the kidneys with peroxisome proliferation. This may relate to the fact that a hyperplastic response for the kidney at a magnitude comparable to that of the liver has not been described.

c: There are not yet any comprehensive data on carcinogenicity testing of compounds that are structural analogs of DEHP and are not associated with peroxisomal proliferation.

K. References

Albro PW, Corbett JT, Schroeder JL, Jordan S, Matthews HB. 1982. Pharmacokinetics, interactions with macromolecules and species differences in metabolism of DEHP. Environ Health Perspect 45:19-25.

Albro PW, Hass JR, Peck CC, Odam DG, Corbett JT, Bailey JF, Blatt HA, Barrett BB. 1981. Identification of the metabolites of di-(2-ethylhexyl)phthalate in urine from the African green monkey. Drug Metab Dispos 9:223-225.

Beevers H. 1969. Glyoxysomes of castor bean endosperm and their relationship to gluconeogenesis. Ann N Y Acad Sci 168:313-324.

Beevers H. 1979. Microbodies in higher plants. Ann Rev Plant Phys - 30:159-193.

Butterworth BE, Bermudexz E, Smith-Oliver T, Earle L, Cattley R, Martin J, Popp J, Strom SC, Jirtle R, Michalopoulos G. 1984. Lack of genotoxic activity of di-(2-ethylhexyl)phthalate (DEHP) in rat and human hepatocytes. Carcinogenesis 5:1329-1335.

Cerruti PA. 1985. Prooxidant states and tumor promotion. Science 227:375-381.

Ciriolo MR, Rossi L, Mavelli I, Rotilio G, Borzatta V, Cristofori M, Barbanti M. 1984. The effects of hypolipidemic agents derived from procetofenic acid on the activity of superoxide dismutase and glutathione peroxidase and on malondialdehyde production of rat liver. Arzneimittelforsch 34:465-467.

De Angelo AB, Garrett CT, Queral AE. 1984. Inhibition of phenobarbital and dietary choline deficiency promoted preneoplastic lesions in rat liver by environmental contaminant diethylhexylphthalate. Cancer Lett 23:323-330

DeDuve C. 1965. Functions of microbodies (peroxisomes). J Cell Biol 27:25a-26a.

DeDuve C, Baudhuin P. 1966. Peroxisomes (microbodies and related particles). Physiol Rev 46:323-357.

De la Iglesia FA, Lewis JE, Buchanan RA, Marcus EL, McMohem G. 1982. Light and electron microscopy of the liver in hyperlipoproteinemic patients under long term gemfibrozil treatment. Atherosclerosis 43:19-37.

Evans IH. 1976. Polyploidization in the rat liver: the role of binucleate cells. Cytobios 16:115-124.

Fahl WE, Lalwani ND, Reddy MK, Reddy JK. 1983. Induction of peroxisomal enzynes in livers of neonatal rats exposed to lactating mothers treated with hypolipidemic drugs. Role of the drug metabolite transfer in milk. Biocnem J 210:875-883.

Fahl WE, Lalwani ND, Watanabe T, Goel SK, Reddy JK. 1984. DNA damage related to increased hydrogen peroxide generation by hypolipidemic drug induced liver peroxisomes. Proc Nat Acad Sci USA; 81:7827-7830.

Ganning AE, Brunk U, Dallner G. 1983. Effects of dietary di(2-ethylhexyl)phthalate on the structure and function of rat hepatocytes. Biochim Biophys Acta 763:72-82.

Ganning AE, Brunk U, Dallner G. 1984. Phthalate esters and their effect on the liver. Hepatology 4:541-547.

Gerhardt B. 1978. Microbodies/Peroxisomes Pflanzlicher Zellen. Springer Verlag, Berlin.

Ghoshal AK, Farber E. 1984. The induction of liver cancer by dietary deficiency of choline and methionine without added carcinogens. Carcinogenesis 5:1367-70.

Gibson GG, Orton TC, Tamburini PP. 1982. Cytochrome P450 induction by clofibrtate. Purification and properties of a hepatic cytochrome P450 relatively specific for the 12- and 11- hydroxylation of dodecanoic acid (lauric acid). Biochem J 203:161-168.

Glauert HP, Reddy JK, Kennan WS, Sattler GL, Rao VS, Pitot HC. 1984. Effect of hypolipidemic peroxisome proliferators on unscheduled DNA synthesis in cultured hepatocytes and on mutagenesis in Salmonella. Cancer Lett 24:147-156.

Gray HR, de la Iglesia FA. 1984. Quantitative microscopy comparison of the peroxisome proliferation by the lipid regulating agent gemfibrozil in several species. Hepatology 4:520-530.

Greengard O. 1977. Enzymic differentiation of human liver: comparison with the rat model. Pediatr Res 11:669-676.

Gupta RC, Goel SK, Earley K, Singh B, Reddy JK. 1985. 32-P-Postlabeling analysis of peroxisome proliferator DNA adduct formation in rat liver *in vivo* and hepatocytes *in vitro*. Carcinogenesis 6:933-936.

Hanefeld M, Kemmer CH, Leonhardt W, Kunze KD, Jaross W, Haller H. 1980. Effects of p-chlorophenoxy isobutyric acid (CPIB) on human liver. Atherosclerosis 36:159-172.

Hruban Z, Swift H. 1964. Uricase localization in hepatic microbodies. Science 146:1316-1318.

Kahl R. 1982. Antioxidants and carcinogen metabolism. Trends Pharmacol Sci 3:72-74.

Kindle H. 1982. The biosynthesis of microbodies (peroxisomes, glyoxysomes). Int Rev Cytol 80:193-229. Kolde G, Rossner A, Thermann H.1976. Effect of clofibrate (alpha-p- chlorophenoxybutyrate-ethyl ester) in male rat liver. Virch Arch [Cell Pathol] 22:73-87.

Kolde G, Rossner A, Thermann H. 1976. Effect of clofibrate (alpha-p-chlorophenoxybutyrate-ethyl ester) in male rate liver. Virch Arch B Cell Pathol; 22:73-87.

Kornbrust DJ, Barfknecht TR, Ingram P, Shelburne JD. 1984. Effect of di(2-ethylhexyl) phthalate on DNA repair and lipid peroxidation in rat hepatocytes and on metabolic cooperation in Chinese hamster V-79 cells. J Toxicol Environ Health 13:99-116

Krahling JB, Gee R, Gauger JA. 1979. Fed. Proc. 38:664.

Lake BG, Gray TJ, Foster JR, Stubberfield GR, Gangolli SD. 1984. Comparative studies on DEHP induced hepatic peroxisome proliferation in the rat and hamster. Toxicol Appl Pharmacol 72:46-60.

Lake BG, Gangolli SD, Grasso P, Lloyd AG. 1975. Studies on the hepatic effects of orally administered di-(2-ethylhexyl)-phthalate in the rat. Toxicol Appl Pharmacol 32:355-367.

Lake BG, Rijcken WRP, Gray TJB, Foster JR, Gangolli SD. 1983. Comparative studies of the hepatic effects of di- and mono-n-octyl phthalates, di-(2-ethylhexyl)phthalate and clofibrate in the rat. Acta Pharm Toxicol 54:167-176.

Lalwani ND, Fahl WE, Reddy JK. 1983a. Detection of a nafenopin binding protein in rat liver cytosol associated with the induction of peroxide proliferation by hypolipidemic compounds. Biochem Biophys Res Commune. 116:388-393.

Lalwani ND, Reddy MK, Mark MM, Reddy JK. 1981. Induction, immunochemical identity and immunofluoresecence localization of a 80,000 molecular weight peroxisome proliferation polypeptide (polypeptide PPA-80) and peroxisomal enoyl-CoA hydratase of mouse liver and renal cortex. Biochemical J 198:177-186.

Lalwani ND, Reddy MK, Qureshi SA, Moehle CM, Hayashi H, Reddy JK. 1983b. Non-inhibitory effect of the antioxidants ethoxyquin, 2(3)-Tert-butyl--4-xydroxyanisole and 3,5-Ditertbutyl-4-hydroxytoluene on hepatic peroxisome proliferation and peroxisomal fatty acid beta-oxidation induced by a hypolipidemic agent in rats. Cancer Res 43:1680-1687.

Lalwani ND, Reddy MK, Qureshi SA, Sirtori CR, Abiko Y, Reddy JK. 1983C. Evaluation of selected hypolipideimc agents for the induction of peroxisomal enzymes and peroxisomal proliferation in the rat liver. Hum Toxicol 2:27-48

Lalwani, ND, Reddy, MK, Ghosh, S, Barnard, SD, Mollelo, JA, Reddy, JK Induction of fatty acid beta oxidation and peroxisome proliferation in the liver of rhesus monkeys by DL-040, a new hypolipidemic agent. Biochem Pharmacol, (in press).

Lazarow PB, DeDuve C. 1976. A fatty acyl-CoA oxidizing system in rat liver peroxisomes; enhancement by clofibrate, a hypolipidemic drug. Proc Natl Acad Sci USA. 73:2043-2046.

Leighton F, Coloma L, Koenig G. 1975. Structure, composition, physical properties and turnover of proliferated peroxisomes. J Cell Biol; 67:281-309.

Lhuguenot JC, Mitchell AM, Milner G, Lock EA, Elcombe CR. 1985. The metabolism of di-(2-ehtylhexyl)phthalate (DEHP) and mono--(2-ethylhexyl)phthalate (MEHP) in the rat. In vivo dose- and time-dependence of metabolism. Preprint distributed by the CMA Special - Programs Division. Published in Toxicol Appl. Pharmacol 80:11-22, 1985.

Maxwell DP, Armentrout VM, Graves, Jr LB.1977. Microbodies in plant pathogenic fungi. Ann Rev Phytopath 15:119-134.

Meyn RE, Jenkins TW. 1983. Variation in normal and tumor tissue sensitivity of mice to ionizing radiation-induced DNA strand breaks in vivo. Cancer Res 43:5668-5673.

Michalopoulos G, Sattler CA, Sattler GL, Pitot HC. 1976. Cytochrome P450 induction by Phenobarbital and 3-methylcholanthrene in primary cultures of hepatocytes. Science 193:907-909.

Mitchell AM, Bridges JW, Elcombe CR. 1984. Factors influencing peroxisome proliferation in cultured rat hepatocytes. Arch Toxicol 55: 239-246.

Mitchell AM, Lhuguenot JC, Bridges JW, Elcombe CR. 1985. Identification of the proximate peroxisome proliferators derived from di(2-ethylhexyl)-phthalate. Preprint distributed by the CMA Special Programs Division. Published in Toxicol Appl Pharmacol 80:23-32, 1985.

Moody DE, Reddy JK. 1976. Morphometric analysis of the ultrastructural changes in the rat liver induced by the peroxisome proliferator SaH 42-348. J Cell Biol 71:768-780.

Moody DE, Reddy JK. 1978. Hepatic peroxisome (microbody) proliferation in rats fed plasticizers and related compounds. Toxicol Appl Pharmacol 45:497-504.

Morton SJ. 1979. The hepatic effects of dietary di-2-ethyl-hexylphthalate. Ph.D. Thesis, The Johns Hopkins University.

Muller M, Moller KM. 1969. Urate oxidase and its association with peroxisomes in Acanthamoeba sp. Eur J Biochem 9:424-430.

Muller M. 1975. Biochemistry of protozoan microbodies. Ann Rev Microbiol 29:267-483.

Novikoff AB, Goldfisher S. 1969. Visualization of peroxisomes (microbodies) and mitochondria with diaminobenzidine. J Histochem Cytochem 17:675-680.

