131°C, has a boiling point of 284.5°C, a density of 1.527, and a solubility of 0.62 gms/100 gms water at 25°C (Towle, et al. 1968). This compound is soluble in alcohol and sparingly soluble in ether.

The major uses of phthalic anhydride are in the synthesis of plasticizers, alkyd resins, unsaturated polyester resins, and in the preparation of various classes of chemical dyes (U.S. EPA, 1973).

Production of phthalic anhydride in 1971 was 4×10^5 tons (Blackford, 1970).

Phthalic anhydride is in equilibrium with phthalic acid in aqueous systems. Under dry conditions, phthalic anhydride is relatively stable at ambient temperature (U.S. EPA, 1973). Elevated temperatures will produce oxidative degradation of phthalic anhydride.

Phthalic anhydride is biodegraded by microorganisms (Ribbons and Evans, 1960; Saegar and Tucker, 1973).

II. EXPOSURE

Phthalic anhydride is used in large quantities and therefore has potential for industrial release and environmental contamination. No monitoring data are available to indicate ambient air or water levels of the compound. Fawcett (1970) has determined 40-200 ppm by volume in phthalic anhydride

off-gas process. Phthalic acid wastes have been noted in waste waters from paint and varnish industries (Mirland and Sporykhina, 1968) and alkyd resin plants (Minkovich, 1960).

Human exposure to phthalic anhydride from foods cannot be assessed, due to a lack of monitoring data.

Release of phthalic acid from parenterally-used plastic medical devices (blood bags, plastic tubings, catheters, etc.) may occur since these materials have been treated with phthalate plasticizers; however, no data on this type of release are available (U.S. EPA, 1973).

Bioaccumulation data on phthalic anhydride were not found in the available literature.

III. PHARMACOKINETICS

Specific information on the metabolism, distribution, absorption, or elimination of phthalic anhydride was not found in the available literature.

IV. EFFECTS

A. Carcinogenicity

A long-term carcinogenesis bioassay in rats and mice fed phthalic anhydride (7,500 ppm; 15,000 ppm) has been conducted by the NCI (1979). The results indicate that oral administration of these levels of the compound produced no carcinogenic effects in either of the species used.

B. Mutagenicity

Information on the mutagenic effects of phthalic anhydride was not found in the available literature.

C. Teratogenicity

Phthalic acid was shown to produce an increase in teratogenic effects in the developing chick embryo following injection (Verrett, et al.

1969). Mammalian testing of phthalic acid for teratogenicity failed to show effects in mice (Koehler, et al. 1971).

D. Reproductive Effects

Inhalation exposure of rats to phthalic anhydride at high levels (100-200 mg/l) has been reported to cause testicular changes and impaired reproductive capability (Protsenko, 1970).

E. Chronic Toxicity

Markman and Savinkina (1964) have reported progressive respiratory damage in workers exposed to phthalic anhydride for two years or more. Workers exposed for six years evidenced marked fibrosis of the lungs.

F. Other Relevant Information

Phthalic anhydride has been implicated as a skin sensitizing agent in some individuals exposed for prolonged periods of time (Amer. Ind. Hyg. Assoc., 1967).

V. AQUATIC TOXICITY

Data concerning the effects of phthalic anhydride to aquatic organisms were not found in the available literature.

VI. EXISTING GUIDELINES

The 8-hour, TWA occupational exposure limit established for phthalic anhydride is 1 ppm (ACGIH, 1977).

PHTHALIC ANHYDRIDE

References

American Industrial Hygiene Association. 1967. Phthalic anhydride: Human toxicity. Amer. Ind. Hyg. Assoc. J. 28: 395.

ACGIH. 1977. Threshold limit values for chemical substances in workroom air.

Blackford, J.L. 1970. Isophthalic acid. Chemical economics handbook, Stanford Research Institute.

Fawcett, R.L. 1970. Air pollution potential of phthalic anhydride. J. Air Pollut. Contr. Assoc. 20: 461.

Koehler, F., et al. 1971. Teratogenicity of thalidomide metabolites. Experientia. 27: 1149.

Markman, G.I. and R.A. Savinkina. 1964. The condition of the lungs of workers in phthalic anhydride production (an x-ray study). Kemerovo. 35.

Mirland, L.A. and V.A. Sporykhina. 1968. Polarographic determination of phthalic acid in waste waters from the paint and varnish industry. Lakokrasch. Mater. Ikh. Primen. 1: 49.

Minkovich, O.A. 1960. The recovery of phthalic anhydride wastes in the manufacture of alkyd resins. Lakokra. Mater. i ikh Primen. 1: 83.

NCI. 1979. Bioassay of phthalic anhydride for possible carcinogenicity. NCI-CG-TR-159.

Protsenko, E.I. 1970. Gonadotropic action of phthalic anhydride. Gig. Sanit. 35: 105.

Ribbons, D.W. and W.C. Evans. 1960. Oxidative metabolism of phthalic acid by soil pseudomonads. Biochem. J. 76: 310.

Saegar, V.W. and E.S. Tucker. 1973. Biodegradation of phthalate esters. In: Flexible vinyls and human safety: An objective analysis. Conference of the Society of Plastics Engineers, Inc., March 20-22. Kiamesha Lake, N.Y.

Towle, P.H., et al. 1968. Phthalic acids and other benzenepolycarboxylic acids. Vol. 15, p. 444. In: A Stauden (ed.), Encyclopedia of chemical technology. 2nd ed. J. Wiley & Sons, New York.

U.S. EPA. 1973. Preliminary hazard assessment of chlorinated naphthalenes, silicones, fluorocarbons, benzenecarboxylates, and chlorophenols.

Verrett, M.J., et al. 1969. Teratogenic effects of captan and related compounds in the developing chick embryo. Ann. N.Y. Acad. Sci. 160: 334.

No. 148

2-Picoline

Health and Environmental Effects

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WASHINGTON, D.C. 20460

APRIL 30, 1980

-1760-

DISCLAIMER

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2-PICOLINE

Summary

Pertinent data could not be found that defined 2-picoline as a carcinogen or a mutagen. Studies on rats indicated that the structure and composition of the liver and the structure and growth pattern of the skin were disrupted in the offspring of tested rats who were given 157 mg per kg body weight daily during their pregnancy.

2-picoline has been shown to produce biochemical and physical changes in the liver, spleen, bone marrow, and lymph nodes.

I. INTRODUCTION

2-picoline (alpha-picoline, 2-methylpyridine; CAS No. 109-06-8) is a colorless liquid possessing a strong unpleasant odor. It has the following physical properties:

Formula:	C_6H_7N
Molecular Weight:	93.12
Melting Point:	-70°C
Boiling Point:	129°C
Vapor Pressure:	8 mm Hg at 20°C
Vapor Density:	3.21

2-picoline is freely soluble in water and miscible with alcohol and ether (Windholz, 1976). 2-picoline is used as an organic solvent and intermediate in the dye and resins industries.

