Studies on the Carcinogenicity of Pentachloroethane in Rats and Mice

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ABSTRACT

Studies on the Carcinogenicity of Pentachloroethane in Rats and Mice. Mennear, J.H., Haseman, J.K., Sullivan, D.J., Bernal, E. and Hildebrandt, P.K. (1982). Fundam. Appl. Toxicol. 2:82-87. The carcinogenicity of chronically administered (41 to 103 weeks) technical-grade pentachloroethane (PCE) was assessed in groups of 50 male and female Fischer 344 rats and B6C3F1 mice. The major contaminant in the PCE sample used for the chronic study was hexachloroethane (4.2%). Prechronic studies (two and 13 weeks repeated dose) employing gavage doses of from 5.0 to 1000 mg/kg/day of PCE failed to reveal specific target organ toxicity in these species. In the absence of treatment-related pathological changes during the prechronic tests, the doses for the chronic studies were set on the basis of survival and body weight gains during the 13-week repeated dose study. During the chronic studies dose levels of 75 and 150 mg/kg for rats and 250 and 500 mg/kg for mice were administered, by gavage, five days per week. The survival of high-dose rats (both sexes) was significantly reduced as compared to the survival of control animals and that of the low-dose males was slightly, but not significantly, reduced. Although the administration of PCE to rats did not increase the incidence of primary tumors, it did produce a significant dose-related increase in the incidence of chronic renal inflammation among males. The survival times of all treated groups of mice were significantly shortened by PCE administration. Despite this reduced survival time, the incidence of hepatocellular carcinoma was significantly increased in all treated groups. With the exception of a dose-related increase in the incidence of hepatocellular adenoma among females, there were no other significant increases in primary tumor incidence in mice. Neither lesions in rats nor hepatocellular carcinoma in mice were considered to be adequate explanations for the decreased survival. The results of the study show that technical-grade PCE, like numerous other chlorinated ethanes, is an hepatocarcinogen for B6C3F1 mice. This interpretation for PCE per se, however, must be tempered because the major contaminant, hexachloroethane, has been shown to produce hepatocellular carcinoma in mice. While the results obtained in rats suggest a species difference in susceptibility, the reduced survival in this species may have contributed to the absence of a carcinogenic effect.

INTRODUCTION

Chlorinated ethanes and ethylenes are commercially important chemicals which have attracted toxicological interest because several representatives of the class have been found to increase the incidence of cancer in laboratory animals. For example, 1,2-dichloroethane, administered by gavage, increased the incidences of tumors in both sexes of B6C3F1 mice and Osborne-Mendel rats (NCI, 1978a). However, an increased incidence of primary tumors in both rats and mice is not the usual pattern of response to the chlorinated ethanes and ethylenes. The more usual observation has been an increased incidence of hepatocellular carcinoma among B6C3F1 mice with no apparent carcinogenicity in Osborne-Mendel rats (hexachloroethane, NCI, 1978b; 1,1,2-trichloroethane, NCI, 1978c, 1,1,2-trichloroethane, NCI, 1978d; tetrachloroethylene, NCI, 1977; and tetrachloroethylene, NCI, 1976a). The results of these earlier carcinogenicity studies have been summarized (Weisburger, 1977) and reviewed (IARC, 1979).

The lack of carcinogenicity of most of the tested chlorinated ethanes and ethylenes in Osborne-Mendel rats has been difficult to interpret because the treatment regimens generally shortened the survival times of the test animals. Therefore, the failure of the treatments to increase tumor incidences in the rats could have been due to the fact that the animals did not survive long enough to develop the lesions. However, it should be pointed out that in most of these earlier studies the survival times of the rats and mice were adversely affected by the treatments. In light of this observation it is possible that Osborne-Mendel rats, or rats in general, are not susceptible to the carcinogenicity of these chemicals. This possibility prompted the National Cancer Institute to initiate a series of chronic carcinogenicity tests of chlorohydrocarbons in several strains of rats. The majority of these studies are still in progress but the comparative testing of pentachloroethane in B6C3F1 mice and Fischer 344 rats has been completed. This communication summarizes the results of that study.

METHODS

Test chemical

Two lots of technical grade pentachloroethane (PCE), obtained from Columbia Chemicals (Columbia, S.C.) were used throughout these studies. Lot number C041676 was used for the...
mentioned.