Novikoff AB, Novikoff PM, Davis C, Quintana N. 1973. Studies in microperoxisomes. V. Are microperoxisomes ubiquitous in mammalian cells? J Histochem Cytochem 21:737-755.

Numoto S, Furukawa K, Furuya K, Williams GM. 1984. The effects of the hepatocarcinogenic peroxisome-proliferating hypolipidemic agents clofibrate and nafenopin on the rat liver cell membrane enzymes GGT and alkaline phosphatase and on the early stages of liver carcinogenesis. Carcinogenesis 5:1603-1611.

Numoto S, Mori H, Furuya K, Levine WG, Williams, G. 1985. Absence of a promoting syncarcinogenic effect in rat liver by the carcinogenic hypolipidemic drug nafenopin given after N-2-Fluorenylacetamide. Toxicol Appl Pharmacol 77:76-85.

Orton TC, Parker GL. 1982. The effect of hypolipidemic agents on the hepatic microsomal drug metabolizing enzyme system of the rat. Induction of cytochrome P450 with specificity towards terminal hydroxylation of lauric acid. Drug Metab Dispos 10:110-115.

Ozasa H, Furuta S, Miyazawa S, Osumi T, Hashimoto T, Mori M, Miura S, Tatibana M. 1984. Biosynthesis of enzymes of rat-liver mitochondrial beta-oxidation. Eur J Biochem 144:453-458.

Peraino C, Staffeldt EF, Carnes BA, Ludeman VA, Blomquist JA, Vesselinovitch SD. 1984. Characterization of histochemically detectable altered hepatocyte foci and their relationship to hepatic tumorigenesis in rats treated once with diethylnitrosamine or benzo(a)pyrene within one day after birth. Cancer Res 44:33-34.

Perera MI, Shinozuka H. 1984. Accelerated regression of carcinogen-induced preneoplastic hepatocyte foci by peroxisome proliferators, BR931, 4-chloro-6-(2,3-xylidino)-2-pyrimidinylthio (N-B-hydroxyethyl) acetamide, and di-(2- ethylhexyl)phthalate. Carcinogenesis 5:1193-8.

Pitot HC, Barsness L, Goldsworthy T, Kitagawa T. 1978. Biochemical characterization of the stages of hepatocarcinogenesis after a single injection of diethylnitrosamine. Nature 271:456-458.

Pitot HC, Sirica AE. 1980. The initiation and promotion in carcinogenesis. Biochim Biophys Acta 605:191-228.

Randerath K, Reddy MV, Gupta RC. 1981. 32P labeling test for DNA damage. Proc Natl Acad Sci USA 78: 6126-6129.

Rao MS, Lalwani ND, Scarpelli DG, Reddy JK. 1982. The absence of gamma-glutamyl transpeptidase activity in putative preneoplastic lesions and in hepatocellular carcinomas induced in rats by the hypolipidemic peroxisome proliferator Wy- 14,643. Carcinogenesis 3:1231-1233.

Rao MS, Lalwani ND, Watanabe T, Reddy JK. 1984. Inhibitory effect of antoioxidants ethoxyquin and 2(3)tert-Butyl4hydroxyanisole on hepatic tumorigenesis in rats fed ciprofibrate, a peroxisome proliferator. Cancer Res 44:1072-1076.

Rao MS, Thorgeirsson S, Reddy JK. 1984b. The effect of peroxisome proliferators on rat hepatocytes transplanted into the anterior chamber of eye. J Cell Biol 98:2032-2090.

Reddy J, Chiga M, Bunyaratvej S, Svoboda D. 1970. Microbodies in experimentally altered cells. VII. CPIB induced hepatic microbody proliferation in the absence of significant catalase synthesis. J Cell Biol 44:226-234.

Reddy JHK, Kumar NS. 1979. Stimulation of catalase synthesis and increase of carnitine acetyltransferase activity in the liver of intact female rats fed clofibrate. J Biochem 85:847-856.

Reddy JK, Jirtle RL, Watanabe TK, Reddy KN, Michalopoulos G, Qureshi SA.1984. Response of hepatocytes transplanted into syngeneic hosts and heterotransplanted into athymic nude mice to peroxisome proliferators. Cancer Res 44:2582-2589.

Reddy JK, Krishnakantha TP, Rao MS. 1975. Microbody (peroxisome) proliferation in mouse kidney induced by methyl clofenopate. Virch Arch [Cell Pathol] 17:295-306.

Reddy JK, Lalwani ND, Reddy MK, Qureshi SA.1982; Excessive accumulation of autofluorescent lipofuchsin in the liver during hepatocarcinogenesis by methyl clofenapate and other hypolipidemic peroxisome proliferators. Cancer Res 42:259-266.

Reddy JK, Lalwani ND. 1983. Carcinogenesis by hepatic peroxisome proliferators: evaluation of the risk of hypolipidemic drugs and industrial plasticizers to humans. CRC Crit Rev Toxicol 12(1):1-68.

Reddy JK, Moody DE, Azarnoff DL, Rao MS. 1976. Di-(2-ethylhexyl)-phthalate: an industrial plasticizer induces hypolipidemia and enhances hepatic catalase and carnitine acetyltransferase activities in rats and mice. Life Science 18:941-945.

Reddy JK, Qureshi SA, Lalwani ND, Reddy MK, Moehle CM.1982. Induction by cirpofibrate of hepatic peroxisome proliferation in rats, pigeons, chickens, cats and Rhesus monkeys. Fed Proc 41:1741.

Reddy JK, Rao MS, Azarnoff DL, Sell S. 1979. Mitogenic and carcinogenic effect of hypolipidemic peroxisome proliferators [4-chloro-6(2,3-xylinido)-2-pyrimidyltio]acetic acid (Wy-14,643) in rat and mouse liver. Cancer Res 39:152-161.

Reddy JK, Reddy KM, Usman MT, Lalwani ND, Rao MS. 1985. Comparison of hepatic peroxisome proliferative effect and its implication for hepatocarcinogenicity of phthalate esters di(2-ethylhexyl)phthalate and di(2-ethylhexyl)adipate with a hypolipidemic drug. Environ Health Perspect (in press).

Regan JD, Setlow RB. 1974. Two forms of repair in the DNA of human cells damaged by chemical carcinogens and mutagens. Cancer Res. 34:3318-3325.

Seccombe DW, Hahn P. 1980. Carnitine acetyltransferase in developing mammals. Biol Neonat 38:90-95.

Sell S, Nichols M, Becker F, Leffert HL. 1974. Hepatocyte proliferation and alpha-fetoprotein in pregnant, neonatal and partially hepatectomized rats. Cancer Res 34:865-871.

Shinozuka H, Sells MA, Sikandar LK, Sell S, Lombardi B. 1979. Effects of a choline devoid diet on the emergence of gamma-glutamyltranspeptidase positive foci in the liver of carcinogen treated rats. Cancer Res 39:2515-2521.

Small GM, Burdett K, Connock MJ. 1983. Localization of carnitine acyltransferases and acyl-CoA beta-oxidation enzymes in small intestinal microperoxisomes (peroxisomes) of normal and clofibrate treated mice. Biochem Int 7:263-272.

Snell K. 1984. Enzymes of serine metabolism in normal, developing and neoplastic rat tissues. Adv Enzyme Regul 22:325-400.

Solt DB, Medline A, Farber E. 1977. Rapid emergence of carcinogen-induced hyperplastic lesions in a new model for the sequential analysis of liver carcinogenesis. Am J Pathol 88:596-610.

Staubli W, Schweizer W, Suter J, Weibel ER. 1977. The proliferative response of hepatic peroxisomes of neonatal rats to treatment with SU-13 437 (nafenopin). J Cell Biol 74:665-689.

Summerfield FW, Tappel AL. 1984a. Vitamin E protects against methyl ethyl ketone peroxide-induced peroxidative damage to rat brain DNA. Mutat Res 126:113-120.

Summerfield FW, Tappel AL. 1984b. Effects of dietary polyunsaturated fats and vitamin E on aging and peroxidative damage to DNA. Arch Biochem Biophys 233:408-416.

Svoboda D, Azarnoff D, Reddy J. 1969. Microbodies in experimentally altered cells. II. The relationship of microbody proliferation to endocrine glands. J Cell Biol 40:734-746.

Svoboda D, Grady H, Azarnoff D. 1967. Microbodies in experimentally altered cells. J Cell Biol 35:127-152.

Svoboda DJ. 1976. Response of microperoxisomes in rat small intestinal mucosa to CPIB, a hypolipidemigc drug. Biochem Pharmacol 25:2750- 2751.

Thorp JM. 1970. Hypocholesteroloemic and other effects of methyl clofenapate, a novel derivative of clofibrate. in Atherosclerosis: Proc 2nd Int Symp. Jones RJ, Ed. pp. 541-562.

Tolbert NE, Essner E. 1981. Microbodies: Peroxisomes and Glyoxysomes. J. Cell Biol 91:271s-283s.

Tolbert NE. 1971. Microbodies: Peroxisomes and glyoxysomes. Ann Rev Plant Phys 22:45-74.

Tolbert NE. 1972. in Algal Physiol Biochem. WD Steart, Ed. Blackwell Scientific Publicationns Ltd, Oxford. pp. 474-504.

Tolbert NE. 1981. Metabolic pathways in peroxisomes and glyoxysomes. Ann Rev Biochem 50:133-157.

Tomaszewski KE, Agarwal DK, Kluwe W, Melnick R. 1985. In vitro increases in hepatic peroxisomal steady state levels of hydrogen peroxide after treatment of rats and mice with carcinogenic peroxisome proliferators. Proc Annu Meet Am Assoc Cancer Res 26:74. Abs. 292.

Tomaszewski KE, Agarwal DK, Melnick RL, Rauckman EJ, Kluwe WM. 1984. Production and degradation of hydrogen peroxide in liver homogenates prepared from rats or mice treated with di(2-ethylhexyl)phthalate. The Toxicologist, 5 (1), 1985. Abstract 851.

Toth B. 1968. A critical review of experiments in chemical carcinogenesis using newborn animals. Cancer Res 28:727-738.

Ward JM, Oshima M, Lynch P, Riggs C. 1984. Di(2-ethylhexyl)phthalate but not phenobarbital promotes N-nitrosodiethylamine-initiated hepatocellular proliferative lesions after short-term exposure in male B6C3F1 mice. Cancer Lett 24:49-55.

Warren JR, Lalwani ND, Reddy JK. 1982. Phthalate esters as peroxisome proliferator carcinogens. Environ Health Perspect 45:35-40.

Watanabe T, Lalwani ND, Reddy JK. 1985. Specific changes in the protein composition of rat liver in response to the peroxisome proliferators ciprofibrate, Wy-14,643 and di-(2-ethylhexyl)phthalate. Biochem J 227 (in press).

VII. TERATOGENESIS AND OTHER REPRODUCTIVE HEALTH EFFECTS

High on the list of public concerns posed by exposure to chemical substances is the potential for infertility (male and female), reproductive failure, malformed offspring, and inherited defects that may affect future generations. The available data on the potential of DEHP to adversely affect reproduction come from animal experiments and deal mostly with testicular atrophy, fetotoxicity, and teratogenicity.