II. EXPOSURE

A. Water

Pertinent data could not be located in the available literature.

B. Food

Pertinent data could not be located in the available literature.

C. Inhalation

2-picoline occurs in the working environment of coke oven workers (Naizer and Mashek, 1974) and is present in cigarette smoke (Brennemann et. al., 1979).

D. Dermal

Pertinent data could not be located in the available literature.

III. PHARMACOKINETICS

A. Absorption

In rats, 2-picoline is rapidly absorbed and taken up by the liver, heart, spleen, lungs, brain, and muscles during the first 10 to 20 minutes after oral administration (Kupor, 1972).

B. Distribution

Pertinent data could not be located in the available literature.

C. Metabolism and Excretion

Most of an administered dose in an acute toxicity study was excreted in the urine within 48 hours (Kuper, 1972).

IV EFFECTS

A. Carcinogenicity

Pertinent data could not be found in the available literature.

B. Mutagenicity

Pertinent data could not be found in the available literature.

C. Teratogenicity

The structure and composition of the liver and the structure and growth pattern of the skin were disrupted in the offspring of treated rats who were administered 157 mg per kg body weight of 2-picoline throughout their pregnancy (Nikiforova and Taskaev, 1974).

D. Other Reproductive Effects

Glycolytic processes and protein formation in the liver was disturbed during the pregnancy of rats inhaling 2-picoline at

the maximum permissable concentration for 4 months. The pregnancy complicated toxicosis which without pregnancy was successfully compensated by the liver (Taskaev, 1979).

E. Chronic Toxicity

The following biochemical and physical changes have been observed in rats after the administration of 2-picoline; changes occurred in the liver carbohydrate metabolism (Taskaev, 1979; Kuper and Gruzdeva, 1974) and changes occurred in protein synthesis of the liver noted after chronic oral (Kuper and Gruzdeva, 1974) and inhalation (Taskaev, 1979) exposure. Administration of low doses results in changes in LDH isoenzyme distribution and activity (Gruzdeva, 1976). The major chronic effects of 2-picoline are injury to the liver (Ovchinnikova, 1978; Taskaev, 1979; Ovchinnikova, 1977) and spleen, bone marrow, and lymph nodes (Semchenko, 1973 and 1972).

F. Other Relevant Information

Pertinent data could not be found in the available literature.

V. AQUATIC TOXICITY

A. Acute Toxicity

Pertinent information could not be found in the available literature.

B. Chronic Toxicity, Plant Effects and Residues

Pertinent information could not be found in the available literature.

C. Other Relevant Information

Pertinent information could not be found in the available literature.

VI. EXISTING GUIDELINES AND STANDARDS

A. Human

The 8-hour, time-weighted average occupational exposure limit for alpha-picoline has been set in Russia at 5 mg/m^3 (Verschueren, 1977). Maximum allowable concentration in Class I waters for the production of drinking waters has been set in the Netherlands at 0.05 mg/l (Verschueren, 1977).

B. Aquatic

Pertinent information could not be found in the available literature.

REFERENCES

Brunnemann, K.D., and et. al., 1978. Chemical Studies on Tobacco Smoke: LXI. Volatile Pyridines: Quantitative Analysis in Mainstream and Sidestream Smoke of Cigarettes and Cigars. Anal. Lett. 11(7): 545-560.

Gruzdeva. K.N., et. al. 1976. Use of Electrophoretic Methods for Determining Lactate Dehydrogenase Isoenzymes in Studying Chronic Poisoning with Pyridine Derivatives. Khromatogr. Elektroforeticheakia Metody Issled. Biol. Aktiv. Soedin. 44-7.

Kuper, V.G. Distribution of alpha-Picoline in Rat Tissue During Acute alpha-Picoline Intoxication. Vop. Patokhimii Biokhim. Belkov. Drugikh Biol. Aktiv. Soedin. 51-2.

Kuper, V.G., and K.N. Gruzdeva. 1974. Concerning the Question of Carbohydrate Metabolism After Chronic Poisoning with alpha-Picoline. Narusheniya Metab., Tr. Naucha. Konf. Med. Inst. Zapadn., Sib., 1st, 261-5.

Naizer, Y., and V. Mashek. 1974. Determination of Pyridine and Its Homologs in the Environment of Coke Plant Workers. Gig. Sanit. (5):76-78.

Nikiforova, A.A., and I.I. Taskaev. 1974. Liver and Skin Morphogenesis in Some Laboratory Animal Embryos Following Poisoning with Pyridine Bases. Reakt. Plast. Epiteliya Soedin. Tkani Norm, Eksp. Patol. Usloviyakh, Dokl. Mezhvuz, Gistol. Konf. 196-9.

Ovchinnikova, L.S. 1977. Morpholgical and Histochemical Changes in White Rats Liver After Acute Poisoning with alpha-Picoline and 2,5-Lutidine. Gig. Aspekty Okhr. Zdorov'ya Naseleniya. 124-5.

Ovchinnikova, L.S., and Lambina. 1978. Morphohistochemical Changes in Liver of White Rats with Subacute Poisoning with Products of Synthetic Rubber Production. Deposited Doc., ISS. Viniti 2667-78, 101-2.

Semchenko, V.V. 1972. Regenerative Processes in Blood-Forming Organs of Experimental Animals During and After Chronic Intoxication by Methylpyridine. Mater. Nauch. Sess., Posvyashch. 50-Letiyu Obrazov. SSSR, Omsk, Gos. Med. Inst. 896-8.

Semchenko, V.V. 1973. Histological and Histochemical Characteristics of Spleen and Lymph Nodes of Rats During Chronic Intoxication with alpha-Picoline and 2,5-Lutidine. Hezenkhima Tkanevya Proizvod. Evol. Ontog., 56-8.

REFERENCES

Taskaev, I.T. 1979. Histological and Cytological Changes in Rat Liver During Experimental Poisoning and Subsequent Pregnancy. Arkh. Anat., Gistol. Embriol. Vol. 76, ISS. 2, 49-54.

Verschueren, K. 1977. Handbook of Environmental Data on Organic Chemicals. Van Nostrand Reinhold Company. New York.

Windholz, Martha et. al. (editors). 1976. The Merck Index. Merck & Co., Inc. Rahway, N.J.

No. 149

Polynuclear Aromatic Hydrocarbons (PAH)

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
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DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

SPECIAL NOTATION

U.S. EPA's Carcinogen Assessment Group (CAG) has evaluated polynuclear aromatic hydrocarbons and has found sufficient evidence to indicate that this compound is carcinogenic.