### TABLE 1

Impurities Identified in Pentachloroethane

<table>
<thead>
<tr>
<th>Chemical</th>
<th>Lot No. C0102077&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Lot No. C0102077&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetone</td>
<td>---</td>
<td>0.08&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Hexachloroethane</td>
<td>10.4&lt;sup&gt;d&lt;/sup&gt;</td>
<td>4.2&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Pentachlorobutadiene</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>1,2,4,5-Tetrachlorobutadiene</td>
<td>--&lt;sup&gt;0.01&lt;sup&gt;d&lt;/sup&gt;</td>
<td>---</td>
</tr>
<tr>
<td>1,1,1,2-Tetrachloroethane</td>
<td>--&lt;sup&gt;0.01&lt;sup&gt;d&lt;/sup&gt;</td>
<td>---</td>
</tr>
<tr>
<td>1,1,2,2-Tetrachloroethane</td>
<td>--&lt;sup&gt;0.01&lt;sup&gt;d&lt;/sup&gt;</td>
<td>0.03&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Tetrachloroethylene</td>
<td>0.55&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.05&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Trichloroethylene</td>
<td>--&lt;sup&gt;0.01&lt;sup&gt;d&lt;/sup&gt;</td>
<td>0.13&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>1,1-Trichloropropene</td>
<td>---</td>
<td>--&lt;sup&gt;0.01&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup>Used for prechronic studies.

<sup>b</sup>Used for chronic study.

<sup>c</sup>Quantitated by vapor-phase chromatography.

<sup>d</sup>Quantitated using vapor-phase chromatography/mass spectrometry.

<sup>e</sup>Identified by mass spectrometry but not quantitated.

Prechronic studies and lot number C0102077 were used for the chronic study. Both lots were stored at -20°C.

PCE was qualitatively identified through elemental analysis and infrared and nuclear magnetic resonance spectrometry. Impurities in the samples were identified and quantitated by vapor-phase chromatography and mass spectrometry. The comparative concentrations of the impurities identified in the two lots are summarized in Table 1.

During the course of the studies, the bulk chemical was periodically analyzed, using infrared spectroscopy and gas chromatography. There were no significant differences between periodic analyses, indicating that chemical decomposition had not taken place. The detailed methods and results of these analyses have been published elsewhere (NTP, 1981).

**Animals**

Fischer 344 rats and B6C3F<sub>1</sub> mice of each sex were used throughout these studies. Animals employed in the prechronic studies were obtained from the Frederick Cancer Research Center (Frederick, MD) while those for the chronic study were obtained from the Charles River Breeding Laboratories (Portage, MI). All animals were acclimated to laboratory conditions for 9 to 12 days prior to experimentation.

During prechronic studies rats were housed individually and mice were housed in groups of five. During the chronic study both species were housed in groups of five. Mice and rats were housed in the same animal room at a temperature of 23 ± 4°C.

Room air was changed from 10 to 12 times per hour and a 12-hour light:dark cycle was employed. Animals were assigned to treatment groups by the use of a table of random numbers. The animals had free access to Wayne Lab Blox and tap water.

**Dosage preparation**

PCE was mixed with corn oil at concentrations which allowed for the administration of gavage doses of 5.0 mL/kg in rats and 10 mL/kg in mice. The PCE/corn oil mixtures were stored at 4°C for no longer than seven days. Earlier chemical analyses had shown that these mixtures were stable, at room temperature, for at least seven days. The dosage mixtures were analyzed for PCE at approximately two-month intervals during the chronic study. The results of these analyses showed that the mean concentration of PCE was 2.3% higher than intended with a range of from -6.0% to +9.0%.

**Study design**

The objective of the prechronic studies (two weeks and 13-weeks repeated dose) was to collect toxicology data to facilitate the selection of the maximum tolerated dose (MTD) for administration during the chronic study. The MTD is defined as the highest dose that can be administered chronically without significantly reducing the survival of the test animals by other than carcinogenic mechanisms (NCI, 1976b). Parameters assessed during the prechronic studies included: gross appearance, survival, body weight gains, and gross and microscopic pathological changes.

During the two-week repeated dose study, groups of five animals of both sexes and species received 14 consecutive daily gavage doses of either corn oil or the PCE/corn oil mixture (10, 50, 100, 500, or 1000 mg/kg). Individual body weights were recorded prior to the first dose and on days 7 and 14. All animals were necropsied and sections of lung, liver and spleen were prepared for microscopic examination. Other tissues were preserved in formalin for possible future reference. Terminal sacrifice took place on day 15.

In the 13-weeks study, groups of 10 animals of both sexes and species received five gavage doses per week of either corn oil or PCE in corn oil. The dose levels of PCE were 5.0, 10, 50, 125, or 250 mg/kg/day for rats and 5.0, 10, 50, 100, or 500 mg/kg/day for mice. Body weights were recorded at the time of the initial dose then at weekly intervals. Thirty weeks after the initial dose the animals were sacrificed and necropsied. Complete histopathological examinations were performed on all control and high-dose group animals (see pathology section for list of tissues examined).

Groups of 50 animals of both sexes and species were subjected to the chronic treatment. The PCE dosage levels used were 75 and 150 mg/kg/day for rats and 250 and 500 mg/kg/day for mice. Control animals received gavage doses of corn oil in volumes equal to the volumes of PCE mixture administered to the highest dose groups. Treatments were administered by gavage five times per week for 103 weeks. Surviving animals were killed during week 104. All animals were observed for signs of morbidity three times per day. Group body weights (determined by weighing tared cages containing up to five animals) were recorded at approximately two-week intervals. The mean body weights of the various treatment groups were determined by dividing the total weight of surviving animals in a group by the number of surviving animals in that group. This value was used for the calculation of doses for all animals in the group.