A. Male Reproductive Effects

After a single oral administration of DEHP to male Wistar rats both DEHP and MEHP are found in the testis, reaching a maximum within 6 to 24 hours after dosing (Oishi and Hiraga 1982). The ratio of MEHP to DEHP in the testis at 6 hours was the highest among the tissues examined. The amount of parent compound reaching the testis is relatively low, however. Using radiolabeled DEHP, Tanaka et al. (1975) found at most 0.036% and 0.13% of the radioactivity in the rat testis after intravenous or oral administration, respectively, within 24 hours after administration. Among tissues the affinity was lowest for testis and brain with either route of administration.

1. Testicular Atrophy.

At high dosages, exposure of male rats to DEHP causes testicular atrophy characterized by degeneration of seminiferous tubules. The testicular effects appear to be related both to dose and duration of exposure. A diet containing 2% DEHP fed to 5-week-old Wistar rats produced testicular atrophy in one week with average testicular weights

of 0.82 grams compared to 1.45 grams in untreated control rats (Oishi and Hiraga, 1980a). In the NTP subchronic bioassay similar effects were found in F344 rats after 90 days when 1.2% DEHP was fed in the diet. In the NTP chronic bioassay, 0.6% DEHP in the diet caused testicular atrophy after 2 years. The course of development of the lesions produced by DEHP is unclear, with competing unsubstantiated claims that the spermatogonial cells or the Sertoli cells are the target cells and with insufficient study of early events, dose, and dose-rate responses to establish the pathogenesis. The nature of the lesion, however, is clearly generalized atrophy of all the germinal tissue without appreciable overt necrosis. Reduction in sperm number is not associated with morphologically abnormal sperm (Douglas et al 1985). As one might expect, the activities of succinic dehydrogenase and adenosine triphosphatase are reduced within atrophic testes (Seth et al 1976). Testosterone secretion in response to human chronic gonadotropin is decreased after DEHP administration (Oishi and Hiraga, 1979). In addition to testicular atrophy, reductions in the weights of seminal vesicles and prostates were reported in 4-week-old rats but not in 15-week-old rats (Gray and Gangolli 1985, unpublished). Co-administration of testosterone or gonadotrophins did not protect against phthalate-induced testicular atrophy.

Mechanistic studies of DEHP associated testicular atrophy have centered on the role of zinc. Zinc is found normally at relatively high concentrations in testicular tissue and zinc deficient diets are known to reduce the rate of growth and development of immature testes. The atrophic testes associated with DEHP administration contained decreased concentrations of zinc (Oishi and Hiraga 1980a). Zinc concentrations

in liver were also reduced. In a comparative study of phthalate esters, Foster et al (1980) reported that following oral administration to rats for 4 days at doses of 7.2 mmol/kg/day, dimethy, diethyl, and dipropyl phthalates produced neither testicular atrophy nor decreased testicular zinc concentrations while di-n-butyl, di-n-pentyl, and di-n-octyl phthalates produced both testicular atrophy and lowering of testicular zinc content. In a similar study with dibutyl phthalate, daily oral administration to young rats at 2000 mg/kg for 4 days resulted in increased urinary excretion of zinc and decreased zinc content in the testes. Co-administration of zinc afforded substantial protection against the testicular damage produced by dibutyl phthalate (Cater et al 1977). Although an association between testicular atrophy and zinc concentration has been established, it is not known whether a cause and effect relationship exists or what the mechanism of testicular atrophy might be.

The effect of age in modifying DEHP induced testicular atrophy received special attention by the Panel. It had been repeatedly observed that oral administration of DEHP produced testicular atrophy at high doses in immature but not in mature rats. Spermatogenesis is not fully developed in rats until about 2 months of age and in this respect young weanling rats resemble male children nearing puberty. It was of interest, therefore, to learn of an unpublished report (Sjoberg et al 1985) in which it was observed that the age difference in rats was seen after oral administration of DEHP but not after repeated intravenous infusions of emulsified DEHP. The data suggested that gastrointestinal absorption of the metabolite MEHP was greater in young rats and that the apparent age discrepancy merely reflected differences in the amounts of

MEHP and/or its metabolites that reached the target tissue. Oishi and Hiraga (1980b) have shown that three monoesters of phthalic acid, including MEHP, are as effective in producing testicular atrophy in rats as their respective diesters.

Testicular atrophy can be produced by DEHP administration in mice as well as in rats (NTP bioassay) but the effects are less pronounced than in rats. In one study, male mice fed 2% DEHP in the diet for 7 days had reduced testicular zinc concentrations but no decrease in testicular weights (Oishi and Hiraga 1980c). The relative resistance of mice to testicular atrophy as compared to rats may be due to the relatively greater zinc concentrations found normally in the testes of mice. Hamsters are also more resistant than rats to testicular atrophy following intubation of DEHP in corn oil (Gray et al 1982). The Panel is aware of one unpublished report (Rhodes et al 1985) in which oral and intraperitoneal administration of DEHP (5 mmol/Kg) to marmosets for 14 days was said not to produce testicular atrophy.

2. Male Fertility and Dominant Lethal Effects.

In view of the evidence summarized above that DEHP can cause testicular atrophy in rodents, it would not be surprising if affected males had reduced fertility. Evidence of reduced fertility has indeed been obtained in experimental male animals. The data came principally from studies in mice that were designed to detect dominant lethal effects and in which male reproductive capacity was simultaneously investigated. (References to dominant lethal assays in mice are listed in the chapter on mutagenesis).

In one set of experiments (Autian 1982), groups of 7 to 9 male mice were injected with DEHP subcutaneously on experimental days 1, 5, and 10 at 10 dose levels ranging from 1 to 100 ml/Kg. Each mouse was mated with a virgin female mouse on day 21 following the first injection and for the next three consecutive days. The incidence of pregnancies issuing from dosed males was reduced at all dose levels in a dose-related way. There were also increased numbers of preimplantation losses and early fetal deaths and a corresponding reduction in the number of live fetuses per litter. In a second set of experiments, groups of 10 male mice were treated with DEHP subcutaneously on days 1, 5, and 10 at dose levels of 1, 2, 5 or 10 ml/Kg. Each male was mated with a different female every fifth day up to 21 days and then every week up to 8 weeks. Experiments of this sort account for the possibility that spermatagonial cells in various stages of development (the developmental cycle in mice takes about 7 weeks) may differ in susceptibility to the test substance. The resulting data were used to generate a so-called mutagenic index (early fetal deaths/total implants per pregnancy) which showed a dose-related trend with slight increases compared to controls at all mating intervals. In a similar experiment by the same group (Singh et al 1974), male ICR mice were treated with single intraperitoneal injections of DEHP or MEHP at one-third, one-half, and two-thirds of the acute LD_{50} dose. After both compounds, weekly matings over a 12-week-period produced a reduction in incidence of pregnancies, reductions in number of implantations per pregnancy and of litter size, and early fetal deaths. The effects were most noticeable during the first three weeks of mating, indicating that late stage spermatogenial cells had been affected. Similar antifertility

effects were found when the same methods were applied to di-2-ethylhexyl adipate and to diethyl adipate in mice (Singh et al 1975a).

On the other hand, when DEHP, MEHP, or EH were tested in a similar dominant lethal assay protocol, except for administration by gavage in corn oil for five consecutive days, the resulting fertility indices and implants per pregnancy were within the normal range for all three compounds (Rushbrook et al 1982). (See also the chapter on mutagenicity.) The Panel noted that the reports of the positive dominant lethal effects of DEHP all came from one laboratory and that subsequent breeding experiments to demonstrate germ cell mutations have not been conducted.

Conclusions. The Panel concluded that for both DEHP and MEHP there is evidence of adverse effects on male reproductive performance including reduced fertility in mice and testicular atrophy in rats and mice. Information regarding low dose effects, mechanisms of action, or possible germ cell mutations is unfortunately lacking.

B. Female Reproductive Effects

Few studies have addressed the possibility of ovarian atrophy comparable to the testicular atrophy in males. Seth et al. (1976) gave prepubertal female rats three intraperitoneal injections of DEHP (5 ml/Kg) on days 1, 5, and 10. On day 22 of the experiment the animals were killed and no detectable differences were found histologically in the ovaries of dosed and control rats. It may be, however, that adverse effects might have been found in older rats with maturing ova. Nikonorow et al (1973) administered 1.7 g/Kg DEHP in olive oil by gavage daily to Wistar rats for 3 months pre-mating. Administration before

gestation had no effect on conception, litter size, or fetal abnormalities.

In the body DEHP reaches the female reproductive organs and crosses the placenta into the fetus. In one study, for example, radiolabeled DEHP administered once intraperitoneally at a dose of 1 or 5 ml/Kg to pregnant Sprague-Dawley rats on either day 5 or day 10 of gestation was present in the maternal blood, fetal tissue, amniotic fluid, and placenta throughout the remainder of the gestation period (Singh et al 1975b). Less than 1% of the administered dose was found in these tissues at any of the measured times and none of the tissues had consistently higher levels than the maternal blood. This study showed that radioactivity was transmitted across the placenta to the fetus and that the radioactivity was detectable for at least 15 days post injection. There were no clinial signs of maternal toxicity. Placental transport of DEHP has also been demonstrated in guinea pigs using a placental perfusion technique (Kihlstrom 1983).

C. Fetotoxicity and Teratogenicity.

The possible effects of DEHP on the fetus have been investigated in the rat, hamster, mouse, and chick embryo. In the rat, fetotoxic effects have been demonstrated but few or no terata. For example, Singh et al (1972) administered 5 or 10 ml/Kg DEHP in cottonseed oil intraperitoneally to pregnant Sprague-Dawley rats on days 5, 10, and 15 of gestation. On the 20th day of gestation the rats were killed and examined. Compared to control rats, DEHP exposed rats had more resorbed fetal sites and fewer and smaller live fetuses. No skeletal abnormalities were found, but 22% gross abnormalities (type not

specified) were found compared to 2% gross abnormalities in control rats. Similarly Nikonorow et al (1973) reported that groups of 10 pregnant Wistar rats receiving 0.34 or 1.7 g/kg DEHP daily by gavage for the 21 days of gestation had increased numbers of resorptions and decreased fetal body weights. No gross abnormalities were found in the fetuses. Nakayama et al (1968) administered 5 or 2.5 ml/Kg DEHP orally to rats between days 7 and 13 of pregnancy. About 50% of the implants were resorbed but no teratogenic effect was found. Onda et al (1976) fed DEHP to pregnant Wistar rats at dose levels of 2, 1, 0.4, and 0.2 gm/Kg/day. Here, too, increases in numbers of resorptions and decreases in fetal body weights were found.

Tomita et al (1982) conducted in vivo/in vitro experiments in Syrian hamsters in which pregnant hamsters were given 0.5 ml DMSO containing DEHP or MEHP orally on the 11th day of gestation. The range of doses tested was from 3.75 to 15 g/Kg for DEHP and from 0.375 to 1.5 g/Kg for MEHP. A day later the cells were excised and cultured. Both DEHP and MEHP produced chromosomal aberrations and morphologic transformation in the embryonic cells.

In mice, DEHP is both fetotoxic and teratogenic. Nakamura et al (1979) gave a single oral dose (0.05, 0.1, 1.0, 2.5, 5, or 10 ml/Kg) of DEHP to ddY X CBA mice on day 7 of gestation. The three highest doses were severely embryotoxic with almost no live fetuses. The 1.0 ml/Kg dose produced 59% late fetal deaths, 18% skeletal abnormalities and 8% other gross abnormalities. The skeletal abnormalities included elongated and fused ribs, absence of tail bones, abnormal or incomplete skull bones, and incomplete or missing leg bones. The lowest dose used, 0.05 ml/kg, resulted in decreased fetal body weights. The dose of DEHP producing the background level of fetal deaths (2%) was estimated to be

64 mg/Kg. Shiota et al (1980) fed diets containing 0.05, 0.1, 0.2, 0.4, or 1% DEHP to ICR mice throughout pregnancy. The three higher dose levels resulted in decreased maternal weight and increased resorptions. All the implanted ova died in utero at the 0.4 and 1% levels of DEHP. The rate of malformations increased at 0.2% and above and were principally neural tube and skeletal defects. Onda et al (1974) reported renal cysts and skeletal malformations in mice fed DEHP (details not provided).