POLYNUCLEAR AROMATIC HYDROCARBONS (PAH)

SUMMARY

The first chemicals ever shown to be involved in the development of cancer belong to the polycyclic aromatic hydrocarbon (PAH) class. Several PAH are well-known as animal carcinogens by all routes of administration. Others are not carcinogenic alone, but in certain cases can enhance or inhibit the tumorigenic response of carcinogenic PAH. Numerous studies of workers exposed to coal gas, coal tars, and coke oven emissions, all of which have large amounts of PAH, have demonstrated a positive association between their exposures and lung cancer development. The carcinogenic risk of ingested PAH in humans, however, has not been extensively studied.

No standard toxicity data for aquatic organisms are available for freshwater or marine life. Limited information concerning toxic responses of freshwater fish reveals that concentrations of 1,000 μg/l for six months produced an 87% mortality in one warm water species.

I. INTRODUCTION

This profile is based primarily upon the Ambient Water Quality Criteria Document for Polynuclear Aromatic Hydrocarbons (U.S. EPA, 1979a) and the Multi-media Health Assessment Document for Polycyclic Organic Matter (U.S. EPA, 1979b).

Polycyclic aromatic hydrocarbons (PAH) are a diverse class of compounds consisting of substituted and unsubstituted polycyclic and heterocyclic aromatic rings. PAH are formed as a result of incomplete combustion of organic material (e.g., fossil fuels, wood, etc.). This leads to formation of C-H free radicals which can polymerize to form various PAH. Among these PAH are compounds such as benzo(a)pyrene (BaP) and benz(a)anthracene (BaA), which are ubiquitous in the environment and well-known for their carcinogenic activity. The presence in ambient air of over one hundred individual PAH has been reported, but quantitative data on only 26 PAH are available thus far.

Most of the PAH are high melting-point, high boiling-point solids that are very insoluble in water. As the ring size increases, the volatility decreases significantly. The PAH are strong absorbers of ultraviolet light, and PAH fluoresce strongly; both of these properties lead to analytical methods for detection of trace quantities. Because of their high melting points and low water solubilities and vapor pressures, most PAH are generally associated with particulate matter. In air, they are adsorbed on small diameter particles that can be easily inhaled. In water, PAH appear to also be primarily associated with particulate matter. Based upon water treatability of PAH, the compounds appear to exist in equal proportions in three forms; bound to large suspended particles; bound to finely dispersed particles, and as the dissolved form (U.S. EPA, 1979a).

PAH adsorbed to airborne particulate matter appear to be fairly stable in the environment. Nevertheless, some photooxidation occurs with atmospheric PAH since quinone derivatives have been detected in the atmosphere, and their concentrations increase during the summer when the light intensity is greatest.

Considerable study on the microbial and chemical stability and degradation of PAH in the aquatic environment has been conducted. In general, the low molecular weight molecules appear to biodegrade relatively rapidly while PAH containing more than three rings appear to be extremely stable. The first step in the microbial degradation process appears to be the formation of ortho-dihydrodiols which rapidly react to open the ring. PAH also appear to be light sensitive in aquatic systems, but the rate of degradation is difficult to determine experimentally since the vast majority of the compounds are adsorbed to particulate matter. Recent studies have shown that adsorption of many PAH compounds to sediments is a major transport process in aqueous systems. Studies in water treatment of municipal and industrial sewage indicate that about two-thirds of the PAH can be eliminated by sedimentation and biodegradation. If this secondary effluent is subjected to chemical treatment (chlorination or ozonation) the remaining PAH can be degraded.

II. EXPOSURE

A. Water

Based upon work by Basu and Saxena (1978) the average concentrations of BaP, carcinogenic PAH (BaP, benzo(j)fluoranthene, indeno(1,2,3-cd)-pyrene), and total PAH (above 3 compounds plus benzo(g,h.i)perylene, benzo-(b)fluoranthene, and fluoranthene) in U.S. drinking water are 0.55 ng/l, 2.1 ng/l, and 13.5 ng/l, respectively. No drinking water monitoring data on

other PAH compounds are available. The low con- centrations are somewhat a reflection of the extremely low water solu- bilities of PAH compounds. Slightly higher drinking water values have been reported in Europe (e.g. 3-5 ng/l carcinogenic PAH and 40-60 ng/l total PAH), but these differences will have relatively negligible effects on the calculated daily intake values through drinking water compared to other sources (U.S. EPA, 1979a). Assuming that a human consumes approximately 2 liters of water per day, the daily intake of PAH via drinking water would be:

0.55 ng/l x 2 liters/day = 0.0011 μg/day (BaP)
2.1 ng/l x 2 liters/day = 0.0042 μg/day (carcinogenic PAH)
13.5 ng/l x 2 liters/day = 0.0270 μg/day (total PAH)

B. Food

It is difficult to evaluate the human dietary intake of PAH through foods since the amount not only depends on the food habits of the individual and the style of cooking, but it also depends upon the origin of the foods. In order to provide a reasonably accurate estimate of the PAH dietary intake, average concentrations of PAH in representative food items would have to be available. Unfortunately, as of this date, these data have not been generated. However, examination of the available food monitoring data does suggest that a typical range of concentrations for PAH and BaP are 1.0-10.0 ppb and 0.1-1.0 ppb, respectively (U.S. EPA, 1979a). Combining these ranges with average total daily food consumption by man from all types of foods of 1600 g/day, the following estimates of dietary PAH and BaP intake are possible:

0.1 - 1.0 ppb x 1600 g/day = 0.16 - 1.6 μg/day (BaP)
1.0 - 10 ppb x 1600 g/day = 1.6 - 16 μg/day (PAH)

The U.S. EPA (1979a) has estimated the weighted average bioconcentration factors for the edible portion of all aquatic organisms consumed by Americans. These range from 120 to 24,000, and are based on the octanol-/water partition coefficients for each compound.

C. Ambient Air

It is not possible to determine the average intake of PAH from inhalation of ambient air in the United States because the monitoring data have focused mostly on BaP concentrations. However, by making some assumptions, it is possible to provide estimates that are reasonably close to probable actual values. Using the 1974-1975 Los Angeles monitoring data from Gordon (1976), the relative amounts to carcinogenic PAH and total PAH compared to the average BaP concentration are presented below.

	BaP	Carcinogenic PAH	Total PAH
Ambient conc. ng/m^3	0.5-2.9	2.0	10.9
Inhalation intake, micrograms/day[a]	0.0095-0.0435	0.038	0.207

[a]Assumed average air breathed per day was 19 m^3

III. PHARMACOKINETICS

There are no data available concerning the pharmacokinetics of PAH in humans. Nevertheless, it is possible to make limited assumptions based on the results of animal studies conducted with several PAH, particularly BaP. The metabolism of PAH in human and animal tissues has been especially well-studied, and has contributed significantly to an understanding of the mechanisms of PAH-induced cancer.

