variants. The evidence includes the many individual case reports of benzene-induced pancytopenia that proceed to acute myelogenous leukemia and erythroleukemia, the accumulated case reports of leukemia associated with benzene exposures, and, most importantly, the epidemiological evidence indicating a greater risk for leukemia among benzene-exposed individuals.

It would appear that the evidence indicating an increased risk of leukemia on exposure to benzene for various periods of time and at various concentrations is overwhelming. Unfortunately, the data are not adequate for deriving a scientifically valid dose-response curve. Such a curve may be estimated on the basis of various assumptions; these assumptions, however, usually represent hypotheses that, although they may be valid, are not yet proven. Hence the estimation of a dose-response curve is not appropriate in this report, which deals with the currently available scientific knowledge of health effects, but is undertaken in the benzene Risk Assessment Document.

REFERENCES: Benzene Toxicity In Man

1. Adelstein, A.M. Occupational mortality: cancer. Ann. Occupat. Hyg. 15:53-57, 1972.

2. Akman, N., Domanic, N., Muftuoglu, A.U. Paroxysmal nocturnal hemoglobinuria: report of a case with features of intravascular consumption coagulopathy. Hacettepe Bull. Med. Surg. 4:159, 1971.

3. Aksoy, M., Dincol, K., Akgun, T., Erdem, S., Dincol, G. Haematological effects of chronic benzene poisoning in 217 workers. Brit. Journal Industrial Med. 28:296-302, 1971.

4. Aksoy, M., Erdem, S., Dincol, G. The reaction of normal and thalassaemic individuals to benzene poisoning: the diagnostic significance of such studies. IN: Abnormal Haemoglobins and Thalassaemia Diagnostic Aspects, Academic Press, Inc., New York, 1975.

5. Aksoy, M., Dincol, K., Erdem, S., Akgun, T., Dincol, G. Details of blood changes in 32 patients with pancytopenia associated with long-term exposure to benzene. Brit. J. Industr. Med. 29:56-64, 1972.

6. Aksoy, M., Dincol, K., Erdem, S., Dincol, G. Acute leukemia due to chronic exposure to benzene. Am. Journal Med. 52:160-166, 1972.

7. Aksoy, M., Erdem, S., Akgun, T., Okur, O., Dincol, K. Osmotic fragility studies in three patients with a aplastic anemia due to chronic benzene poisoning. Blut 13:85-90, 1966.

8. Aksoy, M., Erdem, S., Dincol, K., Hepyuksel, T., Dincol, G. Chronic exposure to benzene as a possible contributary etiologic factor in Hodgkin's disease. Blut 38:293-298, 1974.

9. Aksoy, M., Erdem, S. Ann. N.Y. Acad. Sci. 165(30):15, 1969.

10. Aksoy, M., Erdem, S., Dincol, G. Types of leukemia in chronic benzene poisoning. A study in thirty-four patients. Acta Haematologica 55:65-72, 1976.

11. Aksoy, M., Erdem, S., Dincol, G. Leukemia in shoe-workers exposed chronically to benzene. Blood 44(6): 837-841, 1974.

12. Aksoy, M., Erdem, S., Dincol, G. Two rare complications of chronic benzene poisoning: Myeloid metaplasia and paroxymal nocturnal hemoglobinuria. Report of two cases. Blut 30:255-260, 1975.

13. Aksoy, M., Erdem, S., Erdogan, G., Dincol, G. Acute leukaemia in two generations following chronic exposure to benzene. Human Heredity 24:70-74, 1974.

14. Aksoy, M., Erdem, S., Erodogan, G., Dincol, G. Combination of genetic factors and chronic exposure to benzene in the aetiology of leukaemia. Hum. Hered. 26:149-153, 1976.

15. Aksoy, M., Erdem, S. Some problems of hemoglobin patterns in different thalassemic syndromes showing the heterogeneity of beta-thalassemic genes. Annals N.Y. Acad. Sci., 165:13-24, 1969.

16. Aksoy, M. Testimony before Occupational Safety and Health Adminstration, U.S. Dept. of Labor, July 13, 1977.

17. Andjelkovic, D., Taulbee, J., Symons, M. Mortality experience of a cohort of rubber workers, 1964-1973. J. of Occup. Med., 18:387-394, 1976.

18. Andjelkovich, D., Taulbee, J., Symons, M., Williams, T. Mortality of rubber workers with reference to work experience. J. of Occup. Med., 19;397-405, 1977.

19. Andre, R., Dreyfus, B. Anemie hemolytique grave associee a un prupura hemorragique thrombopenique. Role probable due bensol. Transfusion massive. Splenectomie, guerison. Sangre 22:57-65, 1951.

20. Appuhn, E., Goldeck, H. Fruh- und spatschaden der blutbildung durch benzol und seine homologen. Arch. Gewerbepath u Gewerbehygiene 15:399-428, 1957.

21. Bass, M. Sudden sniffing death. JAMA 212(12) :2075-2079, 1970.

22. Bazenova, R.V. The functional condition of the stomach, pancreas and liver of workers employed in undertakings using benzene. Gigiena Truda I Professional'nye Zabolevanija 6(5):35-39, 1962.

23. Bean, R.H.D. Phenylbutazone and leukaemia: a possible association. Brit. Med. J. 2:1552, 1960.

24. Benzene: Uses, Toxic Effects, Substitutes. Occupational Safety and Health Series. International Labour Office, Geneva, 1968.

25. Bernard, J., Basset, A. Results of an inquiry on benzolism in the aeronautic industry. Sang 17: 120, 1946.

26. Bernard, J., Braier, L. Les leucoses benzeniques. Proceedings of the Third International Congress of the International Society of Hematology, Cambridge, England, Aug. 21-25, 1950. (New York, Grune & Stratton, pp. 251-263, 1951).

27. Bernard, J. La lymphocytose benzenique. Sangre 15: 501-505, 1942.

28. Bickel, L. Ueber beziehungen zwischen akuter aplastischer anamie, akuter aleukamischer lymphadenose und agranulozytose. Wien Klin Wochenschr 42:1186, 1929.

29. Binet, L., Conte, M., Bourliere, F. Intoxication benzolique mortelle chex une femme vendant des sacs en cuir synthetique. Presence de benzene dans le sang. Bull. Mem. Soc. Med. Hop. Paris 61:118, 1945.

30. Biscaldi, G.P. Acute panmyelophthisis due to benzene. Description of a case with favourable outcome. Med. Lavoro 64:363-374, 1973.

31. Biscaldi, G.P., Robustelli Della Cuna, G., Pollini, G. Segni di evoluzione leucemica dell'emopatia benzolica. Haematologica 54:579-589, 1969.

32. Blaney, L. Early detection of benzene toxicity. Ind. Med. 19:227-228, 1950.

33. Bodey, G.P., Freireich, E.J. Acute leukemia, Chapter 13 IN: Hemotology Principals and Practice. Charles E. Mengel, Emil Frei, Ill, Ralph Nachman, eds. Year Book Medical Publishers, Inc., Chicago, 1972. pp. 385.

34. Bogetti, B., Vassallo, M. Sul rischio di benzolismo nelle falegnamerie per l'uso di collanti sintetici. Lavoro e Medicina 19(2):33-38, 1965.

35. Bousser, J., Neyde, R., Fabre, A. Un cas d'hemopathie benzolique tres retardee a type de lymphosarcome. Arch. Mal. Prof. 9:130, 1948.

36. Bousser, J., Tara, S. Apropos de trois cas de leucemie myeloide chronique provoques par le benzol. Arch. Mal. Prof. 12:399-404, 1951.

37. Bowditch, M., Elkins, H.B. Chronic exposure to benzene (benzol). I. The industrial aspects. The Journal of Industrial Hygiene and Toxicology 21(8):321-330, 1939.

38. Brown, S.M. Letters to the Editor. Leukemia and potential benzene exposure. J. Occup. Med. 17(1):5-6, 1975.

39. Browning, E. Benzene. IN: Toxicity and Metabolism of Industrial Solvents. Elsevier, Publisher. Amsterdam, 1965.

40. Caprotti, M., Colombi, R., Corsico, R. Ulcers in the mucous membrane of the colon in benzene poisoning - Clinical and radiological study. Lavoro Umano 14(9):445-452, 1962.