In chick embryos, Lee et al. (1974, 1977) reported that 0.05 ml - DEHP injected into the yolk sac of 3-day-old embryonated eggs was toxic and caused fetal growth retardation and non-specific malformations particularly in the central nervous and skeltal systems. In dying embryos the most conspicuous change was degeneration of extraembryonic blood vessels.

Thomas et al (1979) failed to produce teratogenic effects in rabbits by intravenous injections of MEHP (1.14, 5.69, or 11.38 mg/Kg) daily for 13 days starting on the 6th day of gestation. The two higher dose levels produced some maternal deaths. The teratogenic effects of MEHP were also evaluated in the rat (Ruddick et al 1981). Groups of 15 Wistar rats were given MEHP daily by gavage (225, 450, or 900 mg/Kg) on days 6 to 15 of gestation. MEHP was lethal to 3, 4, and 11 mothers in the respective dosage groups. The experiment was then repeated at lower dosages (50, 100, or 200 mg/Kg). Maternal weight gains were reduced at the 100 and 200 mg/Kg dose levels. Litter weights and litter sizes were reduced at the 450 mg/Kg dose level but not at lower levels. Excess teratologic effects were not found.

Di-2-ethylhexyl adipate (DEHA) was tested for teratogenicity (along with six other adipates) in Sprague-Dawley rats by intraperitoneal injections (1, 5, or 10 ml/Kg) on days 5, 10 and 15 of gestation (Singh et al 1973). Although the authors conclude that all the adipic acid esters studied had some deleterious effects upon the developing embryo and fetus, the tabular data for DEHA showed no significant differences from control data.

Conclusions. The Panel concludes that DEHP is fetotoxic for rats and mice and teratogenic for mice, producing abnormalities of the skeletal and nervous systems. The major metabolite of DEHP, MEHP, is fetotoxic for the rat.

D. References

Autian J. 1982. Antifertility effects and dominant lethal assays for mutagenic effects of DEHP. Environ Health Perspect 45:115-118.

Cater BR, Cook MW, Gangolli SD, Grasso P. 1977. Studies on dibutyl phthalate-induced testicular atropny in the rat: Effect on zinc metabolism. Toxicol Appl Pharmacol 41:609-618.

Douglas GR, Hugenholtz AP, Blakey DH. 1985. Genetic toxicology of phthalate esters: Mutagenic and other genotoxic effects. Environ Health Perspect (in press).

Foster PMD, Thomas LV, Cook MW, Gangolli SD. 1980. Study of the testicular effects and changes in zinc excretion produced by some n-alkyl phthalates in the rat. Toxicol Appl Pharmacol 54:392-398.

Gray TJB, Rowland IR, Foster PMD, Gangolli SD, 1982. Species differences in the testicular toxicity of phthalate esters. Toxicol Lett 11:141-147.

Gray TJB, Gangolli SD. 1985. Aspects of the testicular toxicity of phthalate esters (in press).

Kihlstrom I. 1983. Placental transfer of diethylhexyl phthalate in the guinea-pig placenta perfused in situ. Acta Pharmacol et Toxicol 53:23-27.

Lee H-Y, Kalmus GW, Levin MA. 1974. Effects of phthalate esters (plasticizers) on chick embryos and chick embryonic cells. Growth 38:301-312.

Lee H-Y, Auslander SE, Kalmus GW. 1977. Toxicity of di(2-ethylhexyl) phthalate in chick embryos gel electrophoretic analysis of serum proteins. Comp Biochem Physiol 56C:9-12.

Nakamura Y, Yagi Y, Tomita I, Tsuchikawa K. 1979. Teratogenicity of di-(2-ethylhexyl)phthalate in mice. Toxicol Lett 4:113-117.

Nakayama N. 1968. Toxicological studies on di-(2-ethylhexyl-epoxy-hexahydro-phthalate) and di-(iso-decylepoxyhexahydrophthalate) in mice. Japan J Publ Health 15:397.

Nikonorow M, Mazur H and Piekacz H. 1973. Effect of orally administered plasticizers and polyvinyl chloride stabilizers in the rat. Toxicol Appl Pharmacol 26:253-259.

Oishi S, Hiraga K. 1979. Effect of phthalic acid esters on gonadal function in male rats. Bull Environ Contam Toxicol 21:65-67.

Oishi S, Hiraga K. 1980a. Testicular atrophy induced by phthalic acid esters: Effect on testosterone and zinc concentrations. Toxicol Appl Pharmacol 53:35-41.

Oishi S, Hiraga K. 1980b. Testicular atrophy induced by phthalic acid monoesters: Effects of zinc and testosterone concentrations. Toxicology 15:197-202.

Oishi S, Hiraga K. 1980c. Effect of phthalic acid esters on mouse testes. Toxicol Lett 5:413-416.

Oishi S, Hiraga K. 1982. Distribution and elimination of di-(2-ethyl-hexyl)phthalate (DEHP) and mono-2-ethylhexyl phthalate (MEHP) after a single oral administration of DEHP in rats. Arch Toxicol 51:149-155.

Onda H, Kodama H, Yamada N, Ota H. 1974. Studies on the toxic effects of phthalate acid esters. 3. Teratology in mice. Japan J Hyg 29:177.

Onda H, Kodama H, Yamada N, Ota H. 1976. Effect of phthalate ester on reproductive performance in rat. Japan J Hyg 31:507-512.

Rhodes C et al. 1985. Comparative pharmacokinetics and subacute toxicity of di(2-ethylhexyl)phthalate (DEHP) in rats and marmosets: extrapolation of effects in rodents to man (in press).

Ruddick JA, Villeneuve DC, Chu I, Nestmann E, Miles D. 1981. An assessment of the teratogenicity in the rat and mutagenicity in Salmonella of mono-2-ethylhexyl phthalate. Bull Environ Contam Toxicol 27:181-186.

Rushbrook CJ, Jorgenson TA, Hodgson JR. 1982. Dominant lethal study of di-(2-ethylhexyl)phthalate and is major metabolites in ICR/SIM mice. Environ Mutagen 4:387.

Seth PK, Srivastava SP, Agarwal DK, Chandra SV. 1976. Effect of di-(2-ethylhexyl)phthalate (DEHP) on rat gonads. Environ Res 12: 131-138.

Shiota K, Chou MJ, Nishimura H. 1980. Embryotoxic effects of di-(2-ethylhexyl)phthalate (DEHP) and di-n-butyl phthalate (DBP) in mice. Environ Res 22:245-253.

Singh AR, Lawrence WH, Autian J. 1972. Teratogenicity of phthalate esters in rats. J Pharm Sci 61:51-55.

Singh AR, Lawrence WH, Autian J. 1973. Embryonic-fetal toxicity and teratogenic effects of adipic acid esters in rats. J Pharm Sci 62: 1596-1600.

Singh AR, Lawrence WH, Autian J. 1974. Mutagenic and antifertility sensitivities of mice to di-(2-ethylhexyl)phthalate (DEHP) and dimethoxyethyl phthalate (DMEP). Toxicol Appl Pharmacol 29:355-46.

Singh AR, Lawrence WH, Autian J. 1975a. Dominant lethal mutations and antifertility effects of di-2-ethylhexyl adipate and diethyl adipate in male mice. Toxicol Appl Pharmacol 32:566-576.

Singh AR, Lawrence WH, Autian J. 1975b. Maternal-fetal transfer of 14C-di-(2-ethylhexyl)phthalate and 14C-diethyl phthalate in rats. J Pharm Sci 64:1347-1350.

Sjoberg P, Lindqvist NG, Ploen L. 1985. Age-dependent response of the rat testes to di-(2-ethylhexyl)phthalate (in press).

Tanaka A, Adachi T, Takahashi T, Yamaha T. 1975. Biochemical studies on phthalic esters. I. Elimination, distribution and metabolism of di-(2-ethylhexyl)phthalate in rats. Toxicology 4:253-264.

Thomas JA, Schein LG, Gupta PK, McCafferty RE, Felice PR, Donovan MP. 1979. Failure of monoethylhexyl phthalate to cause teratogenic effects in offpspring of rabbits. Toxicol Appl Pharmacol 51:523-528.

Tomita I, Nakamura Y, Aoki N, Inui N. 1982. Mutagenic/carcinogenic potential of DEHP and MEHP. Environ Health Perspect 45:119-125.

VIII. CONSUMER EXPOSURE TO DEHP

The exposure of the general public to DEHP is believed to be extensive as a result of its widespread usage in consumer products. The principal sources of direct human exposure result from the formulation of plastic products and the migration of DEHP from those products during use. Included among the diversity of products in which DEHP is employed are blood storage bags, dialysis units, flooring materials, wall coverings, upholstery, shoes, vehicle seats, toys and infant items, food wrappers, and numerous pesticide products, where it serves as a solvent, carrier, or plasticizer. Exposure of people to DEHP is possible as a result of:

(1) Inhalation of DEHP which has volatilized from various products,

(2) Dermal absorption as a result of direct skin contact,

(3) Ingestion of foods or drinking water containing DEHP. Ingestion of DEHP may also occur as a result of sucking activity to agents, such as pacifiers, which contain high percentages by weight of DEHP, and

(4) Intravenous from blood transfusions or other medical procedures.

Given the broad nature of the products that contain DEHP it follows that exposure in the population will be widespread and not limited to any particularly exclusive subsegment of the population. Nevertheless, certain subsegments in the population can be expected to be exposed to significantly greater amounts of DEHP.

The broadest detailing of potential human exposure to DEHP derives from a 1980 report of the U.S. EPA. The Agency attempted to quantify

exposure for a wide range of people: patients undergoing blood transfusion, including hemophiliacs; patients on kidney dialysis; surgical patients undergoing cardiopulmonary bypass; the general population with respect to food and water consumption; and children from specific products. With respect to food, it was estimated that through consumption of commodities with a high likelihood of DEHP contamination (margarine, bread, etc.), the estimated average daily adult exposure is 209.8 ug. Levels in community drinking water, on the whole, are thought to be negligible, although individual instances of contamination may be high.

Considerably higher exposures may occur for those persons receiving transfused blood. Estimates of exposure range widely depending on numerous variations with a high exposure, although not worst-case, being on the order of about 50 mg DEHP after transfusion with several units of blood. In the U.S., about 3,000,000 people are exposed to DEHP from transfusions each year.

Another group receiving high exposure to DEHP consists of those undergoing dialysis. Each dialysis patient is estimated to receive about 90 mg DEHP per treatment. In the U.S. there are about 50,000 dialysis patients potentially exposed to DEHP. With respect to hemophiliacs, there is also the possibility of high DEHP exposure as a result of the many transfusions they undergo. Based on estimates at the high end of the exposure scale, the EPA (1980) determined that a hemophiliac may be exposed to up to 760 mg of DEHP annually. The number of hemophiliacs likely to be exposed to DEHP is in the 10,000 range.