A. Absorption

Regardless of the route of exposure, it can be demonstrated in laboratory animals that PAH are readily absorbed across all epithelia which are in contact with the external environment (Rees, et al. 1971; Kotin, et al. 1969; Vainio, et al. 1976). The fact that PAH are generallly high lipid-soluble neutral molecules greatly facilitates their passage through the predominantly lipid-like cell membranes of animals, including man.

B. Distribution

Upon reaching the bloodstream, PAH are rapidly distributed to most internal body organs (Kotin, et al. 1969; Bock and Dao, 1961; Dao, et al. 1959; Flesher, 1967). Under experimental conditions with laboratory animals, the route of exposure has little apparent influence on the tissue localization of PAH. Extensive localization in the fat and fatty tissues (e.g., breast) is observed (Bock and Dao, 1961; Schlede, et al. 1970 a,b) and suggests that these tissues may act as a chemical trap, creating a situation for sustained release of the unchanged substance. In pregnant rats, it is apparent that BaP and 7,12-dimethylbenz(a)anthracene, but probably not 3-methylcholanthrene, are capable of transplacental passage and localization in the fetus (Shendrikova and Aleksandrov, 1974).

C. Metabolism

PAH are metabolized by the microsomal mixed-function oxidase system, also known as aryl hydrocarbon hydroxylase. This enzyme system is readily inducible and is found in most mammalian tissues, although predominantly in the liver. In conjunction with various P-450 type cytochromes, this enzyme complex is involved in detoxification of many xeno-

biotics, but may also catalyze the formation of reactive epoxide metabolites, themselves leading to carcinogenesis. A second microsomal enzyme, epoxide hydrase, converts epoxide metabolites of PAH to vicinal glycols, a process which may also be of critical importance in the process of carcinogenesis.

Because of the importance of metabolic activation for the expression of carcinogenic effects by PAH, the chemical fate of many representative compounds in mammalian cells has been extensively explored (U.S. EPA, 1979a). By far the most widely studied of the PAH has been BaP, one of the principal carcinogenic products from the combustion of organic material. The metabolites of BaP (and all PAH) can be divided into a water-soluble and an organic solvent-soluble fraction. Components of the latter fraction are primarily ring-hydroxylated products, quinones, and labile epoxide intermediates. For BaP there are at least three dihydrodiols, three quinones, and four phenols which can be detected as positional isomers. The K-region (4,5-) and non-K-region (7,8-; 9,10-) epoxides are precursors of the corresponding vicinal diols, which are formed by the action of the epoxide hydrase enzyme. A subsequent oxidative attack by aryl hydrocarbon hydroxylase may convert the non-K-region diols to vicinal diol epoxides, one of which (7,8-diol-9,10-epoxide) is an ultimate carcinogenic form of BaP.

In the water-soluble fraction containing BaP metabolites are mainly conjugates of hydroxylated products with glutathione, glucuronic acid, and sulfate. This group of metabolies is tentatively regarded to be composed of non-toxic excretion products.

The general scheme of metabolism for unsubstituted PAH closely parallels that for BaP, although several other major environmental PAH have not been studied. It is also evident that K-region derivatives of PAH may be preferred targets for conjugation and excretion, whereas non-K-region epoxides undergo further reductions and oxidative attack to form toxicologically important molecules. For PAH bearing alkyl substituents (e.g., DMBA, MCA), the primary metabolites formed are hydroxymethyl derivatives. Nevertheless, epoxidation reactions at K-region and non-K-region aromatic double bonds occur which are catalyzed by aryl hydrocarbon hydroxylase. Removal of activated intermediates occurs by conjugation with glutathione or glucuronic acid, or by further metabolism to tetrahydrotetrols.

D. Excretion

Over forty years ago, researchers recognized that various PAH were excreted primarily through the hepatobiliary system and the feces (Peacock, 1936; Chalmers and Kirby, 1940). However, the rate of disappearance of various PAH from the body, and the principal routes of excretion are influenced both by structure of the parent compound and the route of administration (Heidelberger and Weiss, 1959; Aitio, 1974a,b). Moreover, the rate of disappearance of a PAH (i.e., benzo(a)pyrene) from body tissues can be stimulated markedly by prior treatment with inducers of microsomal enzymes (e.g., benzo(a)pyrene, 7,12-dimethylbenz(a)anthracene, 3-methylcholanthrene, chrysene) (Schlede, et al. 1970a,b). Likewise, it has been shown that inhibitors of microsomal enzyme activity, such as parathion and paraoxon, can decrease the rate of BaP metabolism in certain animal tissues (Weber, et al. 1976). From the available data concerning excretion of PAH in animals, it is apparent extensive bioaccumulation is not likely to occur.

IV. EFFECTS

A. Carcinogenicity

PAH were the first compounds ever shown to be associated with carcinogenesis. As of this date, carcinogenic PAH are still distinguished by several unique features: (1) several of the PAH are among the most potent carcinogens known to exist, producing tumors by single exposures to microgram quantities; (2) they act both at the site of application and at organs distant to the site of absorption; and (3) their effects have been demonstrated in nearly every tissue and species tested, regardless of the route of administration (U.S. EPA, 1979a). Among the more common PAH, at least one, BaP, is ubiquitous in the environment. In animals, PAH produce tumors which resemble human carcinomas. The demonstration that organic extracts of particulate air pollutants are carcinogenic to animals has raised concern over the involvement of PAH in human cancer formation (Hoffmann and Wynder, 1976).

Oral administration of PAH to rodents can result in tumors of the fore-stomach, mammary gland, ovary, lung, liver, and lymphoid and hematopoietic tissues (U.S. EPA, 1979a). Exposure to very small doses of PAH by inhalation or intratracheal instillation can also be an effective means of producing tumors of the respiratory tract. However, for both oral and intratracheal routes of administration, BaP is less effective than other PAH (e.g., DMBA, MCA) in producing carcinomas. However, BaP has a remarkable potency for the induction of skin tumors in mice that cannot be matched by any other environmental PAH. Therefore, caution must be exercised in considering the carcinogenicity of PAH as a class, or in using BaP as a representative example in evaluating the carcinogenic risk of PAH.

The presence of PAH in the air, or as components of soot, tars, and oils, have long been associated with an excess incidence of cancer in human populations (U.S. EPA, 1979a,b). However, it has never been possible to study a population having exposure to PAH in the absence of other potential carcinogens, cocarcinogens, tumor initiators, or tumor promoters.