41. Chang, Im Won. Study on the threshold limit value of benzene and early diagnosis of benzene poisoning. Journal Cath. Med. Coll. 23:429-434, 1972.

42. Clinical Hematology, Seventh Edition. M.M. Wintrobe, G. Richard Lee, Dane R. Boggs, Thomas C. Bithell, John W. Athens, John Foerster, eds. Lea and Febiger, Philadelphia, PA, pp. 1458, 1974.

43. Cooke, J.V. The occurrence of leukemia. Blood, 9:340, 1954.

44. Corisco, R., Biscaldi, G.P., Lalli, M. Benzene-induced changes in the size of haemopoietic and haematic cells. Lavoro Umano 19(1):16-27, 1967.

45. Craveri, A. Fibrinolysis, blood platelets, fibrinogen and other blood-coagulation tests in clinical benzene poisoning. Medicina del Lavoro 53(11):722-727,1962.

46. Croizat, P., Guichard, A., Revol, L., Creyssel, R., meunier. Etude anatomo-clinque et chimique d'un cas de maladie de Marchiafava-micheli. Sang 19:218, 1948.

47. Curletto, R., Ciconali, M. Haematological disorders in benzene poisoning. Medicina del Lavoro 53(8-9): 505-546, 1962.

48. Damashek, W. What do aplastic anemia, PNH and hypoplastic leukemia have in common? Blood 30:251, 1967.

49. DeGowin, R.L. Benzene exposure and aplastic anemia followed by leukemia 15 years later. JAMA 185: 748-751, 1963.

50. Delore, P., Borgomano. Leucemie aique au cours de l'intoxication benzenique. Sur l'origine toxique de certaines leucemies aigues et leurs relations avec les anemies graves. J. Med. Lyon 9:227-233, 1928.

51. Di Guglielmo, G., Iannaccone, A. Inhibition of mitosis and regressive changes of erythroblasts in acute erythropathy caused by occupational benzene poisoning. Acta. Haemat. 19:144-147, 1958.

52. Di Guglielmo, R., Ricci, M. Prima descrizione di un caso di mielosi eritremica da benzolo nella sua varieta cronica. Settimana Med. 46:365-368, 1958.

53. Doskin, T.A. Effect of age on the reaction to a combination of hydrocarbons. Hygiene and Sanitation 36:379- 384, 1971.

54. Drouet, P.L., Pierquin, L., Herbeuval, R. Lymphomatose chronique chez une benzolique. Sang. 18:246-249, 1947.

55. Erf, L.A., Rhoads, C.P. The hematological effects of benzene (benzol) poisoning. Journal of Industrial Hygiene and Toxicology 20(8):421-435, 1939.

56. Favre-Gilly, M., Bruel, Mlle. Syndrome hemorragique benzolique avec simple alteration morphologique des plaquettes. De l'utilite d'examen systematique des plaquettes sur lame chez les ouvriers exposes au benzol. Arch. Mal. Prof. 91:274-277, 1948.

57. Ferrara, A., Balbo, W. Malattia emolitica in soggetto esposto a rischio professionale di tipo benzolico. Riv. Infort. Mal. Prof. 44:713, 1957.

58. Forni, A.M., Cappellini, A., Pacifico, E., Vigliani, E.C. Chromosome changes and their evolution in subjects with past exposure to benzene. Arch. Environ. Health 23:385-391, 1971.

59. Forni, A., Moreo, L., Chromosome studies in a case of benzene-induced erythroleukaemia. Europ. Journal Cancer 5:459-463, 1969.

60. Forni, A., Moreo, L. Cytogenetic studies . . . . . in benzene leukaemia. Europ. Journal Cancer 3:251-255, 1967.

61. Forni, A., Pacifico, D., Limonta, A. Chromosome studies in workers exposed to benzene or toluene or both. Arch. Environ. Health 22:373-378, 1971.

62. Forni, A., Vigliani, E.C. Chemical leukemogenesis in man. Ser. Haemat. 7:210-223, 1974.

63. Galavotti, B., Troisi, F.M. Erythro-leukaemic myelosis in benzene poisoning. British Journal of Industrial Medicine 7:79-81, 1950.

64. Gall, E.A. Benzene poisoning with bizarre extra-medullary hematopoiesis. Arch. Pathol. 25:315-326, 1938.

65. Gaultier, M., Gervais, P., de Traverse, P.-M., Fournier, P.-E., Coquelet, N.-L., Loygue, A.-M., Housset, H. Genetic variations in the hemoblogin caused by the professional environment. Arch. Mal. Prof. 29: 197-203, 1970.

66. Girard, R., Mallein, M.L., Bertholon, J., Coeur, P., Tolot, F. Leucocyte alkaline phosphatase and benzene exposure. Med. Lavoro 61:502-508, 1970.

67. Girard, R., Mallein, M.L., Bertholon, J., Coeur, P., Cl. Evreux, J. Etude de la phosphatase alcaline leucodytaire et du caryotype des ouvriers exposes au benzene. Arch. Mal. Prof. 31(1-2):31-38, 1970.

68. Girard, R., Mallein, Mme., Fourel, R., Tolot, F. Lymphose et intoxication benzolique professionnelle chronique. Arch. Mal. Prof. 27:781-786, 1966.

69. Girard, R., Mallein, M.L., Jouvenceau, A., Tolot, F., Revol, L., Bourret, J. Etude de la sensibilite aux toxiques industriels des porteurs de trait thalassemique. (32 sujets soumis a surveillance hematologique prolongee) Le Journal de Medecine de Lyon 48:1113-1126, 1967.

70. Girard, R., Prost, G., Tolot, F. Comments on indemnification for benzene induced leukemia and aplasia. Arch. Mal. Prof. 32(9):581-583, 1971.

71. Girard, R., Revol, L. La frequence d'une exposition benzenique au cours des hemopathies graves. Nouv Revue Fr. Hemat. 10;477-484, 1970.

72. Girard, R., Rigaut, P., Bertholon, J., Tolot, F., Bourret, J. Les expositions benzeniques meconnues. Leur recherche systematique au cours des hemopathies graves. Enquetes chez 200 hemopathiques hospitalises. Arch. Mal. Prof. 29:723-726, 1968.

73. Girard, R., Tolot, F., Bourret, J. Malignant hemopathies and benzene poisoning. Medicina del Lavoro 62:71-76, 1971.

74. Girard, R., Tolot, F., Bourret, J. Hydrocarbures benzeniques et hemopathies graves. Arch. Mal. Prof. 31(12):625-636, 1970.

75. Goguel, A., Cavigneaux, A., BErnard, J. Benzene leukaemia. Institut National de la Sante et de la Recherche Medicale 22(3):421-441, 1967.

76. Goguel, A., Cavigneaux, A., Bernard, J. Benzene leukemias in the Paris region from 1950 to 1965. Nouv. Rev. Franc. Hemat. 7:465-480, 1967.

77. Goldstein, B.D. Hemototoxicity in man, Chapter 7 IN: Benzene Toxicity, A Critical Evaluation. Sidney Laskin and Bernard Goldstein, eds. In Press, 1977.

78. Goldwater, L.J. Disturbances in the blood following exposure to benzol. J. Lab. Clin. Med. 26:957-973, 1941.

79. Goldwater, L.J., Tewksbury, M.P. Recovery following exposure to benzene (benzol). J. Indust. Hyg. 23:217-231, 1941.

80. Gorini, P., Colombi, R., Pecorari, D. Investigation on the origin of the macrocytosis in the cytoplastic anemia from chronic benzene poisoning. Lav. Umano 11:121-133, 1959.

81. . . . . Benzene poisoning in rotogravure printing. Journal of Industrial Hygiene and Toxicology 21(8):395-420, 1939.