Of greatest concern to the present problem is the quantification of exposure to DEHP by infants. In 1980, EPA concluded that "no

information is available on the amount of DEHP ingested by infants from plastic baby products." These products would include pacifiers, teethers, rubber pants and a number of other such soft and pliable infant items. Subsequent to that EPA assessment was a comprehensive report by Arthur D. Little (ADL) (1985) on factors affecting exposure to DEHP from children's products. This report assessed the types and frequencies of early childhood activities, such as sucking behavior, that may affect exposure as well as usage patterns with respect to age of various DEHP-containing products and the migration potential of DEHP.

The CPSC has estimated the oral exposure of young children to DEHP from contact with items used by children. These estimations are based on simulation-type studies including DEHP leaching rates from pacifiers, teethers, and vinyl toys in human saliva and artifical saliva under conditions where the item was applied with physical force to simulate sucking, gumming, or chewing. The amount of force applied and the length of exposure time of were varied. The CPSC then made estimates of child-item usage so that a total exposure could be estimated. The estimates were based on the use of low or high DEHP releasing pacifiers and moderate or heavy mouthing of the child-item. The collective estimated total exposure from mouthing contact from the pacifiers, teethers, and vinyl toys for the 0-36-month-old child ranged from 62 mg to 665 mg.

The CPSC also estimated the extent of dermal absorption based on the migration of DEHP into cotton-saturated lanolin which was used to simulate human skin. Based on the obtained migration rate of DEHP into

the lanolin and the estimated daily contact with various child-items, such as playpens and vinyl baby pants, the CPSC estimates a collective yearly exposure to these two items of 216 mg (96 mg from the playpen and 120 mg from the rubber pants, assuming a 10 percent absorption efficiency).

The procedures the CPSC used to calculate this range of possible exposures have been reviewed and criticized by Rodricks and Turnbull (1984). These authors contend that some of the assumptions employed by the CPSC, such as presumed higher dermal absorption efficiency, are likely to overestimate exposure. For example, total dermal absoption of DEHP over five days in the rat was about 5% of the total applied; yet it is widely accepted that the rat skin is considerably more permeable than the human. Despite the critique of the CPSC estimates by Rodricks and Turnbull (1984), there was generally close agreement with total DEHP exposure estimates between these two groups, with the Rodricks and Turnbull (1984) estimates being only about 50% lower depending on the exposure scenarios.

Although these reports are in reasonable agreement, this should not be of great comfort since they start by analyzing the same data base. The major point is that they are establishing possible exposure levels by using what appear to be reasonable but essentially non-validated methods.

The most direct method for estimating exposure is the determination of DEHP/metabolite levels in the urine of children. Multiple species (rats, dogs, mini-pigs) observations indicate that DEHP is excreted as a metabolite in the urine at about 37%-84% in 24 hours (Ikeda et al 1980). In the African green monkey and in humans, up to 80% of DEHP appears in

the urine as glucuronide metabolites (Peck and Albro 1982). This suggests that quantification of human exposure data is achievable, and would not also be a test of validation of previous predictive methods but could then be used in quantitative risk assessment. Previous studies, as noted above, such as those by ADL (1985) and ITRI (1983), have not been directed toward the attainment of data that could be employed to predict initial exposure.

In conclusion, exposure to DEHP is widespread, affecting most segments of society. Particular subgroups will receive considerably greater exposure than the general public. These include persons receiving normal transfusions and hemophiliacs as well as those undergoing dialysis. Also, young children often use products with high levels of DEHP, such as pacifiers. While attempts to model exposure mathematically and via in vitro models have been made for early childhood exposure, no estimates of urinary excretion levels have been published. Since a large percentage of DEHP is excreted as a metabolite in the urine of multiple models and probably in humans, this type of quantification could be used to derive a normal distribution of childhood exposure.

References

ADL (Arthur D. Little, Inc.) 1985. Factors that effect exposure to DEHP from children's products. Report to Chemical Manufacturers Association.

Ikeda GJ, Sapienza PP, Couvillion TM, Farber TM, and Van Loon EJ. 1980. Comparative distribution, excretion, and metabolism of di-(2-ethylhexyl)phthalate in rats, dogs, and miniature pigs. Food Cosmet Toxicol 18:637-642.

Inhalation Toxicology Research Institute (ITRI). 1983. Phthalate ester migration from polyvinyl chloride consumer products: Phase I final report. Consumer Product Safety Commission, Contract CPSC-IAG-81-1387.

Peck CC, Albro PW. 1982. Toxic potential of the plasticizer di(2-ethylhexyl)phthalate in the context of its disposition and metabolism in priamtes and man. Environ Health Perspect 45:11-17.

Rodricks JV, Turnbull D. 1984. Assessment of possible carcinogenic risk resulting from exposure to di(2-ethylhexyl)phthalate (DEHP) in children's products. Environ. Corporation. Report prepared for Chemical Manufacturers Association.

U.S. EPA. 1980. Priority review level-1:di-(2-ethylhexyl)phthalate (DEHP). Office of Toxic Substances, Washington, DC (Draft).

IX. RISK ASSESSMENT

A report from the Office of Science and Technology Policy issued in February 1985 remarks that "It is apparent that human cancer risk assessment is still in an evolutionary state and that a number of emerging areas of science will impact on this process in the future." (OSTP, 1985). This statement is particularly germane to the considerations of risk assessment for DEHP. Specifically, no adequate models exist for estimating cancer risk for materials that may not act as complete carcinogens. It should be noted that while the animal bio-assays indicate that DEHP is a complete carcinogen, the possibility exists that DEHP is largely a promoter and that risk estimates will need to be revised as newer data and better models are developed.

A. Carcinogenic Effects

As reported in an earlier chapter, a well-conducted carcinogenesis bioassay, carried out according to current standards, has shown experimental exposure to DEHP to produce statistically significant increases in malignant neoplasms and likely precursor lesions in both sexes in two species of laboratory animals (the rat and the mouse) (NTP 1982), thus making it appear that DEHP acts like a complete carcinogen in these two species. In view of these results, it would seem appropriate to conduct a formal risk assessment using a common, or usual, model for low dose extrapolation. The OSTP report (1985) notes (p. 80) that "...the multi-stage model developed by Armitage and Doll is perhaps the most frequently employed of the low dose extrapolations currently in use." Problems exist, however, in the use of this, or any other model.

It has been assumed that the whole animal bio-assay procedures in current use are capable of discovering "complete" carcinogens -- those capable of both initiating the carcinogenic process and also carrying the process forward through whatever later stages ("promotion", "progression") are necessary to produce frank, observable cancers. It is thus reasonable to argue that a complete carcinogen should be associated with hereditary damage to, or modification of, the genetic material of the cell -- and that this damage could be demonstrated by responses in one or more short-term biological tests. This may be particularly important for regulatory purposes, for, as Boutwell (1964) has argued if no genetic or transmissible change has occurred, then the process may be reversible with cessation of exposure, implying a possible threshold dose below which carcinogenesis would not take place. As the chapter on the results of the short-term testing shows, there is little or no evidence that DEHP acts as a mutagen through direct damage to DNA or as an early stage carcinogen.

The lack of evidence from short-term tests that the mechanism of action of DEHP proceeds through a mutagenic-initiating process has led to consideration of other possible mechanisms. One such possible mechanism is put forth in the chapter of this report dealing with peroxisomal proliferation. In essence, what is suggested is that the carcinogenic action of DEHP involves a secondary mechanism, mediated through DEHP's action as a peroxisome proliferator, which in turn is associated with a high level of formation of reactive oxygen species, which in turn produces DNA damage, leading to carcinogenesis. The carcinogenic process envisioned is the usual one of producing some damage to the genetic material of the cell, which is then incorporated

into the daughter cells through one or more cell replications, leading to eventual tumor development.

Evidence of the effect of peroxisome inducers is seen in the enlargement of the liver "immediately after the initiation of the feeding of the proliferator compound." As the chapter points out, however, "the mode of action of the peroxisome proliferators...would only be manifest after a certain concentrationn of effector molecules were to be reached at the sites responsible for regulating the event of peroxisome proliferation." This argument suggests that if there were insufficient exposure to a proliferation-stimulus compound, no proliferation would occur, and carcinogenesis would not take place. That is, an indirect mechanism for carcinogenesis such as peroxisome proliferation implies the existence of a threshold dose below which there will be no excess cancer risk.

Problems that exist with the peroxisome proliferation theory are pointed out in the related chapter in this report. No experimental evidence has yet been developed to demonstrate the postulated H_2O_2 (or other "reactive oxygen species") effects on DNA in systems involving peroxisome proliferation. It is possible, of course, that effects have not been seen because the measures used are too insensitive to demonstrate them. Peroxisome proliferation has been shown in other tissues -- namely the kidney, and possibly, to a small extent, intestinal tissue. In the NTP bio-assay studies an excess of cancers or preneoplastic lesions has not been seen in these tissues.

In view of these difficulties, the CHAP looked upon the peroxisomal proliferation theory of carcinogenesis as having considerable scientific interest and merit, but not yet sufficiently well supported to be fully

accepted as the essential mechanism of DEHP carcinogenesis. Further, no generally accepted system or procedure for extrapolation appears to be at hand to estimate thresholds for carcinogens in either an animal or human population, as appears to be implied by this particular hypothesis. A related hypothesis concerning the liver proliferation-stimulation qualities of DEHP derives from the fact of rapid proliferation which makes more likely the appearance of DNA damage, or defect, which then provides the basis for the two part development of neoplasms, i.e., DNA damage incorporated into daughter generations of cells through one or more cell divisions. This process also implies a possible threshold, namely the dose of DEHP that would not induce cell proliferation, and hence not increase the likelihood of DNA damage or the incorporation of that damage into succeeding generations of cells.

The major data concerning the carcinogenic potential of DEHP derive from studies conducted by the National Toxicology Program and are contained in NTP Report 217 (NTP 1982). The experimental design and the results of the long-term study are described in detail in that report, and are reviewed in Chapter V of this report. Fisher 344 rats and B6C3F1 mice of both sexes were followed for a full lifetime. Survival of control and treated animals was comparable. Excess hepatocellular carcinomas and neoplastic nodules were observed in both sexes and both species as shown in Table IX-1 below.

TABLE IX-1

Hepatocellular Carcinomas and Neoplastic Nodules
Animals with Neoplasms/Total Animals

	Rats		Mice	
Dose	Males	Females	Males	Females
0	3/50	0/50	14/50	1/50
low	6/49	6/49	25/48	12/50
high	12/49	13/50	29/50	18/50

Because of what appeared to be excessive reported food consumption by the mice (about 9 grams per day reported per animal) in the NTP Report 217 (NTP 1982), the dose data in the mice were converted to a mg/kg basis using an estimated average daily consumption of 3.9 grams per animal. Neglecting this adjustment for what appears to be clearly excessive consumption leads to a lower estimate of risk (Turnbull and Rodricks, 1985). The food fed the mice was not in pelleted form and the 9 grams per day appears to represent food disappearance, rather than actual consumption, and would include substantial scattering and waste of the food.

Table IX-2
Daily Food Consumption by Rats and Mice

	Rats: Daily Consumption			Mice: Daily Consumption				
		Reported mg/kg			Reported mg/kg		Adjusted mg/kg	
Doses	ppm	Males	Females	ppm	Males	Females	Males	Females
low	6000	322	394	3000	672	799	308	344
high	12000	674	774	6000	1325	1821	632	780

Computations of the unit risk for the experimental animals, i.e., the probability of developing a hepatocellular carcinoma or neoplastic nodule per mg/kg consumption of DEHP, were made assuming the generalized multi-stage model of carcinogenesis, using the Global 83 computer program of Howe and Crump in its unrestricted form. This form does not constrain the multistage model to a number of stages (or dose raised to a power) equal to or less than the number of doses in the experiment. The doses used are those as given in Table IX-2, using the adjusted doses for the mice (in view of the likely disappearance through scattering of some of the food and thus non-consumption of some of the 9

grams per day reported by NTP), and the data as given by NTP Report 217 for the rats. Table IX-3 gives the excess risk for the experimental animals over background. The largest excess is for male mice, although this is not much greater than for the female mice. There was no consistent sex difference.