Convincing evidence from air pollution studies indicates an excess of lung cancer mortality among workers exposed to large amounts of PAH-containing materials such as coal gas, tars, soot, and coke-oven emissions (Kennaway, 1925; Kennaway and Kennaway, 1936, 1947; Henry, et al. 1931; Kuroda, 1937; Reid and Buck, 1956; Doll, 1952; Doll, et al. 1965, 1972; Redmond, et al. 1972, 1976; Mazumdar, et al. 1975; Hammond, et al. 1976; Kawai, et al. 1967). However, no definite proof exists that the PAH present in these materials are responsible for the cancers observed. Nevertheless, our understanding of the characteristics of PAH-induced tumors in animals, and their close resemblance to human carcinomas of the same target organs, suggests PAH pose a carcinogenic threat to man, regardless of the route of exposure.

B. Mutagenicity

The demonstration of mutagenicity in bacterial and mammalian cells by exposure to PAH is generally equated with the capability to induce tumor formation. This assumption is based on the participation of a common electrophilic metabolite in producing the carcinogenic/mutagenic event, and the common target site in the cell (i.e., DNA or other components of the genome) for the effect to be produced.

In recent years, considerable research effort has been directed at determining the mutagenicity of various PAH derivatives as a means of identifying structural features associated with the biological effect produced.

Working with bacterial mutants which can be reverted to histidine independence by a chemically-induced mutation, epoxides of carcinogenic PAH were shown to possess significant mutagenicity (U.S. EPA, 1979a). Further work with cultured mammalian cells established that carcinogenic PAH can produce forward mutations when a drug metabolizing enzyme system is available (Huberman and Sachs, 1974, 1976).

Numerous attempts have been made to correlate exposure to PAH with the induction of chromosomal aberrations. Although variations in chromosome number and structure accompany PAH-induced tumors in rodents, it is not clear whether these changes are consistently observable (U.S. EPA, 1979a,b). No evidence in the published literature has been found to indicate that PAH may produce somatic mutations in the absence of neoplastic transformation.

C. Teratogenicity

PAH are not generally regarded to have significant teratogenic activity. BaP showed no effect on the developing embryo in several mammalian and non-mammalian species (Rigdon and Rennels, 1964; Rigdon and Neal, 1965). In contrast, DMBA and its hydroxymethyl derivatives apparently are teratogenic in the rat, but only at high doses (Currie, et al. 1970; Bird, et al. 1970).

D. Other Reproductive Effects

Little additional information is presently available to indicate whether PAH present a significant hazard to reproductive success. Furthermore, effects on the fetus which may be due to maternal toxicity or experimental conditions (e.g., injection vehicle, stress) have not been adequately dissociated from true embryotoxicity or teratogenesis.

E. Chronic Toxicity

Little attention has been paid to the non-carcinogenic effects of exposure to PAH. Nevertheless, it is known that tissues of the rapidly proliferating type (e.g., intestinal epithelium, bone marrow, lymphoid organs, testis) seem to be the preferred targets for PAH-induced cytotoxicity (U.S. EPA, 1979). This action is probably due to a specific attack on DNA of cells in the S phase of the mitotic cycle (Philips, et al. 1972).

Acute and chronic exposure to various carcinogenic PAH has resulted in selective destruction of hematopoietic and lymphoid elements, ovotoxicity and anti-spermatogenic effects, adrenal necrosis, and changes in the intestinal and respiratory epithelia (U.S. EPA, 1979a). For the most part, however, tissue damage occurs at dose levels that would also be expected to induce carcinomas, and thus the threat of malignancy predominates in evaluating PAH toxicity. For the non-carcinogenic PAH, there is a shortage of available data concerning their involvement in toxic responses.

V. AQUATIC TOXICITY

A. Acute Toxicity

Standard toxicity determinations for freshwater or marine organisms have not been conducted for any PAH. The marine worm, Neanther arenaceodenta, was exposed to crude oil extracts, and LC_{50} values for various PAH ranged from 300 to 1,000 μg/l (Neff, et al. 1976a,b). A 90 percent lethality, determined from photodynamic response, was obtained for the protozoa, Paramecium caudatum at an for anthracene concentration of 0-1 μg/l in one-hour exposures (Epstein, 1963). Bluegill sunfish (Lepomis macrochirus) displayed an 87% mortality at concentration of 1,000 μg/l benzo-a-anthracene.

B. Chronic

Standard toxicity studies using either freshwater or marine organisms have not been conducted on any PAH. A six-month study of benzo-(a)pyrene on the bluegill sunfish (Lepomis macrochirus) produced 87 percent mortality at a concentration of 1,000 ug/l (Brown, et al. 1975).

C. Plants

Studies of the effects of PAH on freshwater or marine plants could not be located in the available literature.

D. Residues

In short-term modeling of freshwater ecosystem studies, three-day bioconcentration factors for benzo(a)pyrene of 930, 5,258, 11,536, 82,231, and 134,248 were obtained for the mosquito-fish (Gambusia affinis), the algae Oedogonium cardiacum, the mosquito Culex pipiens quinquefasciatus, the snail Physa sp., and cladoceran Daphnia pulex, respectively (Lu, et al. 1977). For anthracene, a 1-hour bioconcentration factor of 200 was obtained for Daphnia magna (Herbes, 1976). For marine molluscs, bioconcentration factor values ranged from 8.2 for the clam (Rangia cuneata) (Neff, et al. 1976a) to 242 for the eastern oyster (Crassostrea virginica) (Couch, et al., in press).

VI. EXISTING GUIDELINES AND STANDARDS

Neither the human health and aquatic criteria derived by U.S. EPA (1979a), which are summarized below, have not gone through the process of public review; therefore, there is a possibility that these criteria may be changed.

A. Human

To date, one recommended standard for PAH as a class has been developed. The World Health Organization (1970) recommends a concentration of PAH in water not to exceed 0.2 μg/l. This recommended standard is based on the composite analysis of six PAH in drinking water: (1) fluoranthene, (2) benzo(a)pyrene, (3) benzo(g,h,i)perylene, (4) benzo(b)-fluoranthene, (5) benzo(k)fluoranthene, and (6) indeno(1,2,3-cd)pyrene.

In the occupational environment, a Federal standard has been promulgated for coke oven emissions, based primarily on the presumed effects of the carcinogenic PAH contained in the mixture as measured by the benzene soluble fraction of total particulate matter. Similarly, the American Conference of Governmental Industrial Hygiensists recommends a workplace exposure limit for coal tar pitch volatiles, based on the benzene-soluble fraction containing carcinogenic PAH. The National Institute for Occupational Safety and Health has also recommended a workplace criterion for coal tar products (coal tar, creosote, and coal tar pitch), based on measurements of the cyclohexane extractable fraction. These criteria are summarized below:

Substance	Exposure Limit	Agency
Coke Oven Emissions	0.150 mg/m^3, 8-hr. time-weighted average	U.S. Occupational Safety and Health Administration
Coal Tar Products	0.1 mg/m^3, 10-hr. time-weighted average	U.S. National Institute for Occupational Safety and Health
Coal Tar Pitch Volatiles	0.2 mg/m^3, (benzene soluble fraction) 8-hr. time-weighted average	American Conference of Governmental Industrial Hygienists

Based on animal bioassay data, and using the "one-hit" model, the U.S. EPA (1979a) has set draft ambient water quality criteria for BaP and dibenz(a,h)anthracene (DBA) which will result in specified risk levels of human cancer as shown in the table below.

