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


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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

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of 0.82 grams compared to 1.45 grams in untreated control rats (Oishi and Hiraga, 1980a). In the \textit{TF} subchronic bioassay similar effects were found in F344 rats after 90 days when 1.2\% DEHP was fed in the diet. In the \textit{TFP} chronic bioassay, 0.6\% UFHP 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, dimethyl, 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 (Sjooerg 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 (MTP 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 spermatogonial 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 mitogenic 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 spermatogonial 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 clinical 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 Mikonorow 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 skeletal 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


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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, teetners, 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 artificial 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 absorption 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 ITFI (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


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 peroxosome 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 concentration 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**

<table>
<thead>
<tr>
<th>Rats</th>
<th>Animals with Neoplasms/Total Animals</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rats</td>
</tr>
<tr>
<td></td>
<td>Dose</td>
</tr>
<tr>
<td>0</td>
<td></td>
</tr>
<tr>
<td>low</td>
<td></td>
</tr>
<tr>
<td>high</td>
<td></td>
</tr>
</tbody>
</table>

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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 1992), 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

<table>
<thead>
<tr>
<th>Rats: Daily Consumption</th>
<th>Mice: Daily Consumption</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reported</td>
<td>Reported</td>
</tr>
<tr>
<td>mg/kg</td>
<td>mg/kg</td>
</tr>
<tr>
<td>Doses</td>
<td>ppm</td>
</tr>
<tr>
<td>low</td>
<td>6000</td>
</tr>
<tr>
<td>high</td>
<td>12000</td>
</tr>
</tbody>
</table>

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)*

<table>
<thead>
<tr>
<th>Species/Sex</th>
<th>Maximum likelihood estimate</th>
<th>Upper 95% confidence limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rat - Male</td>
<td>.000154</td>
<td>.000471</td>
</tr>
<tr>
<td>- Female</td>
<td>.000285</td>
<td>.000523</td>
</tr>
<tr>
<td>Mouse - Male</td>
<td>.000678</td>
<td>.001122</td>
</tr>
<tr>
<td>- Female</td>
<td>.000545</td>
<td>.000752</td>
</tr>
</tbody>
</table>

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 \((\text{Human body weight}/\text{Animal body weight})^{1/3}\). 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 preceding chapter:
1. **Average daily** adult dietary exposure: 209.8 μg

   (On a mg/kg/day basis, assuming an average adult weighs 70 kg, equals
   
   \[
   209.8/(70 \times 1000) = 0.003 \text{ mg/kg/day}.
   \]

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

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 3,500,000 newborns a year. This implies total lifetime estimates of exposure (in excess of adult-exposures noted above)

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

   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 x 12.8 = 0.0086784 = 8.68 x 10^{-3}

95% UCL 0.001122 x 12.8 = 0.014362 = 14.36 x 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 x 6.7 = 0.0045426 = 4.54 x 10^{-3}

95% UCL 0.001122 x 6.7 = 0.0075174 = 7.52 x 10^{-3}

1. Average adult dietary exposure

Exposure: 0.003 mg/kg/day

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

95% UCL : 43.1 x 10^{-6}
2. Persons receiving blood transfusions

Exposure: $38.01 \times 10^{-6}$ mg/kg/day
Risk: NLE $243.1 \times 10^{-6}$
95% UCL $402.4 \times 10^{-6}$

3. Dialysis patients

Exposure: $0.075630$ mg/kg/day
Risk: NLE $656.3 \times 10^{-6}$
95% UCL $1086.6 \times 10^{-6}$

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: NLE $258.1 \times 10^{-6}$
95% UCL $427.4 \times 10^{-6}$

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  $4.6 \times 10^{-6}$
        25% UCL  $7.6 \times 10^{-6}$
estimated high dose  MLE  $15.6 \times 10^{-6}$
        95% UCL  $25.8 \times 10^{-6}$

If there are $3.6 \times 10^6$ 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 these response 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: $655 + 3 \times 216 = 1303$ mg). From an average daily adult exposure of 209.8 ug, one gets a total lifetime exposure of $\frac{209.8}{1,000} \times 18,250$ 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

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day dose-relationship study of di(2-ethylhexyl)phthalate in rats.
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testing by continuous breeding. DEHP: Reproduction and Fertility
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to humans resulting from exposure to di(2-ethylhexyl)phthalate
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 usually 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

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>White:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>3.7</td>
<td>4.6</td>
<td>+26</td>
</tr>
<tr>
<td>Females</td>
<td>3.9</td>
<td>3.8</td>
<td>- 2</td>
</tr>
<tr>
<td>Non-white:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>5.1</td>
<td>6.9</td>
<td>+35</td>
</tr>
<tr>
<td>Females</td>
<td>3.1</td>
<td>3.7</td>
<td>+20</td>
</tr>
</tbody>
</table>

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 States 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.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary liver</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White: males</td>
<td>2.9</td>
<td>2.6</td>
<td>2.8</td>
</tr>
<tr>
<td>females</td>
<td>1.3</td>
<td>1.2</td>
<td>1.5</td>
</tr>
<tr>
<td>Black: males</td>
<td>5.7</td>
<td>5.2</td>
<td>5.7</td>
</tr>
<tr>
<td>females</td>
<td>1.5</td>
<td>2.1</td>
<td>2.2</td>
</tr>
<tr>
<td><strong>Gall bladder</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White: males</td>
<td>1.1</td>
<td>1.0</td>
<td>0.7</td>
</tr>
<tr>
<td>females</td>
<td>2.2</td>
<td>1.8</td>
<td>1.4</td>
</tr>
<tr>
<td>Black: males</td>
<td>0.7</td>
<td>1.1</td>
<td>0.5</td>
</tr>
<tr>
<td>females</td>
<td>1.6</td>
<td>1.3</td>
<td>1.0</td>
</tr>
<tr>
<td><strong>Biliary passages</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White: males</td>
<td>1.6</td>
<td>1.6</td>
<td>1.1</td>
</tr>
<tr>
<td>females</td>
<td>1.0</td>
<td>1.1</td>
<td>0.8</td>
</tr>
<tr>
<td>Black: males</td>
<td>1.2</td>
<td>1.1</td>
<td>0.9</td>
</tr>
<tr>
<td>females</td>
<td>0.8</td>
<td>0.7</td>
<td>0.6</td>
</tr>
</tbody>
</table>

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

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.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>White males</td>
<td>0.9</td>
<td>0.8</td>
<td>0.7</td>
<td>-15</td>
</tr>
<tr>
<td>Non-white males</td>
<td>0.3</td>
<td>0.3</td>
<td>0.2</td>
<td>-24</td>
</tr>
</tbody>
</table>

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.

<table>
<thead>
<tr>
<th></th>
<th>TNCS Incidence</th>
<th>Lifetime probability in %</th>
<th>SEER Incidence</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whites</td>
<td>3.4</td>
<td>.242</td>
<td>3.6</td>
<td>0.8</td>
</tr>
<tr>
<td>Non-whites</td>
<td>0.8</td>
<td>.047</td>
<td>0.8</td>
<td>0.3</td>
</tr>
</tbody>
</table>
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 17% 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. 18-2. TESTICULAR CANCER

FIVE YEAR RELATIVE SURVIVAL RATES

AGE ADJUSTED (1970 US STD) INCIDENCE AND MORTALITY RATES

NOTE: WHITE MALES
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


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