TABLE IX-3

Excess Risk for Hepatocellular Carcinomas and Neoplastic Nodules Following Exposure to DEHP (Lifetime risk per mg/kg/day)

Species/Sex	Maximum likelihood estimate	Upper 95% confidence limit
Rat - Male	.000154	.000471
- Female	.000285	.000523
Mouse - Male	.000678	.001122
- Female	.000545	.000752

The usual procedure for converting these unit risks for the experimental animals to unit risks for humans involves taking into account the relative size of the experimental animals and humans. This is usually done by multiplying by a factor of (Human body weight/Animal body weight)$^{1/3}$. For converting the unit risk data for rats to unit risk data for adult humans, this would involve the multiplier $(70/0.4)^{1/3} = 5.6$. For the mouse data this multiplier is $(70/0.033)^{1/3} = 12.8$. The OSTP in its review of chemical carcinogenesis (OSTP, 1985) notes that "calculating average daily dose on a body weight rather than on a surface area basis can reduce the estimated human risk by approximately 6 fold when rat data are used for modelling human response

and up to 14 fold for mouse data."* The OSTP report further goes on to say "...it must be emphasized that experience in this area is very limited and that the use of any standardized dosage scale for species scale-up is only a crude approximation..." (OSTP 1985, p. 82).

One further caution is in order, again as noted by OSTP. "Estimation of lifetime cancer risks is also complicated if...the exposures...fall far short of a normal lifespan. For example, if a multi-stage mechanism is assumed, then the effect of early termination of exposure will be dependent on the stages of the carcinogenic process that are influenced by the exposure." In general, the later the stage that is affected, the lower the risk will become as a consequence of less than lifetime exposure. Thus the estimates given here should be looked upon as likely upper limit estimates. In Table IX-3 both maximum likelihood estimates and upper 95% confidence limits estimates are given. The maximum likelihood estimates are usually grossly non-robust, i.e., quite small changes in the experimental results can lead to very large changes in the maximum likelihood estimate (Thorslund 1985). The upper 95% confidence limit, on the other hand, is much more stable.

B. Other Biological Effects

The biological effects of exposure to DEHP are not confined to the increase in neoplasia seen in some tissues (and, coincidentally, decrease in other tissues). Damage to testicular tissue has been seen. NTP also reports reduced thyroid, testicular and pituitary tumors in

---

* OSTP apparently assumes a 325 gram rat and a 25 gram mouse.

male rats, which they speculate may be due to reduced growth (see Chapter V).

Studies on the reproductive toxicity associated with DEHP (Reel et al 1984) conducted by the Research Triangle Institute led to significant reductions in fertility in CD-1 mice in pairs fed at 0.01% (100 ppm) in the diet during the 7 day pre-mating period and the 98 day cohabitation period. In the mouse, 10 ppm are roughly equivalent to 1 mg/kg. If the dose of 100 ppm (10 mg/kg) is looked upon as a LOEL and a safety factor of 1000 is applied (NAS 1977), then a "safe" dose for reproductive effects of .01 mg/kg would be implied.

A study conducted by the British Industrial Biological Research Association. (BIBRA 1984) reported liver enlargement in male rats fed DEHP for 21 days. Concentrations were 0.01, 0.06, 0.1, 0.6 and 1.2 percent in the diet (lowest dose level = 100 ppm). Increases in liver size were found at all dose levels, with the increases statistically significant at the higher doses. Liver enlargement did appear at the lowest dose, with great differences among the animals suggesting wide variation in susceptibility (i.e., in thresholds for these animals). Treating the lowest dose as a LOEL, and assuming that approximately 20 ppm in the diet equal 1 mg/kg for the rat, and applying the customary safety-factor of 1000 to a LOEL, yields a "safe" dose for liver enlargement of 0.005 mg/kg. What a 21 day feeding is comparable to in humans is not clear.

C. Quantitative Risk Assessment

The following exposure data are given in the preceeding chapter:

1. Average daily adult dietary exposure: 209.8 ug

   (On a mg/kg/day basis, assuming an average adult weighs 70 kg, equals

   209.8/(70 x 1000)= 0.003 mg/kg/day).

2. Persons receiving blood transfusions

   a) 50 mg/transfusion

   b) 3,000,000 persons receive a transfusion each year - or approximately 1/70th of the population, i.e., an average of one transfusion per life-time.

   c) This implies an average individual exposure from transfusions of

$$\frac{50 \text{ mg}}{70 \text{ kg}} \times \frac{1}{\substack{25,500 \\ \text{days in} \\ \text{a 70 year} \\ \text{lifetime}}} = 2.8 \times 10^{-5} \text{ mg/kg/day}$$

3. Dialysis patients

   a) 90 mg/treatment

      Assume 50 treatments per year for a period of 30 years. This leads to a total life-time exposure of 90 x 50 x 30 mg = 135,000 mg. This gives, for once a week dialysis:

$$\frac{135,000}{70 \times 25,500} = 0.075630 \text{ mg/kg/day.}$$

   b) There are approximately 50,000 dialysis patients.

4. Hemophiliacs

   a) 760 mg/year

   On a daily basis for however long the patient is treated this implies

$$\frac{760}{70 \text{ kg} \times 365 \text{ days}} = 0.029746 \text{ mg/kg/day}$$

b) There are approximately 10,000 hemophiliacs.

5. Children up to age 3.

a) Total exposure from sucking objects containing DEHP - up to age 3: 62-655 mg.

b) Additional exposure from other plastic items - 216 mg/year (Total, 3 yrs, 648 mg) for "high" exposure. "Low" exposure is assumed to be about one-half of this.

c) There are approximately 3,600,000 newborns a year. This implies total lifetime estimates of exposure (in excess of adult-exposures noted above)

$$\text{low: } 62 + \left(\frac{3 \times 216}{2}\right) \text{ mg} \times \frac{1}{25{,}500 \text{ days}} \times \frac{1}{15 \text{ kg}} = 0.0010 \text{ mg/kg/day}$$

$$\text{high: } (655 + 3 \times 216) \times \frac{1}{25{,}500} \times \frac{1}{15} = 0.0034 \text{ mg/kg/day}$$

Applying these exposure estimates to the unit risk estimates given in Table XI-3 above, gives an estimate of life-time cancer risks, for liver cancers. These estimates are subject to several important assumptions, however. The major assumption introduced into these computations is that excess risk is directly proportional to cumulative lifetime dose as expressed on a mg/kg/day basis. Thus, no distinction is made between receiving this dose in a few large doses spaced over a lifetime (as for example from 2 or 3 transfusions) and receiving the same total dose as a result of much smaller doses uniformly spread out as a consequence of ambient exposures.

The risk computations given here must be looked upon as crude estimates. Because of some biological assumptions made, these estimates are likely to be upper limits or close to upper limits of risk. The lower limits to these risks could be zero - if, for example, true thresholds for

response do exist, and the exposures given earlier do not exceed these thresholds. However, because most of the exposure data are given as averages, even if average exposures lie below a threshold, the possibility exists that exposures of some individuals will exceed these as yet undetermined (and perhaps undeterminable) thresholds. Jacobson et al (Jacobson 1977) reported abnormal liver histopathology in rhesus monkeys undergoing repeated transfusions at exposure levels of DEHP within the range of presumed exposures to children during the first three years of life.

The unit risks given above for the most sensitive sex-species response group (the male mouse) were estimated as:

maximum likelihood estimates: 0.000678

upper 95% confidence limit estimate: 0.001122

The conversion factor (multiplier) considering body size and surface area comparisons for mouse to adult human risk estimates is 12.8. Thus, the dose (in mg/kg/day for lifetime) factors for adults are:

MLE $0.000678 \times 12.8 = 0.0086784 = 8.68 \times 10^{-3}$

95% UCL $0.001122 \times 12.8 = 0.014362 = 14.36 \times 10^{-3}$

For children, assuming a 15 kg average weight for the first three years, the conversion factor is 6.7. Thus the dose (in mg/kg/day for a lifetime) factors for children are:

MLE $0.000678 \times 6.7 = 0.0045426 = 4.54 \times 10^{-3}$

95% UCL $0.001122 \times 6.7 = 0.0075174 = 7.52 \times 10^{-3}$

1. Average adult dietary exposure

Exposure: 0.003 mg/kg/day

Risk estimate (lifetime): MLE : 26.0×10^{-6}

95% UCL : 43.1×10^{-6}

2. Persons receiving blood transfusions

Exposure: 28.01×10^{-6} mg/kg/day

Risk: MLE 243.1×10^{-9}

95% UCL 402.4×10^{-9}

3. Dialysis patients

Exposure: 0.075630 mg/kg/day

Risk: MLE 656.3×10^{-6}

95% UCL 1086.6×10^{-6}

For 50,000 dialysis patients this implies a lifetime excess of liver cancer mortality of 32.8 - 54.3 persons.

If one assumes a (shortened) lifespan of 60 years for dialysis patients and one treatment a week, this implies an excess of 0.55 to 0.91 deaths per year. (These numbers need to be multiplied by the actual average number of treatments per week.)

4. Hemophiliacs

Exposure: 0.029746 mg/kg/day

Risk: MLE 258.1×10^{-6}

95% UCL 427.4×10^{-6}

For 10,000 hemophiliacs this implies an excess of 2.6 - 4.3 deaths due to liver cancer over a lifetime. On an annual basis, assuming a shortened lifespan of 50 years, this implies an excess of 0.05 to 0.90 deaths per year.

5. Children up to age 3

Exposure: low estimates 0.0010 mg/kg/day

high estimates 0.0034 mg/kg/day

Risk:	estimated low dose	MLE	4.6×10^{-6}
		95% UCL	7.6×10^{-6}
	estimated high dose	MLE	15.6×10^{-6}
		95% UCL	25.8×10^{-6}

If there are 3.6×10^{6} births each year, and all use DEHP panties, this implies an annual excess liver cancer mortality of 16.2 (low dose, MLE estimate) to 92.2 (high dose, upper 95% C.L.) deaths, as a consequence of exposure to DEHP.

It has been suggested that rather than use theresponse data for the most sensitive species/sex, one should use some weighted average - e.g., the geometric mean - of all the sex/species response data, although there appears to be no good biological rational for taking such an average. However, if that were done here, the risk estimates would be roughly halved.

D. Other Considerations

If the development of liver cancers following exposure to DEHP is associated mechanistically with liver proliferation and growth, then the exposures on a mg/kg/day basis should be compared with the estimated "safe" dose derived from the BIBRA (1984) experiments commented on earlier, 0.005 mg/kg.

For reproductive effects the estimated "safe" dose (from Reel et al 1984) was 0.01 mg/kg.

The average adult exposure reported here is less than these two "safe" levels, although it must be noted that the likely distribution of exposures would be expected to bring some adult exposures over the "safe" levels.

For persons receiving transfusions (assuming an average of one transfusion per lifetime) the average exposure would be substantially less than the "safe" levels. It must, however, be recognized that transfusions are distributed in a highly skewed fashion among the population (i.e., most people have none, and a small number of persons may have many). An average of one transfusion per lifetime is thus not a meaningful number upon which to base a risk computation for an individual.