BaP

Exposure Assumptions (per day)	Risk Levels and Corresponding Draft Criteria ng/l			
	0	10^{-7}	10^{-6}	10^{-5}
2 liters of drinking water and consumption of 18.7 grams fish and shellfish.	0	0.275	2.75	27.5
Consumption of fish and shellfish only.	0	1.25	12.5	125

DBA

Exposure Assumptions (per day)	Risk Levels and Corresponding Draft Criteria ng/l			
	0	10^{-7}	10^{-6}	10^{-5}
2 liters of drinking water and consumption of 18.7 grams fish and shellfish.	0	0.43	4.3	43
Consumption of fish and shellfish only.		1.96	19.6	196

8. Aquatic

Criteria have not been proposed for the protection of aquatic organisms (U.S. EPA, 1979a).

POLYNUCLEAR AROMATIC HYDROCARBONS

REFERENCES

Aitio, A. 1974a Different elimination and effect on mixed function oxidase of 20-methylcholanthrene after intragastric and intraperitoneal administration. Res. Commun. Chem. Path. Phamacol. 9: 701.

Aitio, A. 1974b. Effect of chrysene and carbon tetrachloride administration on rat hepatic microsomal monoxygenase and udglucuronsyltransferase activity. FEBS Lett. 42: 46.

Basu D.K. and J. Saxena. 1978. Polynuclear aromatic hydrocarbons in selected U.S. drinking waters and their raw water sources. Environ. Sci. Technol. 12: 75.

Bird, C.C., et al. 1970. Protection from the embryopathic effects of 7-hydroxymethyl-12-methylbenz(a) anthracene by 2-methyl-1,2-bis-(3 pyridyl)-1-propanone(metopirone ciba) and 8-diethyl-aminoethyl-diphenyl-n-propyl acetate (SKR 525-A). Br. Jour. Cancer 24: 548.

Bock, F.G., and T.L. Dao. 1961. Factors affecting the polynuclear hydrocarbon level in rat mammary glands. Cancer Res. 21: 1024.

Brown, E.R., et al. 1975. Tumors in fish caught in polluted waters: possible explanations. Comparative Leukemia Res. 1973, Leukemogenesis. Univ. Tokyo Press/Karger, Basel, pp. 47-57.

Chalmers, J.G., and A.H.M. Kirby. 1940. The elimination of 3,4-benzpyrene from the animal body after subcutaneous injection. I. Unchanged benzpyrene. Biochem. Jour. 34: 1191.

Couch, J.A. et al. The American oyster as an indicator of carcinogens in the aquatic environment. In: Pathobiology of environmental pollutants - animal models and wildlife of monitors. Storrs, Conn. National Academy of Sciences. (In press).

Currie, A.R., et al. 1970. Embryopathic effects of 7,12-dimethylbenz(a)anthracene and its hydroxymethyl derivatives in the Sprague-Dawley rat. Nature 226: 911.

Dao. T.L., et al. 1959. Level of 3-methylcholanthrene in mammary glands of rats after intragastric instillation of carcinogen. Proc. Soc. Exptl. Biol. Med. 102: 635.

Doll. R. 1952. The causes of death among gas workers with special reference to cancer of the lung. Br. Jour. Ind. Med. 9: 180.

Doll. R., et al. 1965. Mortality of gas workers with special reference to cancers of the lung and bladder, chronic bronchitis, and pneumoconiosis. Br. Jour. Ind. Med. 22: 1.

Doll R. et al. 1972. Mortality of gas workers - final report of a prospective study. Br. Jour. Ind. Med. 29: 394.

Epstein, S.S., et al. 1963. The photodynamic effect of the carcinogen, 3,4-benzpryene, on Paramecium caudatum. Cancer Res. 23: 35.

Flesher, J.S. 1967. Distribution of radioactivity in the tissues of rats after oral administration of 7,12-dimethyl-benz(a)anthracene-^{3}H. Biochem. Pharmacol. 16: 1821.

Gordon, R.J. 1976. Distribution of airborne polycyclic aromatic hydrocarbons throughout Los Angeles. Environ. Sci. Technol. 10: 370.

Hammond, E.C., et al. 1976. Inhalation of benzpyrene and cancer in man. Ann. N.Y. Acad. Sci. 271: 116.

Heidelberger, C., and S.M. Weiss. 1959. The distribution of radioactivity in mice following administration of 3,4-benzpyrene-5C^{14} and 1,2,5,6-dibenzanthracene-9, 10-C^{14}. Cancer Res. 11: 885.

Henry, S.A. et al. 1931. The incidence of cancer of the bladder and prostate in certain occupations. Jour. Hyg. 31: 125.

Herbes, S.E. 1976. Transport and bioaccumulation of polycyclic aromatic hydrocarbons (PAH) in aquatic systems. In: Coal technology program quarterly progress report for the period ending December 31, 1975. Oak Ridge National Lab., Oak Ridge, TN. ORNL-5120. pp. 65-71.

Hoffmann D. and E.L. Wynder. 1976. Respiratory carcinogenesis. In: chemical carcinogens C.E. Searle (ed.) ACS Monograph 173, Amer. Chem. Soc. Washington, D.C.

Huberman, E., and L. Sachs. 1974. Cell-mediated mutagenesis of mammalian cells with chemical carcinogens. Int. Jour. Cancer 13: 32.

Huberman, E., and L. Sachs. 1976. Mutability of different genetic loci in mammalian cells by metabolically activated carcinogenic polycyclic hydrocarbons. Proc. Natl. Acad. Sci. 73: 188.

Kawai, M., et al. 1967. Epidemiologic study of occupational lung cancer. Arch. Environ. Health 14: 859.

Kennaway, E.L. 1925. The anatomical distribution of the occupational cancers. Jour. Ind. Hyg. 7: 69.

Kennaway, E.L., and N.M. Kennaway. 1947. A further study of the incidence of cancer of the lung and larynx. Br. Jour. Cancer. 1: 260.

Kennaway, N.M., and E.L. Kennaway. 1936. A study of the incidence of cancer of the lung and larynx. Jour. Hyg. 36: 236.

Kotin, P., et al. 1969. Distribution, retention, and elimination of C^{14}-3,4 benzpyrene after administration to mice and rats. Jour. Natl. Cancer Inst. 23: 541.

Kuroda, S. 1937. Occupational pulmonary cancer of generator gas workers. Ind. Med. Surg. 6: 304.