82. Guasch, J., Pelayo, E., Vallespin, J. Anemia benzolica complicada con leucemia aguda a los seis anos de evolucion. Sangre 4:129-146, 1959.

83. Guberan, E., Kocher, P. Pronostic lointain de l'intoxication benzolique chronique: controle d'une population 10 ans apres l'exposition. Schweiz. Med. Wachr. 101: 1789-1790, 1971.

84. Hamilton, A. General Review. Benzene (benzol) poisoning. Arch. Path. 11:434-454, 1931.

85. Hamilton-Paterson, J.L., Browning, E. Toxic effects in women exposed to industrial rubber solutions. Brit. Med. J. 1:349-352, 1944.

86. Harris, R.L. Testimony before occupational Safety and Health Administration. U.S. Dept. of Labor, August 8, 1977.

87. Health Effects of Benzene - A Review. The National Research Council, Committee on Toxicology, National Academy of Sciences, Washington, D.C. 1976.

88. Helmer, K.J. Accumulated cases of chronic benzene poisoning in the rubber industry. Acta Medica Scand. 118: 354-375, 1944.

89. Hernberg, S., Savilahti, M., Ahlman, K., Asp, S. Prognostic aspects of benzene poisoning. Brit. Journal Industr. Med. 23:204-209, 1966.

90. Hunter, F.T. Chronic exposure to benzene (benzol). II. The clinical effects. Journal of Industrial Hygiene and Toxicology 21(8):331-354, 1939.

91. Hunter, D. Industrial toxicology. Quarterly Journal of Medicine pp. 185-250, 1944.

92. Hutchings, M., Drescher, S., McGovern, F.B., Coombs, F.A. Investigation of benzol and toluol poisoning in Royal Australian Air Force workshops. The Medical Journal of Australia 2(23):681-693, 1947.

93. Infante, P.F., Rinsky, R.A., Wagoner, J.K., Young, R.J. Leukaemia in benzene workers. Lancet, 2:76- 78, 1977.

94. Ishimaru, T., Okada, H., Tomiyasu, T., Tsuchimoto, T., Hoschino, T., Ichimaru, M. Occupational factors in the epidemiology of leukemia in Hiroshima and Nagasaki. Amer. J. Epidem. 93:157-165, 1971.

95. Ito, T. Study on the sex difference in benzene poisoning. Report 1. On the obstacles in benzene workers. Showa Igakukai Zasshi 22:268-272, 1962.

96. Inceman, S., Tangun, Y. Impaired platelet-collangen reaction in a case of acute myeloblastic leukemia due to chronic benzene intoxication. Turk. Tip. Cemig. Mecm. 35;417-424, 1969.

97. Justin-Besancon, L., Pequignot, H., Barillon, A. Leucose aigue survenue 27 ans apres exposition aux vapeurs benzoliques. La Semaine des Hopitaux 35:186-188, 1959.

98. Kahn, H., Muzyka, V. The chronic effect of benzene on prophyrin metabolism. Work-Environm. Health 10-140-143, 1973.

99. Kahn, KH.A., Muzyka, V.I. The effect of benzene on the Δ-aminolevulic acid and porphyrin content in the cerebral cortex and in the blood. Industrial Hygiene and Profession Associated Disorders 3:59-60, 1970.

100. Kauppila, O., Setala, A. Chronic benzene poisoning. Report of five cases. Annuals Medicinae Internae Fenniae 45:49-51, 1956.

101. Kiec, E., Kunski, H. A case of chronic lymphatic leukemia due to prolonged exposure to benzene. Med. Pracy 16;362-365, 1965.

102. Kinoshita, Y., Terada, H., Saito, H., et al. A case of myelogenous leukemia. Journal of Japan Haematological Society pp. 85-96, 1965.

103. Kliche, N., Meubrink, H., Wahl, F. Chronische benzolschaden bei dachdeckern. Z. Ges Hyg. 15:310-316, 1969.

104. Kohli, P., Brunner, H.E., Siegenthaler, W. Erythroleukamie nach chronischer benzolintoxikation. Untersuchung der ferro- und erythrocytenkinetik mit radioaktivem eisen und chrom. Schweiz. Med. Wschr. 97:368-373, 1967.

105. Kolesar, D., Ballog, O. Studies by fluorescent microscopy of the effect of occupational benzene exposure on leucocyte nuclei changes. Bratislavske Lekarske Listy 4511(4):212-219, 1965.

106. Koslova, T.A., Volkova, A.P. Blood picture and phagocytic activity of leucocytes in workers having contact with benzene. Gig. Sanit. 25:29-34, 1960.

107. Koslova, T.A. The effect of benzene on the organism at high air temperature. Abstract. Air Pollution Translations, Vol. 1, F-7308, AP-56, HEW, 1969.

108. Kuhlmann, D., Von. Mitteilung einer todlichen benzolvergiftung aus der schuhindustrie. Zbl. Arbeitsschutz 9:62-64, 1959.

109. Lange, A., Smolik, R., Zatonski, W., Szymanska, J. Serum innumoglobulin levels in workers exposed to benzene, toluene and xylene. Int. Arch. Arbeitsmed. 31:37-44, 1973.

110. Lange, A., Smolik, R., Zatonski, W., Glazman, H. Leukocyte agglutinins in workers exposed to benzene, toluene and xylene. Int. Arch. Arbeitsmed. 31:45-50, 1973.

111. . . . . mortality among chemists. J. Nat. Cancer Inst., 43:1159-1164, 1969.

112. Liaudet, J., Combaz, M. Leucemie myeloide chronique chez un chimiste petrolier de 35 ans, manipulant du benzene depuis l'age de 18 ans. Journal Europ. Toxicol. 6(6):309-313, 1973.

113. Lob, M. L'action du benzene sur les thrombocytes et sur certaines activities enzymatiques. Archives des Maladies Professionnelles 24(4-5):371-374, 1963.

114. Ludwig, Von H., Werthemann, A. Benzol-Myelopathien. Schweiz Med. Wschr. 92:378-384, 1962.

115. Mallein, M.L., Bryon, P.A., Fiere, D., Girard, R. Cryptoleucose aigue ou "anemie refractaire" benzenique. (Deux nouveaux cas). Arch. Mal. Prof. 32:577-579, 1971.

116. Mallory, T.B., Gall, E.A., Brickley, W.J. Chronic exposure to benzene (benzol). III. The pathologic results. Journal of Industrial Hygiene and Toxicology 21(8):355-377, 1939.

117. Mancuso, T.F., Brennan, J.J. Epidemiological considerations of cancer of the gallbladder, bile ducts and salivary glands in the rubber industry. J. Occup. Med., 12(9): 333-341, 1970.

118. Mancuso, T.F., Ciocco, A., El-Attar, A.A. An epidemiological approach to the rubber industry. J. Occup. Med., 10(5):213-232, 1968.

119. Marchal, G., Duhamel, G. L'anemie hemolytique dans les leucemies. Sangre 21:254-261, 1950.

120. Marchand, M.M. Un cas mortel de leucoso benzolique. Arch. Mal. Prof. 21:576-477, 1960.

121. Maugeri, S., Colombi, R., Pollini, G., Strosselli, E., Corsico, R. Evolution and characteristics of benzol blood dyscrasia. Med. Lavoro 56:544-560, 1965.

122. Mazzella Di Bosco, M. Considerations on some cases of benzene leucosis in shoe-factory workers. Lavoro Umano 16(3):105-121, 1964.

123. McLean, J.A. Blood dyscrasia after contact with petrol containing benzol. The Medical Journal of Australia 47(II):845-849, 1960.

124. McMichael, A.J., Andjelkovic, D.A., Tyroler, H.A. Cancer mortality amond rubber workers: an epidemiological study. Annals N.Y. Aca. Sci., 271:125-137, 1976.

125. McMichael, A.J., Spirtas, R., Gamble, J.F., Tousey, P.M. Mortality among rubber workers: relationship to specific jobs. J. of Occup. Med., 18:178-185, 1976.