For dialysis patients and hemophiliacs the average lifetime daily exposures would exceed the putative "safe" levels by 6 to 15 times.

For children, whose extra exposures to DEHP are assumed to continue up to age 3, the 3 year exposures spread out over a lifetime are less than the putative "safe" levels. It should be noted, however, that the high estimates of childhood exposure indicate a contribution of roughly about 1/3 of the dose of DEHP that the estimated average daily adult exposure contributes ("high" childhood exposure: 655 + 3 x 216 = 1303 mg). From an average daily adult exposure of 209.8 ug, one gets a total lifetime exposure of $\frac{209.8}{1,000}$ x 18,250 days = 3,829 mg assuming 50 years of adult-type exposures. "Low" childhood exposures contribute about 10% as much as the adult exposures.

For perspective, trends in cancer incidences for the liver, kidney, and testis are presented in Appendix II.

E. References

BIBRA (British Industrial Biological Research Association). 1984. A 21 day dose-relationship study of di(2-ethylhexyl)phthalate in rats. A confidential report to Chemical Manufacturers Association, Washington, D.C.

Boutwell R. 1964. Some biological aspects of skin carcinogenesis. Prog Expt Tumor Research 4:207-250.

Jacobson MS, Kevy SV, Grand RJ. 1977. Effects of a plasticizer from polyvinyl chloride on the subhuman primate: a consequence of chronic transfusion therapy. J Lab Clin Med 89:1066-1079.

NAS 1977. National Academy of Sciences/National Research Council. Safe Drinking Water Committee. Dringing Water and Health. Washington, D.C.

NTP 1982. National Toxicology Program. Technical Report No. 217. Carcinogenesis Bioassay of di (2-ethylhexyl) phthalate (DEHP). March 1982, NTP-80-27. NIH publication No. 82-1773.

OSTP Office of Science and Technology Policy . 1985. Chemical Carcinogens: A review of the science and its associated principles. Federal Register 50(50):10372-10442, March 14, 1985.

Reel JR, Wolkowksi-Tyl R, Lawton AD, and Lamb JC. 1984. Fertility testing by continuous breeding. DEHP: Reproduction and Fertility Assessment in CD-1 Mice when administered in the feed. Report by the Research Triangle Institute to the National Toxicology Program, NTP-84-079.

Thorslund T. 1985. Estimation of lifetime cancer risks using a multi-stage theory of carcinogenesis. (In preparation.)

Turnbull D, Rodricks JV. 1985. Assessment of possible carcinogenic risk to humans resulting from exposure to di(2-ethylhexyl)phthalate (DEHP). J Am Coll Toxicol 5 :111-146.

F. Appendix II. Trends in Liver, Kidney, Testis Cancer

Organs to be considered in examining possible risk from exposure to DEHP include liver, kidney and testis. In the experimental animals cancers are seen in the liver; there is peroxisome proliferation in the kidney, and, at the doses given, there is damage to the testicular tissue with an accompanying decrease in testicular tumors. Because of the widespread use of DEHP, and, if DEHP is a human carcinogen, the possibility needs to be examined that changes may have occurred in the incidence and mortality from cancers at these primary sites.

Before examining the data, some caveats are in order. Finding changes in the time course of cancer does not in any way establish cause-effect relationships. The most that time or space correlations in epidemiology ("ecologic epidemiology") can do is suggest hypotheses to be tested, or to be ruled out. The strongest statements that can usually be made from ecologic studies are ususally of the form: "The data are consistent with (or not consistent with) the hypothesis that..." Further, there is not necessarily site-for-site specificity between findings in animal studies and findings in humans. Finally, arguments must be considered about the presumed consequences of exposure at low doses, and the observed consequences of exposure at high doses. Thus, one of the logical consequences of some of the data given below is that it becomes necessary to argue that a material which is tissue damaging and anti-proliferative at high doses, might possibly be carcinogenic at low doses. To date, there is no experimental evidence to support this surmise.

Data are presented here on incidence and mortality from cancers of the liver, kidney, and testis for the period roughly following the end

of World War II. They are presented as background to assist in thinking about DEHP as a possible public health problem. As noted above, they do not in themselves constitute proof or demonstration of anything more than perhaps the need to explore further.

1. Liver

a. Incidence and Mortality Data

Liver cancer data have been difficult to interpret for time trends because of changes in the International Classification of Diseases (ICD) conventions and definitions since ICD 6 and 7. Problems of how to deal with reports of mortality from liver cancer, that do not specify if the disease was primary to the liver or metastatic, are particularly troublesome. Riggen et al. (1983) note that for liver and biliary tract cancers (ICD numbers 155 and 156 for ICD 6 and 7, and 197.8 for ICD 8) for "codes 156, ICD 6 and 7 secondary and unspecified cannot be separated. For this reason death rates for 1950-1959 and 1970-1979 are not comparable and the comparison should not be used."

For the period covered by the 8th ICD, the 1960's compared to the 1970's, Riggin et al. report the following age standardized mortality rates in the United States for cancers of the liver, gall bladder and biliary passages (Table IX-4):

TABLE IX-4

Mortality from Cancers of the Liver, Gall Bladder and Biliary Passages

Rates per 100,000
Age standardized to U.S. population, 1970

		1960-1969	1970-1979	Percent change
White:	Males	3.7	4.6	+26
	Females	3.9	3.8	- 2
Non-white:	Males	5.1	6.9	+35
	Females	3.1	3.7	+20

The data in Table IX-4 are for the combined sites, liver, gall bladder and biliary passages. Incidence and mortality data for each of these specific sites separately are available for the recent past from the Third National Cancer Survey (Cutler 1975) and from the National Cancer Institute's SEER program (Young 1981). Each of these surveys was of roughly a 10% sample of the United States population. The samples were not random samples and represent a somewhat more urban population than the United Staes as a whole, and do not cover identical population groups or areas for the two surveys. Data, by site, are given in Table IX-5.

Table IX-5

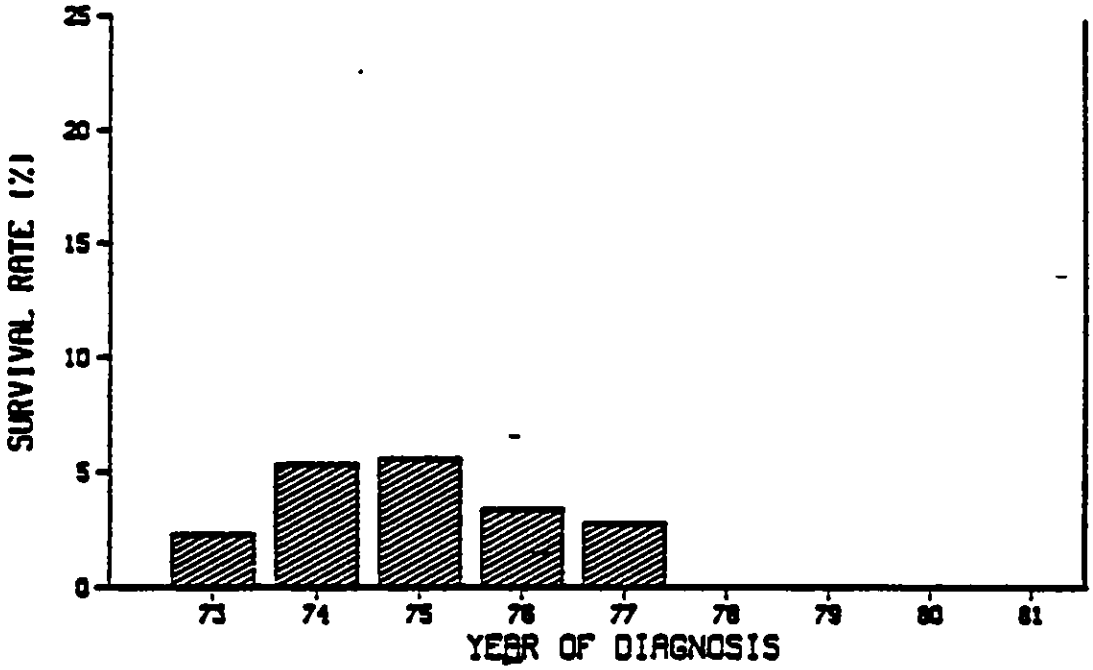
Incidence and Mortality from Liver, Gall Bladder and Biliary Passage Cancers 1969-1977
Third National Cancer Survey and SEER
Rates per 100,000. Age standardized to 1970.

		TNCS (1969-1971)	SEER (1973-1977)	
		Incidence	Incidence	Mortality
Primary liver				
White:	males	2.9	2.6	2.8
	females	1.3	1.2	1.5
Black:	males	5.7	5.2	5.7
	females	1.5	2.1	2.2
Gall bladder				
White:	males	1.1	1.0	0.7
	females	2.2	1.8	1.4
Black:	males	0.7	1.1	0.5
	females	1.6	1.3	1.0
Biliary passages				
White:	males	1.6	1.6	1.1
	females	1.0	1.1	0.8
Black:	males	1.2	1.1	0.9
	females	0.8	0.7	0.6

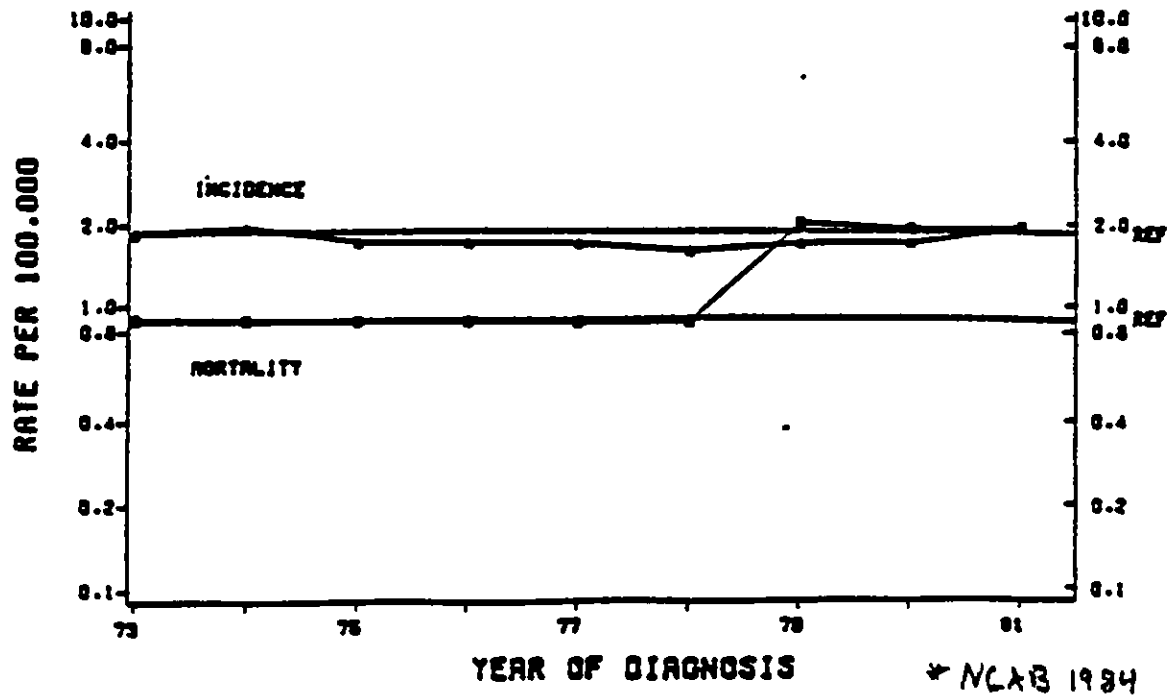
The difficulties still inherent in these data are seen in the mortality-incidence comparisons for primary liver cancer from the SEER sample, in which mortality is reported to be higher than incidence for comparable population groups. It would appear that some of the unspecified (as to primary or metastatic) liver cancer cases which should have been reported as primary may have been excluded from the SEER incidence data while being (appropriately) reported in the mortality data for the same regions and population sub-groups. Figure IX-1, Liver, as presented to the National Cancer Advisory Board, November 26, 1984 (their figure V.B-7) shows a sharp jump in mortality from 1978 to 1979, with no related change in incidence (NCAB 1984). This would argue that recent mortality data are not comparable with earlier data.