Lu, P. et al. 1977. The environmental fate of three carcinogens: benzo-(a)-pyrene, benzidine, and vinyl chloride evaluated in laboratory model ecosystems. Arch. Environ. Contam. Toxicol. 6: 129.

Mazumdar, S., et al. 1975. An epidemiological study of exposure to coal tar pitch volatiles among coke oven workers. APCA Jour. 25: 382.

Neff, J.M., et al. 1976a. Effects of petroleum on survival, respiration and growth of marine animals. In: Sources, Effects and Sinks of Hydrocarbons in the Aquatic Environment. Proceedings of a symposium, American University, Washington, D.C., American Institute of Biological Sciences. p. 520.

Neff, J.M., et al. 1976b. Accumulation and release of petroleum-derived aromatic hydrocarbons by four species of marine animals. Mar. Biol. 38: 279.

Peacock, P.R., 1936. Evidence regarding the mechanism of elimination of 1,2-benzpyrene, 1,2,5,6-dibenzanthracene, and anthracene from the bloodstream of injected animals. Br. Jour. Exptl. Path. 17: 164.

Philips, E.F., et al. 1972. In vivo cytotoxicity of polycyclic hydrocarbons., Vol. 2. p. 75 In: Pharmacology and the Future of Man. Proc. 5th Intl. Congr. Pharmacology, 1972, San Francisco.

Redmond, C.K., et al. 1972. Long term mortaility study of steelworkers. Jour. Occup. Med. 14: 621.

Redmond, C.K., et al. 1976. Cancer experience among coke by-product workers. Ann. N.Y. Acad. Sci. p.102.

Rees, E.O., et al. 1971. A study of the mechanism of intestinal absorption of benzo(a)pyrene. Biochem. Biophys. Act. 225: 96.

Reid, D.D., and C. Buck, 1956. Cancer in coking plant workers. Br. Jour. Ind. Med. 13: 265.

Rigdon, R.H., and J. Neal. 1965. Effects of feeding benzo(a)pyrene on fertility, embryos, and young mice. Jour. Natl. Cancer Inst. 34: 297.

Rigdon, R.H., and E.G. Rennels. 1964. Effect of feeding benzpyrene on reproduction in the rat. Experientia 20: 1291.

Schlede, E., et al. 1970a. Stimulatory effect of benzo(a)pyrene and phenobarbital pretreatment on the biliary excretion of benzo(a)pyrene metabolites in.the rat. Cancer Res. 30: 2898.

Schlede, E. et al. 1970b. Effect of enzyme induction on the metabolism and tissue distribution of benzo(a)pyrene. Cancer Res. 30:2893.

Shendrikova, I.A., and V.A. Aleksandrov. 1974. Comparative characteristics of penetration of polycyclic hydrocarbons through the placenta into the fetus in rats. Byull. Eksperiment. Biol. i Medit. 77: 169.

U.S. EPA. 1979a. Polynuclear Aromatic Hydrocarbons: Ambient Water Quality Criteria (Draft).

U.S. EPA. 1979b. Multi-media Health Assessment of Polycyclic Organic Matter. (Draft) prepared under contract to U.S. EPA by J. Santodonato, et al., Syracuse Research Corp.

Vainio, H., et al. 1976. The fate of intratracheally installed benzo-(a)pyrene in the isolated perfused rat lung of both control and 20-methylcholanthrene pretreated rats. Res. Commun. Chem. Path. Pharmacol. 13: 259.

Weber, R.P., et al. 1976. Effect of the organophosphate insecticide parathion and its active metabolite paraoxon on the metabolism of benzo(a)pyrene in the rat. Cancer. Res. 34: 947.

World Health Organization. 1970. European standards for drinking water. 2nd ed. Geneva.

No. 150

Pyridine

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
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DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

PYRIDINE

Summary

Pyridine has not shown carcinogenic effects following repeated subcutaneous administration to rats; the compound did not show mutagenic activity in the Ames Salmonella assay.

A single study has indicated that pyridine produced developmental abnormalities when administered to chicken embryos.

Chronic exposure to pyridine produces CNS disturbances and may produce adverse hepatic and renal effects.

Pyridine has been shown to be toxic to freshwater fish at concentrations ranging from 100,000 to 1,580,000 μg/l. For freshwater invertebrates, toxic concentrations of pyridine range from 575,000 to 2,470,000 μg/l.

I. INTRODUCTION

Pyridine (CAS number 110-86-1) is a colorless liquid possessing a sharp, penetrating odor. It has the following physical properties:

Formula:	C_5H_5N
Molecular Weight:	79.1
Melting Point:	-42°C
Boiling Point:	115.3°C
Density:	0.982
Vapor Pressure:	10 mm Hg at 13.2°C (Sax, 1975)
Solubility:	miscible with water, alcohol, ether, and other organic solvents (Windholz, 1976)

Pyridine is a weak base and forms salts with strong acids. It is used as a solvent for anhydrous mineral salts, in various organic synthetic preparations, and in analytical chemistry (Windholz, 1976). The estimated annual production of pyridine is in excess of 60 million pounds (Federal Register 43:16688, April 19, 1978).

II. EXPOSURE

A. Water

Pertinent data could not be located in the available literature.

B. Food

Reported levels of pyridine in foods include: from 0.02 to 0.12 ppm, ice cream; 0.4 ppm, baked goods; 1.0 ppm, non-alcoholic beverages; 0.4 ppm, candy. Pyridine has also been found to occur naturally in coffee and tobacco (Furia, 1975).

C. Inhalation

Pyridine may be produced and released during the combustion of coke and as a combustion product in cigarette smoke (Graedel, 1978).

The major release of pyridine is from emissions from manufacturing and chemical processes. Based on total annual production, the U.S. EPA (1976) has estimated a significant potential emission of pyridine during manufacture.

D. Dermal

Pertinent data could not be located in the available literature.

III. PHARMACOKINETICS

A. Absorption

Absorption of pyridine occurs through the respiratory and gastro-intestinal tracts, but probably not through the skin (Gosselin, et al. 1976).

B. Distribution

Pertinent data could not be located in the available literature.

C. Metabolism and Excretion

Pyridine may be partly excreted unchanged or may be methylated at the N-position (Patty, 1963) and excreted as N-methyl pyridinium hydroxide, its chief metabolite (Browning, 1965). Methylation occurs in mice but not in rats, and it may occur to some extent in man The fate of the majority of absorbed pyridine is not known (Browning, 1965).

IV. EFFECTS

A. Carcinogenicity

Subcutaneous injection of pyridine at levels of 3 to 100 mg/kg twice weekly for a year did not produce tumors in rats (Mason, et al. 1971).

B. Mutagenicity

Pyridine did not show mutagenic effects with activation in the Ames Salmonella assay (Commoner, 1976).