126. McMichael, A.J., Spirtas, R., Kupper, L.L. An Epidemiologic study of mortality within a cohort of rubber workers. J. of Occup. Med. 15:458-464, 1974.

127. McMichael, A.J., Spirtas, R., Kupper, L.L., Gamble, J.F. Solvent exposure and leukemia among rubber workers: an epidemiologic study. J. Occup. Med. 17(4):234-239, 1975.

128. Merklen, Pr., Israel, L. Intoxication par le benzol: aleucie hemorragique, autrement dit "hypoleucie hemorragique avec anemie". Sangre 8:700-709, 1934.

129. Miller, R.W. Etiology of childhood leukemia. Pediat. Clin. North America 13:267, 1966.

130. Mina, L.R. Changes in the carbonic anhydrase of the blood and the endophenoloxydases of the leucocytes in chronic benzene and monochlorobenzene poisoning. Igiena 8(3):231-240, 1959.

131. Modan, B., Segal, S., Shani, M., Sheba, C. Aplastic anemia in Israel: evaluation of the etiological role of chloramphenicol on a community-wide basis. Am. J. of the Med. Sci., 270(3):441-445, 1975.

132. Monaenkova, A.m., Snegova, G.V. Cerebral circulation in some occupational poisonings: lead, carbon disulfide, benzene. Gig. Tr. Prof. Zabol. 17(4):33-37, 1973.

133. Monaenkova, A.M., Zorina, L.A. Hemodynamics and heart muscle changes in chronic benzene poisoning. Gig. Truda Prof. Zabolevaniya 4:30-34, 1975.

134. Monson, R.R., Nakano, K.K. Mortality among rubber workers. I. White male union employees in Akron, Ohio. Am. J. of Epidemiology 103(3):297-303, 1976.

135. Monson, R.R., Nakano, K.K. Mortality among rubber workers. II. Other employees. Am. J. of Epidemiology, 103(3): 297-303, 1976.

136. Monteverde, A., Grazioli, C., Fumagalli, E. The effect of fibrinogen and platelets on the thromboelastogram in benzene poisoning. Medicina del Lavoro 54(2):95-102, 1963.

137. Nissen, N.I., Ohlsen, A.S. Erythromyelosis. Oversigt og et tilfaelde hos en benzolarbejder. Ugeskr. Laeg. 114:737-742, 1952.

138. Pagnotto, L.D., Elkins, H.B., Brugsch, H.G., Walkley, E.J. Industrial benzene exposure from petroleum naphtha--I. Rubber coating industry. Am. Ind. Hyg. Assoc. J., 22:417-21, 1961.

139. Paterni, L., Sarnari, V. Involutional myelopathy due to benzene poisoning, with the appearance of a mediastinal reticulosarcoma at an advanced stage. Securitas 50(10):55-59, 1965.

140. Poinso, MM.R., Bondil, J.-N., Ruf. G. Leucose lymphoide benzenique. Bull Soc. Med. Hosp. Paris 70:13-16, 1954.

141. Pollini, G., Colombi, R. Changes in the osmotic resistance of the leucocytes in persons exposed to benzene. Lavoro Umano 16(4):177-184, 1964.

142. Rawson, R., Parker, F., Jackson, H. Industrial solvents as possible etiologic agents in myeloid metaplasia. Science 6:541-542, 1941.

143. Recommended Standard for Occupational Exposure to Benzene. U.S. Department of Health, Education, and Welfare. NIOSH 74-137, 1974.

144. Redmond, C.K., Ciocco, A., Lloyd, J.W., Rush, H.W. Long-term mortality study of steelworkers. VI. Mortality from malignant neoplasms among coke oven workers. J. Occup. Med., 14:621-629, 1972.

145. Redmond, C.K., Strobino, B.R., Cypress, R.H. Cancer experience among coke by-product workers. Annals N.Y. Acad. Sci., 271:102-115, 1976.

146. Review of the Health Effects of Benzene. By the Committee on Toxicology of the National Academy of Sciences. National Research Council, Washington, D.C. December, 1975.

147. Revnova, N.V. Concerning auto-immunity shifts in chronic occupational benzol poisoning. Gig. Tr. Prof. Zabol. 7:38-42, 1962.

148. Robustellie della Cuna, G., Favino, A., Biscaldi, G.P., Pollini, G. Trasformazione in leucemia acuta di un caso di mielopatia involutiva benzolica. Haematologica 57:65-89, 1972.

149. Roth, L., Dinu, I.V., Turcanu, P., Moise, G. Cytologic and immunochemical features of benzene induced reticuloses. Timisoara Med. 17:29-38, 1972.

150. Roth, L., Turcanu, P., Dinu, I., Moise, G. Monocytosis in those who work with benzene and chronic benzene poisoning. Folia Haematol. 100:213-224, 1973.

151. Roth, L., Turcanu, P., Servan, V., Moise, G. Qualitative veranderungen der lymphozyten nach benzolabsorption. Zschr. Inn. Med. 20:932-935, 1970.

152. Rundles, R.W. Chronic granulocytic leukemia, Chapter 80 IN: Hemotology. McGraw-Hill Book Co., New York, 1972. pp. 681.

153. Saite, G., Dompe, M. Sul rischil benzolico nei principali stabilimenti rotocalcograifci di Milano. Med. Lavoro 38:269-285, 1947.

154. Saita, G. Mielosi aplastica e successiva mielosi leucemica leucopenica, provocate da benzolo. Med. Lavoro 36:143-159, 1945.

155. Saita, G., Moreo, L. Talassemia ed emopatie professionali. Nota I - Talassemia e benzolismo cronico. Medicina del Lavoro 50(1):25-44, 1959.

156. Saita, G., Moreo, L. Haemolytic attack following inhalation of a single massive doze of benzol. Medicina del Lavoro 52(11):713-716, 1961.

157. Saita, G., Moreo, L. A case of chronic benzene poisoning with a Pelger-Huet type leucocyte anomaly. Medicina del Lavoro 57(5):331-335, 1966.

158. Saita, G., Sbertoli, C., Farina, G.F. Thromboelastographic investigations in benzene haemopathy. Medicina del Lavoro 55(11):655-664, 1964.

159. Saita, G., Sbertoli, G. L'agglutinogramma nell'intossicazioue cronica da benzolo. Med. Lavoro 45:250-253, 1962.

160. Saita, G., Vigliani, E.C. Th action of benzene in inducing leukemia. Med. Lavoro 53(10):581-586, 1962.

161. Savilahti, M. Over 100 cases of benzene poisoning in a shoe factory. Archiv fur Gewerbopathologie und Gewerbehygiene 15:147-157, 1956.

162. Selling, L. A preliminary report of some cases of purpura haemorrhagica due to benzol poisoning. Bull. John Hopkins Hosp. 21:33-37, 1910.

163. Selling, L., Osgood, E.E. Chronic benzene poisoning. International Clinics 3:52-63, 1935.

164. Sellyei, M., Kelemen, E. Chromosome study in a case of granulocytic leukaemia with "Pelgerisation" 7 years after benzene pancy topenia. Europ. J. Cancer 7:83-85, 1971.

165. Smolik, ... Rappaport, H., Toth, B., Raha, C.R., Tomatis, L., Feldman, R., Ramahi, H. Studies on the toxicity of petroleum waxes. Toxicol. & Applied Pharmacol. 4:1-62, 1962.

166. Smolik, R., Grzybek-Hryncewicz, K., Lange, A., Zatonski, W. Serum complement level in workers exposed to benzene, toluene and zylene. Int. Arch. Arbeitsmed. 31:243-247, 1973.

167. Sobczyk, W., Siedlecka, B., Gajewska, Z. EEG recordings in workers exposed to benzene compounds. Med. Pracy 24:273-283, 1973.

168. Solov'eva, E.A. Morphological changes of blood platelets and of megakarycocytes in chronic benzene poisoning. Gig. Tr. Prof. Zabol. 7(11):57-60, 1963.

169. Sroczynski, J., Kossmann, S., Wegiel, A. Coagulation system in experimental poisoning with benzene vapors. Bul. Slezby Sanit. Epidemiol Wojewodztwa Katowickiego 15:131-134, 1971.