Fig IX-1. LIVER CANCER *

FIVE YEAR RELATIVE SURVIVAL RATES



AGE ADJUSTED (1970 US STD) INCIDENCE AND MORTALITY RATES



* NCAB 1984

NOTE: WHITE MALES & FEMALES

2. Testicular Cancer

a. Incidence and Mortality Data

Testicular cancer incidence has been increasing, probably since the beginning of the century. It is most common in young men and in whites. Data comparable to that given above for liver cancer are given in Tables IX-7 and IX-8. While incidence has increased rapidly (Davies 1981, Schottenfeld, 1982), mortality has declined (Riggin 1983), apparently reflecting substantial improvements in treatment.

TABLE IX-7

Mortality from Cancer of the Testis
1950's-1970's
Rates per 100,000. Age standardized to U.S. population, 1970.

	1950-59	1960-69	1970-79	% change 1950's-1970's
White males	0.9	0.8	0.7	-15
Non-white males	0.3	0.3	0.2	-24

TABLE IX-8

Cancer of the Testis
Incidence and Mortality
TNCS (1969-71) and SEER (1973-77)
Rates per 100,000. Age standardized to 1970.

	TNCS		SEER	
	Incidence	Lifetime probability in %	Incidence	Mortality
Whites	3.4	.242	3.6	0.8
Non-whites	0.8	.047	0.8	0.3

b. Epidemiology

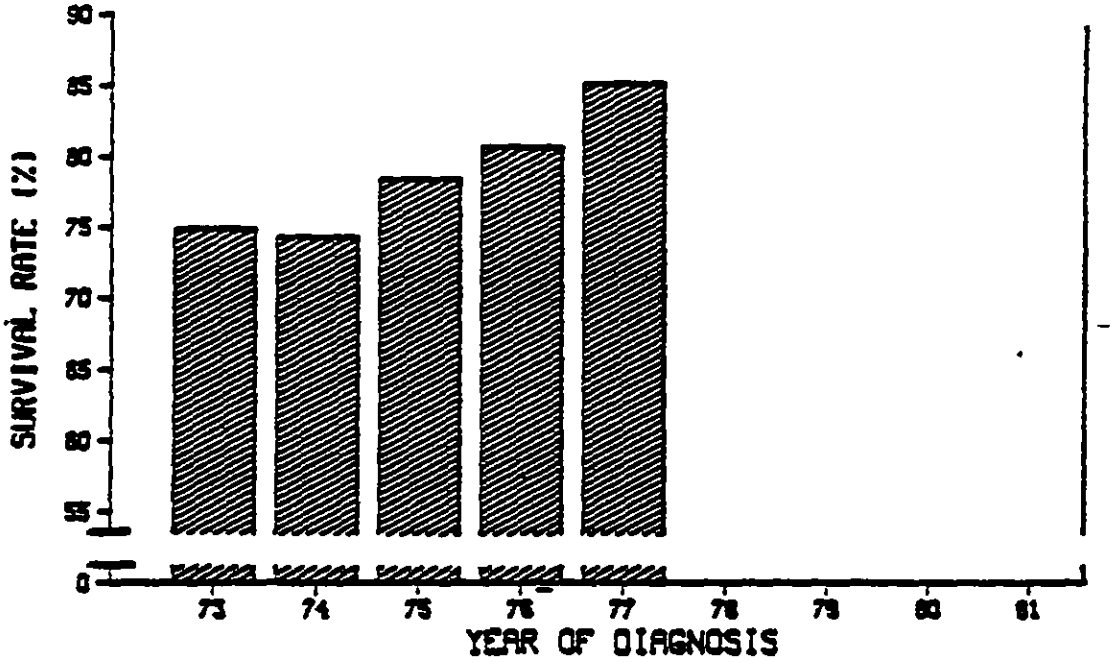
Testicular cancer is mainly a cancer of young white men (Schottenfeld 1982). From ages 15 to 34 it is among the three most common cancers for white males, accounting for about 12% of all white male cancer deaths. There has been some increasing mortality among younger men and decreasing mortality among older men. This suggests the possible introduction of an environmental agent or agents to which younger persons are more likely to be exposed. This effect is strongly shown in the data from the cancer registries of the State of Connecticut and from Denmark. Rates are highest in the highest socio-economic classes (Davies 1981), thus perhaps explaining some of the white/non-white differences in the United States.

To date the major risk factors uncovered include "cryptorchidism, gonadal dysgenesis, genetic factors, and perhaps specific exogenous factors." Schottenfeld and Warschauer (1982) in their review of the epidemiology of testicular cancer recommend that "perinatal work histories should be scrutinized during the critical periods of pre-conception, gestation and pre- puberty." Davies (1981) notes that some authors report that data on testicular cancer mortality in England and Wales is associated with material prosperity. (In Britain, mortality as well as incidence has risen.)

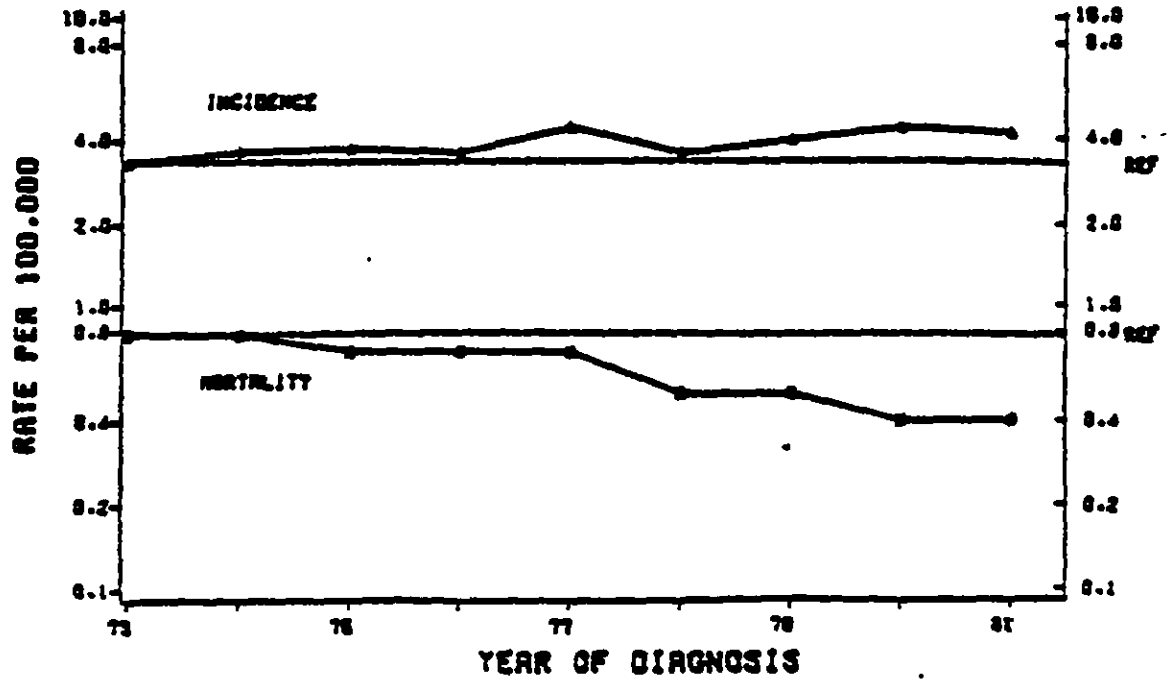
Figure 2, from the National Cancer Institute, shows the increased incidence and decreased mortality associated with substantial recent improvements in relative survival rates.

Fig. IX-2. TESTICULAR CANCER *

FIVE YEAR RELATIVE SURVIVAL RATES



AGE ADJUSTED (1970 US STD) INCIDENCE AND MORTALITY RATES



NOTE: WHITE MALES

* NCAB 1984

b. Epidemiology

Incidence and mortality for kidney cancers have been increasing in the United States. The disease is more common in men than in women (about 2 fold) and also more common in whites than in blacks. Some proportion of kidney cancers has been associated with cigarette smoking (Morrison and Cole 1982) and there are reports of association with some industrial exposures. The male/female ratio for kidney cancers is less than for lung cancer, and the black/white ratios are in the opposite direction (i.e., are less than unity for kidney cancers, and greater than unity for lung cancers), implying other avenues of causation. At times some studies have found an urban excess, but this is not a consistent finding. Coffee drinking has been suggested as an etiologic factor but Morrison and Cole (1982) list this along with other aspects of dietary intake as "questionable." These authors note that there have been few studies of the causes of cancer of the kidney. Associations have been reported with exposures to asbestos and to coke oven emissions.

4. References

Cutler SJ, Young JL Jr. 1975. Third National Cancer (TNCS). Survey: Incidence data. National Cancer Institute Monograph 41, DHEW Publication No. (NIH) 75-787.

Davies JM. 1981. Testicular Cancer in England and Wales: Some epidemiologic aspects. Lancet, April 25, 1981, pp. 928-932.

Falk H. 1982. "Liver" in Cancer Epidemiology and Prevention, D. Schottenfeld and J. F. Fraumeni, Jr., eds. W. B Saunders Co., Philadelphia.

Morrison AS, Cole P. 1982. "Urinary tract cancers," in Cancer Epidemiology and Prevention, D. Schottenfeld and J. F. Fraumeni, Jr., eds. W. B Saunders Co., Philadelphia.

NCAB National Cancer Advisory Board. 1984. Annual Cancer Statistics Review, prepared by the Demographic Analysis Section, Biometry Branch, National Cancer Institute, Bethesda, Maryland.

Riggin WB, Van Bruggen J, Acquavella JF, Beaubier J, Mason TJ. 1983. U.S. Cancer Mortality Rates and Trends, 1950-1979. USEPA and National Cancer Institute. EPA-600/1-83-015a.

Schneiderman MA, Decoufle P, Brown C. 1979. Thresholds for Environmental Cancer; Biological and Statistical Considerations. Ann NY Acad Sci 329:92-130.

Schottenfeld D, Warschauer ME. 1982. "Testis" in Cancer Epidemiology and Prevention, D. Schottenfeld and J. F. Fraumeni, Jr., eds. W. B. Saunders Co., Philadelphia.

Waterhouse J, Muir C, Correa P et al, eds. 1976. Cancer Incidence in Five Continents, Vol. 3, IARC Scientific Publications No. 15, Lyon, France.

Young JL Jr, Percy CL, Asire AJ, Berg FW, Cusano M M., Gloeckler LA, Horm JW, Lourie WI, Pollack ES, Shambaugh EM. 1981. Cancer Incidence and Mortality in the United States 1973-77 (SEER). NCI Monograph 57. NIH Pub. No. 81-2330.