C. Teratogenicity

Pyridine caused chick embryo abnormalities in one limited study (Federal Register 43:16688, April 19, 1978).

D. Other Reproductive Effects

Pertinent data could not be located in the available literature.

E. Chronic Toxicity

Prolonged daily exposure to pyridine at levels from 6 to 12 ppm causes mild central nervous system (CNS) disturbances in workers, while exposure from 15 to 330 ppm causes insomnia, nervousness, and low-back or abdominal pain accompanied by frequent urination (Gosselin, et al. 1976).

In animals, the major effects of repeated feeding of pyridine are hepatic and renal injury (Patty, 1963). Chronic exposure to 10 or 50 ppm pyridine vapors causes increased liver/body weight ratios in rats (ILO, 1971).

F. Other Relevant Information

Symptoms in humans associated with inhalation or ingestion of pyridine are CNS depression, and liver and kidney damage (Federal Register 4:16688, April 19, 1978; Gosselin, et al. 1976; Sax, 1975; ILO, 1971). Vapors are also irritating to eyes, skin, and nasal membranes (ACGIH, 1977; Sax, 1975). Skin eruptions induced by pyridine may be provoked by exposure to light (Arena, 1974). Ingestion of pyridine causes CNS depression, heart and gastrointestinal distress, fever, and, at high doses, death; and may stimulate bone marrow production of platelets in low doses (ACGIH, 1977; Gosselin, et al. 1976). Death may be due to either hepatic or renal damage, or from pulmonary injury (Gosselin, et al. 1976; ACGIH, 1977).

Exposure to vapors of pyridine from 1,250 to 10,000 ppm for 1 to 7 hours did not cause mortality in rats, but a 0.1 percent diet of pyridine induced rapid weight loss and death in two weeks (ILO, 1971).

V. AQUATIC TOXICITY

A. Acute Toxicity

McKee and Wolf (1963) have reviewed the effects of pyridine on several aquatic organisms. The freshwater minnow, bleak (Alburnus lucidus), was the most sensitive species tested with threshold toxicities ranging from 100,000 to 160,000 µg/l. Tests with the freshwater mosquitofish (Gambusia affinis) revealed a 96-hour LC_{50} value of 1,300,000 µg of pyridine per liter of turbid water. Orange-spotted sunfish (Lepomis humilis) were killed in one hour from exposure to pyridine at concentrations ranging from 1,480,000 to 1,580,000 µg/l, while goldfish (Carassius auratus) were killed after 10 to 30 hours' exposure to pyridine. Verschueren (1979) has reported a 24-hour LC_{50} value of 1,350,000 µg/l for mosquitofish exposed to pyridine.

Dowden and Bennett (1965) demonstrated a 48-hour LC_{50} value of 2,114,000 µg/l for Daphnia magna exposed to pyridine. McKee and Wolf (1963) reported a threshold effect of 40,000 µg/l for Daphnia sp. Canton and Adema (1978) determined 48-hour LC_{50} values ranging from 1,130,000 to 1,755,000 µg/l for Daphnia magna, and 48-hour LC_{50} values of 575,000 and 2,470,000 µg/l for Daphnia pulex and Daphnia cucullata, respectively.

B. Chronic Toxicity, Plant Effects and Residues

Pertinent data could not be located in the available literature.

C. Other Relevant Information

Thomas (1973) reports that pyridine exposure levels of 5,000 µg/l impart an off-flavor to fish flesh.

VI. EXISTING GUIDELINES AND STANDARDS

A. Human

The 8-hour, time-weighted-average occupational exposure limit for pyridine recommended by the American Conference of Governmental Industrial Hygienists is 5 ppm (ACGIH, 1977).

B. Aquatic

Based on 96-hour LC_{50} data, Hahn and Jensen (1974) have assigned pyridine an aquatic toxicity rating of from 100,000 to 1,000,000 μg/l.

REFERENCES

American Conference of Governmental Industrial Hygienists. 1977. Threshold limit values for chemical substances and physical agents in the workroom environment with intended changes for 1977. Cincinnati, Ohio.

Arena, J.M. 1974. Poisoning: Toxicology-Symptoms-Treatments. 3rd ed., Charles C. Thomas: Springfield, Illinois.

Browning, E. 1965. Toxicity and Metabolism of Industrial Solvents. American Elsevier, New York.

Canton, H.J. and D.D.M. Adema. 1978. Reproducibility of short-term and reproduction toxicity experiments with Daphnia magna and comparison of the sensitivities of Daphnia magna with Daphnia pulex and Daphnia cucullata in short-term experiments. Hydrobioligia. 59: 135.

Commoner, B. 1976. Reliability of bacterial mutagenesis techniques to distinguish carcinogenic and non-carcinogenic chemicals. U.S. EPA, NTIS PB-259 934.

Dowden, B. and H. Bennett. 1965. Toxicity of selected chemicals to certain animals. Jour. Wat. Poll. Cont. Fed. 37: 1308.

Furia, T. 1975. Fenaroli's Handbook of Flavor Ingredients. 2nd ed. CRC Press, Boca Raton, Fla.

Gosselin, R.E., et al. 1976. Clinical Toxicology of Commercial Products. 4th ed. Williams and Wilkins, Baltimore.

Graedel, T. 1978. Chemical Compounds in the Atmosphere. Academic Press, New York.

Hahn, R. and P. Jensen. 1974. Texas A and M University, College Station, Texas. Water Quality Characteristics of Hazardous Materials. Prepared for the National Oceanic and Atmospheric Administration. NOAA-78013001. NTIS PB-285 946/OST.

International Labour Office. 1971. Encyclopedia of Occupational Safety and Health, Vol. 2. McGraw-Hill Book Co., New York.

Mason, M., et al. 1971. Toxicology and carcinogenesis of various chemicals used in the preparation of vaccines. Clin. Toxicol. 4: 185.

McKee, J.E. and H.W. Wolf. 1963. Water Quality Criteria. The Resources Agency of California. State Water Quality Control Board Publication 3-A.

Patty, F. 1963. Industrial Hygiene and Toxicology: Volume 2, Toxicology. 2nd ed. John Wiley and Sons, New York.

Sax, N.I. 1975. Dangerous Properties of Industrial Materials. 4th ed. Van Nostrand Reinhold Co., New York.

Thomas, N.A. 1973. Assessment of fish tainting substances. In: Biological Methods for the Assessment of Water Quality. American Society for Testing and Materials, ASTM-STP-528, p. 178.

U.S. EPA. 1976. Preliminary scoring of selected organic air pollutants. U.S. Environ. Prot. Agency, EPA 450/3-77-008a.

Verschueren, K. 1979. Handbook of Environmental Data on Organic Chemicals. Van Nostrand Reinhold Co., New York.

Windholz, M. (ed.) 1976. Merck Index. 9th ed. Merck and Co., Rahway, New Jersey.