170. Snyder, R., Kocsis, J.J. Current concepts of chronic benzene toxicity. CRC Critical Reviews in Toxicology Pages 265-288, June, 1975.

171. Snyder, R. Relation of benzene metabolism to benzene toxicity. IN: symposium on Toxicology of Benzene and Alkylbenzenes, Braun, D., Editor. Industrial Health Foundation, Pittsburgh, pp. 44-53, 1974.

172. Stewart, R.D., Dodd, H.C., Baretta, E.D., Schaeffer, A.W., Mutchler, J.E. Chronic overexposure to benzene vapor. Toxicol. Applied Pharmacol. 10:381, 1967. (Abstract)

173. Tareeff, E.M., Kontchalovskaya, N.M., Zorina, L.A. Benzene leukemias. Acta. Unio. Int. Contra. Can Crum 19:751-755, 1963.

174. Tauber, J. Instant benzol death. Journal Occup. Med. 12:91-92, 1970.

175. Thorpe, J.J. Author response. J. Occup. Med., 17:6, 1975.

176. Thorpe, J.J. Epidemiologic survey of leukemia in persons potentially exposed to benzene. Journal of Occupational Medicine 16(6):375-382, 1974.

177. Thienes, C.H., Haley, T.J. Cardiac Poisons. IN; Clinical Toxicology, Chapter 5, 5th edition, Lee and Febrger, Philadelphia, 1972.

178. Torres, A., Giralt, M., Raichs, A. Coexistencia de antecadentex benzolicos cronicos y plasmocitoma multiple. Presentacion de dos casos. Sangre 15:275-279, 1970.

179. Tough, I.M., Smith, P.G., Court Brown, W.M., Harnden, D.G. Chromosome studies on workers exposed to atmospheric benzene. Europ. Journal Cancer 6:49-55, 1970.

180. Tyroler, H.A. Testimony before occupational Safety and Health Administration. U.S. Dept. of Labor, August 8, 1977.

181. Tzanck, A., Dreyfuss, A., Jais, M. Hemopathie postbenzolique at leucoblastose medullaire. Sangre 11:550-557, 1937.

182. Undritz, E. Un cas d'intoxication professionnelle par des vapeurs de benzine, collophane et huile de lin. Le Progres Medical 69(16):569-570, 1938.

183. U.S. Dept. of HEW. Mortality in 1950 by occupation and industry. Vital Statistics - Special Reports. 53(1-5), 1961-1963.

184. Vannucchi, V. Mielosi acute da benzolismo cronico con aspetto iniziale di aplasia e aspetto successivo di leucemia o di eritroleucemia. Riv. Crit. Clin. Med. 57:51, 1957.

185. Van Ravesteyn, A.H. Chronische benzolvergiftiging en leucaemie. Nederl. Tijdschr. Geneesk. 85:4038-4044, 1941.

186. Van Schoonhoven Van Beurden, A.J.R.E. Benzolleucaemie. Nederl. Tijdschr. Geneesk. 93:2584-2592, 1949.

187. Vigliani, E.C. Leukemia associated with benzene poisoning. Presented at: Conference on Occupational Carcinogenesis, Abstract 38, March 24-27, 1975.

188. Vigliani, E.C., Forni, A. Benzene and leukemia. Env. Res. 11:122-127, 1976.

189. Vigliani, E.C., Forni, A. Benzene, Chromosome changes and leukemia. Letter to the Editor, Journal Occup. Med. 11:148-149, 1969.

190. Vigliani, E.C., Forni, A. Leucemogenesi professionale. Minerva Med. 57:3952-3955, 1966.

191. Vigliani, E.C., Saita, G. Benzene and leukemia. The New England Journal of Medicine 271(17):872-876, 1964.

192. Vigliani, E.C., Saita, G. Leucemia emocitoblastica da benzolo. Med. Lavoro 34:182-191, 1943.

193. Wilson, R.H. Benzene poisoning in industry. Journal Lab. Clin. Med. 27:1517-1521, 1942.

194. Wurster-Hill, D.H., Cornwell, G.G., McIntyre, O.R. Chromosomal aberrations and neoplasm - a family study. Cancer 33(1):72-81, 1974.

195. Zini, C., Alessandri, M. Anomalia leucocitaria pseudo-pelgeriana in un caso di emopatia benzolica con leucosi acuta terminale. Haematologica 52:258-266, 1967.

196. Gerarde, H.W. Toxicology and Biochemistry of Aromatic Hydrocarbons. pp. 97-108, Elsevier Publishing Company, New York, 1960.

197. Kraybill, H.F. A survey of NCI viewpoints on carcinogenic risk of benzene exposure. National Cancer Institute.

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

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FEB 22 1985

OFFICE OF
RESEARCH AND DEVELOPMENT

SUBJECT: Transmittal of Interim Quantitative Cancer Unit Risk Estimates Due to Inhalation of Benzene

FROM: Bernard D. Goldstein
Assistant Administrator
for Research and Development (RD-672)

TO: Charles L. Elkins
Acting Assistant Administrator
for Air and Radiation (AR-443)

The attached report entitled, Interim Quantitative Cancer Unit Risk Estimates Due to Inhalation of Benzene, is an update of the Carcinogen Assessment Group's Final Report on Population Risk to Ambient Benzene Exposures dated January 10, 1979. The revised report has been reviewed by members of your staff and within OHEA. The document was prepared for the Office of Air Quality Planning and Standards by the Office of Health and Environmental Assessment.

In the 1979 report, a unit risk was derived, based on the geometric mean of estimates of risk from three independent epidemiologic studies. Since then, extensive new information relating to the carcinogenic potency of benzene has become available. In addition, an improved methodology for estimating cancer risk has been developed over time.

If you have any questions, please contact Elizabeth L. Anderson (382-7317) or Robert E. McGaughy (382-5889).

Attachment

cc: John O'Connor, OAQPS
David Patrick, OAQPS

Environmental Protection
Agency

February 15, 1985
INTERNAL REPORT

EPA

Research and Development

original

INTERIM QUANTITATIVE CANCER UNIT RISK

ESTIMATES DUE TO INHALATION OF BENZENE

Prepared for

OFFICE OF AIR QUALITY PLANNING AND STANDARDS

Prepared by

CARCINOGEN ASSESSMENT GROUP
Office of Health and
Environmental Assessment
Washington DC 20460

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PREFACE

This document was prepared for the Office of Air Quality Planning and Standards (OAQPS) by the Office of Health and Environmental Assessment (OHEA). Dr. Todd Thorslund, Carcinogen Assessment Group, OHEA, is the author. The document has been reviewed within OHEA and OAQPS.

INTERIM QUANTITATIVE CANCER UNIT RISK ESTIMATES DUE TO INHALATION OF BENZENE

Introduction

In the "Carcinogen Assessment Group's Final Report on Population Risk to Ambient Benzene Exposures" dated January 10, 1979, a "unit risk" due to inhalation of benzene was derived. This unit risk was obtained from the geometric mean of estimates of risk from three independent epidemiologic studies. This was the first time that the U.S. Environmental Protection Agency (EPA) obtained cancer risk estimates due to a chemical exposure based on human epidemiologic data.

Since that original report, extensive new information relating to the carcinogenic potency of benzene has become available. In addition, an improved methodology for estimating cancer risk has been developed over time.

The Carcinogen Assessment Group (CAG) is presently evaluating this new information and preparing an extensive report covering each animal toxicologic study and epidemiologic study. This report will supply the information from which a current, state-of-the-art, quantitative cancer risk assessment for benzene will be derived.

As new information became available, the CAG was asked on several occasions whether or not it would markedly change its unit risk estimate due to the new data. On each occasion, upon a preliminary evaluation, it was apparent in our judgment that only relatively minor "numerical" alterations would result in the joint unit risk estimate from incorporating the new information. With this assurance, the EPA program offices continued to base their decisions on the original report. This was done in order to stay on a mandated regulatory schedule. The schedule would be disrupted if they were forced to wait for a current, state-of-the-art risk assessment for benzene to be completed before

proceeding.

In a petition to the Administrator of the EPA, the Natural Resources Defense Council (NRDC) takes exception to this approach. The NRDC makes the conjecture that the information found in the following sources indicates that EPA has seriously underestimated the unit risk:

- an epidemiologic study of Ohio rubber workers (Rinksy et al., 1981) (updating Infante et al., 1977),
- an epidemiological study of chemical workers submitted to EPA by the Chemical Manufacturers Association (Wong et al., 1983),
- the animal bioassay conducted by the National Toxicological Program (NTP, 1984),
- a further update through 1983 of the rubber workers study by Rinsky et al., and
- a review of the health effects literature and a quantitative risk assessment published by the California Department of Health Services (DHS, 1984).

The time schedule for answering the NRDC petition does not allow for a completion of EPA's updated risk assessment. Fortunately, a May 1984 report entitled "Quantitative Estimates of Risk of Leukemia from Occupational Exposure to Benzene," prepared by Crump and Allen for the Occupational Safety and Health Administration, used the information cited by the NRDC to make risk assessments. This report uses methodology in obtaining risk estimates that is consistent in most respects to that employed by EPA, and it contains much better human exposure estimates in the epidemiologic studies than has been previously available.

The approach to be taken here is to use this secondary source to make interim quantitative unit risk estimates that will be used until the more extensive estimates are completed. However, it must be realized that the new esti-

mates do not represent the optimum use of the information EPA presently has at hand. Even so, due to the structural nature of the type of models used to estimate risk, it is not anticipated that the resulting final estimates will differ by an appreciable amount from the interim estimate developed here. The main advantage of the new estimates will be their scientific credibility.

In the next two sections, unit risks based upon epidemiologic studies and animal studies will be developed using parameters calculated by Crump and Allen. The third section discusses these results. The fourth section develops and gives CAG recommendations for a single composite unit risk estimate, and discusses alternative approaches. The final section summarizes the results and conclusions of this investigation.

Unit Risk Estimates Based on Epidemiologic Studies

Crump and Allen (1984) estimated the lifetime risk due to different durations and levels of exposure to benzene in the work place.

The epidemiologic data sets used to estimate these risks were obtained from a reorganizing of the data collected by Rinsky et al. (1981), Wong et al. (1983), and Ott et al. (1978) in three separate investigations. Other studies, most notably those of Askoy et al. (1979) and Askoy (1978), which dealt with Turkish shoe workers, indicated an association of leukemia with benzene. However, we agree with Crump that the exposure information compared with the studies used is so imprecise that they are not suitable for quantitative estimation.

A computer tape containing follow-up information through 1978, which is an updated version of the cohort discussed by Rinsky et al. (1981), was used. This is the most recent information presently available on the cohort.

The NRDC implies that an update through 1983 of the rubber workers studied by Rinsky et al. (1981) exists. However, the CAG has not been able to locate

such a data base, and, given the usual lag time required for epidemiologic investigations, a study that current is not very likely.

The information contained in Wong et al. (1983), which involves the mortality experience of male chemical workers occupationally exposed to benzene, was used independently and in conjunction with other studies to estimate unit risks.

The study conducted by Ott et al. (1978) was also used in combination with the other studies to estimate risk, but less emphasis was placed on it due to a lack of a clear dose-response relationship.

Crump and Allen (1984) were able to relate observed and expected numbers of cases of leukemia to groupings of various exposure parameters for the three studies. These data are shown in Tables 1-3 and 6-11 of the Crump and Allen (1984) report, included here in Appendix A.

The exposure categories used were denoted as cumulative dose, weighted cumulative dose, and window dose. The "slope" parameter b and its 95% statistical confidence interval were estimated for various assumptions and combinations of data and dose parameters using techniques described by Crump and Allen (1984). These estimated parameters and confidence intervals are shown in Tables 12-17 of the Crump and Allen (1984) report, and are also reproduced in Appendix A.

Once an estimate of the slope parameter b is obtained, it can be translated into a unit risk by a straightforward mathematical manipulation. The transformation depends upon whether the model is of absolute or relative risk, the type of exposure parameter used, and the environmentally exposed population's assumed total and leukemia age-specific death rate.

Mathematically, the risk due to a constant lifetime exposure of x ppm in the air may be expressed as

$$P(x) = \int_0^{\infty} \{h_2(x,t) e^{-\int_0^t [h_2(x,v) + h_1(v)]dv}\} dt$$

where $h_2(x,t)$ is the age-specific death rate at age t due to a constant lifetime exposure at level x, and $h_1(t)$ is the age-specific death rate for all other causes. See Gail (1975) for a derivation of this result.

In the present situation

$$h_2(x,t) = \phi(t)^{\delta} r(x,t)$$

where

$$\delta = \begin{cases} 1 \text{ if a relative risk model} \\ 0 \text{ if an absolute risk model} \end{cases}$$

$\phi(t)$ is the background age-specific leukemia death rate of the environmentally exposed population and

$$r(x,t) = \begin{cases} 0 & t < 2.5 \\ b^*x(t-2.5) & 2.5 \leq t \end{cases}$$

for the cumulative exposure model, and

$$r(x,t) = \begin{cases} 0 & t < 5 \\ b^*x(t-5) & 5 \leq t < 10 \\ 5\, b^*x + \frac{b^*x}{3}(t-10) & 10 \leq t < 15 \\ \frac{20}{3}\, b^*x + \frac{b^*x}{6}(t-15) & 15 \leq t \end{cases}$$

for the weighted cumulative exposure model, and

$$r(x,t) = \begin{cases} 0 & t < 5 \\ b^{*}x(t-5) & 5 \leq t < 15 \\ 10\ b^{*}x & 15 \leq t \end{cases}$$

for the window exposure model. The term $b^{*} = b/(8/24) \times (240/365) = 4.56b$ simply translates the 8 hours/day 240 days/year exposure in the industrial setting used by Crump and Allen (1984) into a continuous lifetime exposure for the U.S. environmental case.

Since there is no information to suggest that the background leukemia and total age-specific death rates for those exposed to benzene in the environment would differ from the U.S. norm, the total U.S. rates taken from 1978 (the most current year available) are used for $\phi(t)$.

Based upon these conventions, the risk due to 1 ppm constant exposure to benzene is calculated for each of the b values and their confidence bounds, as given in Tables 12-17 of Crump and Allen (1984) reproduced in Appendix A. These results are shown in Tables 1-6. A comparison of these results with those derived in the original CAG document and those obtained from animal experiments, as well as a discussion of their relevance, will be the subject of a subsequent section.

Unit Risk Estimates Based on Animal Studies

At the time the CAG originally evaluated the carcinogenic potency of benzene, no animal studies existed demonstrating a carcinogenic response. Benzene and arsenic were pointed out to be the only compounds where human evidence was positive and animal evidence negative.

Some individuals argued that this cast serious doubt on the possibility

TABLE 1. RESULTS FOR RELATIVE RISK MODEL USING CUMULATIVE DOSE

Data set	Unit risk estimate		
	95% lower bound	MLE	95% upper bound
I Rinsky et al. (follow-up from 1950, Table 6)[a]	1.65×10^{-2}	5.10×10^{-2}	1.08×10^{-1}
II Rinsky et al. (follow-up from 1940, Table 2)	1.53×10^{-2}	5.10×10^{-2}	1.13×10^{-1}
III Rinsky et al. (revised exposures, Table 7)	1.78×10^{-2}	6.43×10^{-2}	1.44×10^{-1}
IV Rinsky et al. (Table 6) and Ott et al. (Table 1)	7.78×10^{-3}	2.89×10^{-2}	6.87×10^{-2}
V Same as IV except two questionable cases added	4.45×10^{-3}	2.04×10^{-2}	5.10×10^{-2}
VI Wong et al. (Table 3, SMR=50 assumed for unexposed)	8.76×10^{-4}	1.04×10^{-1}	2.42×10^{-1}
VII Rinsky et al. (Table 6) Ott et al. (Table 1) and Wong et al. (Table 3)	2.67×10^{-2}	7.32×10^{-2}	1.60×10^{-1}
VIII Same as VII except SMR=100 assumed for unexposed	1.56×10^{-2}	3.55×10^{-2}	6.43×10^{-2}

[a]The tables referred to are those given in Crump and Allen (1984), and are reproduced in Appendix A.

TABLE 2. RESULTS FOR ABSOLUTE RISK MODEL USING CUMULATIVE DOSE

Data set	Unit risk estimate		
	95% lower bound	MLE	95% upper bound
I Rinsky et al. (follow-up from 1950, Table 6)[a]	1.02×10^{-2}	2.45×10^{-2}	4.77×10^{-2}
II Rinsky et al. (follow-up from 1940, Table 2)	9.31×10^{-3}	2.20×10^{-2}	4.40×10^{-2}
III Rinsky et al. (revised exposures, Table 7)	1.22×10^{-2}	3.06×10^{-2}	5.99×10^{-2}
IV Rinsky et al. (Table 6) and Ott et al. (Table 1)	7.23×10^{-3}	1.96×10^{-2}	3.79×10^{-2}
V Same as IV except two questionable cases added	7.11×10^{-3}	2.08×10^{-2}	4.04×10^{-2}

[a]The tables referred to are those given in Crump and Allen (1984), and are reproduced in Appendix A.

TABLE 3. RESULTS FOR RELATIVE RISK MODEL USING WEIGHTED CUMULATIVE DOSE

Data set	Unit risk estimate		
	95% lower bound	MLE	95% upper bound
I Rinsky et al. Table 8)[a]	1.30×10^{-2}	4.10×10^{-2}	8.79×10^{-2}
II Rinsky et al. (Table 8) and Ott et al. (Table 10)	7.29×10^{-3}	2.49×10^{-2}	5.59×10^{-2}

[a]The tables referred to are those given in Crump and Allen (1984), and are reproduced in Appendix A.

TABLE 4. RESULTS FOR ABSOLUTE RISK MODEL USING WEIGHTED CUMULATIVE DOSE

Data set	Unit risk estimate		
	95% lower bound	MLE	95% upper bound
I Rinsky et al., 1940-1970 follow-up (Table 8)[a]	7.47×10^{-3}	1.76×10^{-2}	3.36×10^{-2}
II Rinsky et al. (Table 8) and Ott et al. (Table 10)	5.43×10^{-3}	1.40×10^{-2}	2.71×10^{-2}

[a]The tables referred to are those given in Crump and Allen (1984), and are reproduced in Appendix A.

TABLE 5. RESULTS FOR RELATIVE RISK MODEL USING "WINDOW" DOSE

Data set	Unit risk estimate		
	95% lower bound	MLE	95% upper bound
I Rinsky et al. (Table 9)[a]	5.56×10^{-3}	1.67×10^{-2}	2.48×10^{-2}
II Rinsky et al. (Table 9) and Ott et al. (Table 11)	3.60×10^{-3}	1.15×10^{-2}	2.48×10^{-2}

[a]The tables referred to are those given in Crump and Allen (1984), and are reproduced in Appendix A.

TABLE 6. RESULTS FOR ABSOLUTE RISK MODEL USING "WINDOW" DOSE

Data set	Unit risk estimate		
	95% lower bound	MLE	95% upper bound
I Rinsky et al. (Table 9)[a]	4.34×10^{-3}	1.10×10^{-2}	2.17×10^{-2}
II Rinsky et al. (Table 9) and Ott et al. (Table 11)	3.48×10^{-3}	8.98×10^{-3}	2.52×10^{-2}

[a]The tables referred to are those given in Crump and Allen (1984), and are reproduced in Appendix A.

that benzene was a carcinogen. Others argued that it simply meant that the correct exposure route-animal strain-species model had not been adequately tested. Subsequent events have proved the latter view to be correct.

Goldstein et al. (1980) and Maltoni et al. (1983) have shown benzene to be carcinogenic for various strains of rats and mice via the inhalation route. In addition, Maltoni et al. (1983) and the National Toxicology Program (NTP) (July 1984, unpublished) have demonstrated that benzene is also carcinogenic via gavage exposure.

Crump and Allen (1984) evaluated these studies and selected what they considered to be the most relevant end points upon which to base risk extrapolation models. Lacking an independent EPA evaluation of these studies, the approach taken here is simply to adopt Crump and Allen's selection of end-points. This data base is also reproduced and displayed in Appendix A of this report.

Using these 23 selected end points, Crump and Allen (1984) estimated the doses corresponding to an increased risk of 10^{-6} using the multistage model and, where time-to-tumor data existed, the multistage-Weibull model. These results were summarized in their Tables 23 and 24, which are also included in Appendix A.

The dose corresponding to an increased risk of 10^{-6} in an animal experiment may be converted to the risk for a human due to a lifetime exposure of 1 ppm benzene in the air in the following manner.

Let the dose corresponding to an increased risk of 10^{-6} be denoted as x. Assuming that ppm exposures are equivalent between species, our unit risk in inhalation experiments is simply

$$b = \left(\frac{10^{-6}}{x}\right) \left(\frac{24}{8}\right) \left(\frac{7}{5}\right) = \frac{4.2 \times 10^{-6}}{x}$$

where $\left(\frac{10^{-6}}{x}\right)$ is the slope of a linear model required to give a risk of 10^{-6} due to 8 hours/day of exposure for 5 days/week and $\left(\frac{24}{8}\right) \left(\frac{7}{5}\right)$ translate the slope from a 40 hours/week industrial exposure to correspond to a constant exposure.

Using this formula and the values of x given in Table 23, Appendix A, the unit risks based upon animal inhalation studies are obtained. These are reproduced in Table 7.

To obtain the unit risk estimates for animal gavage experiments, the standard assumption used by EPA of equivalence between species on the basis of mg/surface area is used. This is at variance with the Crump and Allen (1984) equivalence assumption of mg/kg between species. We take the unit risk estimate to be

$$b = \left(\frac{10^{-6}}{x}\right) \left(\frac{L}{L_e}\right) \left(\frac{7}{d}\right) \sqrt[3]{\frac{70}{Wa}} \left(\frac{3.19 \times 20}{70}\right)$$

where x is the dose corresponding to a 10^{-6} risk, L/L_e is the fraction of the lifespan the animal was exposed, d is the days/week the animal was exposed, Wa is the weight of the animal in kg, and 3.19 x 20/70 is the estimated dose in mg/kg due to a constant exposure of 1 ppm benzene in the air, assuming 20 m^3 breathed per day, a 70-kg individual, and the weight of 3.19 mg of benzene in one m^3 of air for each ppm.

The values for x are obtained from Table 24, Appendix A, and substituted into the above formula to obtain the estimates shown in Table 8.

A comparison of these results with the human estimates, and a discussion of their relevance, is the subject of the next section.

TABLE 7. UNIT RISK ESTIMATES BASED UPON RODENT INHALATION STUDIES

Data sets	Multistage model	
	MLE	95% upper limit
Bioassays from Goldstein et al. (1980)		
Leukemia, male rats	--	1.11×10^{-3}
Leukemia, male mice	2.06×10^{-6}	5.41×10^{-4}
Bioassays from Maltoni et al. (1983)		
Leukemia, both sexes, rats	1.34×10^{-4}	4.40×10^{-4}
Zymbal gland or nasal cavity carcinoma or leukemia, both sexes, rats	1.12×10^{-3}	1.80×10^{-3}

TABLE 8. UNIT RISK ESTIMATES BASED UPON RODENT GAVAGE STUDIES

	Model			
	Multistage		Multistage-Weibull	
Data sets	MLE	95% upper limit	MLE	95% upper limit
NTP bioassays				
Zymbal gland carcinoma, male rats	1.33×10^{-2}	2.00×10^{-2}	1.38×10^{-2}	2.25×10^{-2}
All squamous cell carcinomas, male rats	1.73×10^{-2}	2.26×10^{-2}	1.94×10^{-2}	2.55×10^{-2}
Zymbal gland carcinoma, female rats	2.20×10^{-2}	3.22×10^{-2}	2.30×10^{-2}	3.55×10^{-2}
All squamous cell carcinomas, female rats	9.61×10^{-3}	1.60×10^{-2}	9.53×10^{-3}	1.78×10^{-2}
Squamous cell carcinoma of preputial gland, male mice	5.19×10^{-2}	1.25×10^{-1}	1.36×10^{-2}	1.61×10^{-1}
All squamous cell carcinomas, male mice	1.61×10^{-2}	1.19×10^{-1}	2.33×10^{-4}	1.50×10^{-1}
Alveolar/bronchiolar carcinoma, male mice	3.61×10^{-2}	6.48×10^{-2}	4.56×10^{-2}	8.29×10^{-2}
Lymphoma, NOS, male mice	2.08×10^{-2}	4.32×10^{-2}	2.92×10^{-2}	6.79×10^{-2}
All squamous cell carcinomas, female mice	8.18×10^{-6}	1.17×10^{-2}	8.98×10^{-6}	1.44×10^{-2}

TABLE 8. (continued)

Data sets	Model: Multistage MLE	Multistage 95% upper limit	Multistage-Weibull MLE	Multistage-Weibull 95% upper limit
NTP bioassays (continued)				
Mammary gland carcinoma, female mice	3.49×10^{-2}	5.71×10^{-2}	4.55×10^{-2}	6.79×10^{-2}
Alveolar/bronchiolar carcinoma, female mice	2.83×10^{-2}	4.21×10^{-2}	4.63×10^{-2}	7.24×10^{-2}
Lymphoma, female mice	9.23×10^{-3}	5.69×10^{-2}	--	3.84×10^{-2}
Bioassays from Maltoni et al. (1983)				
Leukemia, male rats	2.40×10^{-5}	1.33×10^{-2}		
All tumors, male rats	3.20×10^{-5}	2.31×10^{-2}		
Zymbal gland carcinoma, female rats	2.02×10^{-2}	3.28×10^{-2}		
Leukemia, female rats	--	6.32×10^{-3}		
All tumors, female rats	5.76×10^{-2}	8.95×10^{-2}		
Leukemia, both sexes, rats	4.26×10^{-3}	9.55×10^{-3}		
All tumors, both sexes, rats	1.88×10^{-2}	4.40×10^{-2}		

Discussion of Results

Employing the six models and various combinations of data sets and assumptions, a total of 21 unit risk estimates, with their 95% statistical confidence bounds, was obtained using epidemiologic data. These estimates are shown in Tables 1 through 6. The MLEs range from 8.98×10^{-3} to 1.04×10^{-1}, or slightly more than one order of magnitude. The effects of the model assumptions on the unit risk estimates are illustrated by the results shown in Table 9. All of the six models have been fitted to the Rinsky et al. cohort that was followed from 1940 to 1978, and unit risk estimates have been obtained. For the sake of comparison, the risks calculated by Crump and Allen (1984) for a white male exposed 8 hours per working day from age 20 to age 60 are also given. We note a drop in risk going from cumulative to weighted cumulative to window dose, as well as from relative to absolute, with the ratio of the maximum to the minimum risk estimate being less than a factor of five.

All of the models are statistically consistent with the observed data, so that a selection of one model over another is a matter of judgment. The use of information concerning leukemia responses in other studies might suggest the appropriate model. With regard to the dose parameters, Crump and Allen (1984) argue that the weighted cumulative dose is to be preferred, since the temporal leukemia response is based upon that observed in the survivors exposed to the atomic bomb in Hiroshima and Nagasaki. They also argue that the cumulative dose is acceptable but that the window dose has a considerably smaller credibility. With regard to the structural form of the model, little information exists. If all leukemia results from the same mechanism, and benzene affects a stage in this mechanism, then the relative risk model would hold. Crump and Allen (1984) have a slight preference for this form of the model, although no rationale is given. On the other hand, if the action of benzene is different

TABLE 9. RISKS DUE TO 1 PPM BENZENE EXPOSURE
BASED UPON RINSKY ET AL. COHORT, FOLLOW-UP FROM 1940 TO 1978

Exposure parameter	Exposure duration	Model form	
		Relative	Absolute
Cumulative	Lifetime	5.10×10^{-2}	2.20×10^{-2}
	40 working years[a]	6.62×10^{-3}	2.21×10^{-3}
Weighted cumulative	Lifetime	4.40×10^{-2}	1.76×10^{-2}
	40 working years	4.94×10^{-3}	1.90×10^{-3}
Window	Lifetime	1.67×10^{-2}	1.10×10^{-2}
	40 working years	1.75×10^{-3}	1.35×10^{-3}

[a]8 hours/day 5 days/week exposure to 1 ppm from age 20 to age 60.

from other factors producing leukemia, an absolute risk model may be more appropriate. In principle, we would prefer to base our estimate on the most extensive and inclusive body of data available that is of acceptable quality. This argues for making use of all three epidemiologic studies, but requires some adaptation since, due to the availability of information, the Wong et al. study can only be analyzed in one form.

In general, the studies in which the species and route of exposure most closely correspond to the environmentally exposed population are given the most weight in developing unit risk estimates. Also, the route of exposure in the epidemiologic studies and the environment are both by inhalation. As a result, we would place most of our emphasis on the unit risk estimates developed from the epidemiologic studies. Even so, animal studies can supply valuable confirmatory information. However, a number of factors strongly suggest that animal studies are less reliable than those based upon human response.

Among the more important factors for benzene are the following:

- Equivalent exposures were higher in the animal than in the epidemiologic studies, resulting in a greater extrapolation distance to the unit risk.
- The possibility always exists that some unknown qualitative difference between man and rodent could result in a major difference in sensitivity to benzene.
- The risk estimates are upper-bound in nature, and could be considerably above the true risks.

When estimating inhalation risks from gavage studies, the following important considerations also arise:

- An implicit assumption is made that the fraction of benzene delivered to the target organ via gavage in rodents is equal

to the fraction of the benzene delivered to the target organ from the tidal volume of air by man. Such an assumption is highly speculative.

- The approximate surface area correction is employed--a usage which, although standard, is somewhat controversial.

Keeping these factors in mind, we look at the animal results:

In Table 10, all of the animal responses related to leukemia are presented. We note that, with the exception of the NTP gavage study for male mice, these responses are all below the human estimates--which is reassuring. In general, the largest estimates of the unit risk are associated with the gavage studies.

In Table 11, the effects of varying some of the assumptions in the unit risk estimate are explored for the most sensitive end point preputial gland carcinomas in B6C3F1 male mice obtained in a gavage study. We note a change of one order of magnitude due to the difference between the surface area and weight equivalence assumptions. Another change of one order of magnitude results from using a 95% upper-bound rather than a non-zero maximum likelihood point estimate of the linear term. Thus, these two sources of uncertainty, taken together, change the estimate by more than two orders of magnitude.

Also, it should be noted that the Zymbal gland and preputial gland are found only in rodents and not in man. While tumors in these organs are a definite indication of carcinogenicity, they involve an additional extrapolation assumption when attempting to link them quantitatively to tumors in humans.

Considering the points raised and the general guidelines previously discussed, a "best judgment" single unit risk number will be developed by the CAG as requested by OAQPS in the next section.

TABLE 10. ANIMAL-DERIVED ESTIMATES OF UNIT RISK BASED UPON LEUKEMIA OR LYMPHOMA RESPONSE

Investigator	Exposure route	Species-sex	Unit risk estimate
Goldstein et al.	Inhalation	Male rats	1.11×10^{-3}
Goldstein et al.	Inhalation	Male mice	5.48×10^{-4}
Maltoni et al.	Inhalation	Male and female rats	4.41×10^{-4}
Maltoni et al.	Gavage	Male rats	1.33×10^{-2}
Maltoni et al.	Gavage	Female rats	6.32×10^{-3}
NTP	Gavage	Female mice	5.69×10^{-2}