**Pathology**

Necropsies were performed on all animals from the chronic study unless precluded, in whole or in part, by autolysis or cannibalization. Therefore, the number of animals from which particular tissues were examined microscopically varied and was not necessarily equal to the number of animals that were placed on study. Tissues were preserved in 10% neutral buffered formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin. The following tissues and organs were examined microscopically: all tissue masses, skin, mandibular lymph node, mammary gland, salivary gland, bone marrow, bone, costochondral junction, trachea, lungs and bronchi, heart, thyroid, parathyroid, esophagus, stomach, duodenum, colon, mesenteric lymph node, liver, gall bladder...
(mice), pancreas, spleen, kidney, adrenal, urinary bladder, prostate, testis or ovary and uterus, brain and pituitary and any other tissue with gross lesions.

The classification of liver neoplasms was done according to the recommendation of Squire and Levitt (1975) and the National Academy of Sciences (Stewart et al., 1980). The diagnoses represent a consensus of consulting pathologists and the National Toxicology Program Pathology Working Group.

**Statistical analyses**

Data on this experiment are recorded in the Carcinogenesis Bioassay Data System 2 (Linhart et al., 1974). The data elements include descriptive information on the chemicals, animals, experimental design, clinical observations, survival, body weight, and individual pathologic results. Data for this experiment are detailed in the NTP Carcinogenesis Technical Report Series (NTP, 1981).

Differences in survival were analyzed by life table methods (Cox, 1972). For the analysis of tumor incidence data, three different procedures were used to assess dose-response trends and to make pairwise comparisons between dose groups and controls: (1) Life table analysis (appropriate for tumors merely observed at necropsy in animals). For the analysis of tumor incidence data, three animals, experimental design, clinical observations, survival, and the National Toxicology Program Pathology Working Group. Report Series (NTP, 1981).

**RESULTS**

Neither the two weeks nor the 13-weeks repeated dose studies revealed remarkable toxicological effects that could be associated with the administration of PCE. For this reason, the results of these experiments will be summarized in the text but the data will not be presented. The interested reader is referred to the detailed report of the study (NTP, 1982).

**Two weeks repeated dose study**

The results of this study suggested that the rats were somewhat more sensitive to PCE than were mice. The highest dose tested, 1000 mg/kg/day, was lethal to all rats within four days while the same dose was lethal to only one (female) mouse. The 500 mg/kg/day dose was lethal to 3/5 rats of each sex with animals dying between the fourth and tenth days.

Body weight gains for rats receiving up to 100 mg/kg/day were comparable to those of controls, but the animals that survived the 500 mg/kg/day dose exhibited definite weight gain decrements. Body weight gains for mice treated with up to 500 mg/kg/day were comparable to those of controls but female mice treated with the 1000 mg/kg/day dose lost weight during the experiment.

The only grossly observable clinical sign of toxicity was decreased motor activity and lethargy among rats treated with either 500 or 1000 mg/kg/day. Neither gross nor histopathological examinations revealed lesions that could be attributed to the treatment.

**Thirteen weeks repeated dose study**

The results of the two weeks repeated dose study led to the selection of doses of 50, 10, 125, and 250 mg/kg/day for rats and 50, 10, 50, 100, and 500 mg/kg/day for mice in the 13-weeks study. All rats survived the entire 13-weeks period and only rats treated with the 250 mg/kg/day dose failed to gain weight at the same rate as controls (males and females exhibited weight gain decrements of 10 and 17%, respectively). Among mice treated at a dose rate of 500 mg/kg/day, a single female died during the final week and the body weight gain for the high-dose group of females was 29% less than that of controls. The remainder of the mice survived for the duration of the study and their body weight gains were comparable to those of controls.

Gross necropsy of all animals and histopathological examination of tissues from control and high-dose groups failed to reveal treatment related lesions. The findings of this study resulted in the selection of chronic study doses of 75 and 150 mg/kg/day for rats and 250 and 500 mg/kg/day for mice.

**Chronic study in rats**

The effects of chronic administration of PCE on the survival and body weight gains of F344 rats are summarized in Table 2. The survival of rats was adversely affected by the treatments with a significant (p < 0.01) dose-related trend among males. All control males survived until week 91, then 9/50 died between weeks 91 and 104. The initial death among treated males occurred during weeks 10 (150 mg/kg/day group) and 16 (75 mg/kg/day group). By week 60, 11/50 high-dose and 9/50 low-dose males were dead. All control females survived for the first 67 weeks of the study and 12 died between weeks 67 and 104. The pattern of survival among low-dose females was essentially the same as that of control females. The first death among the high-dose females occurred during week 16 and by week 60, 12/50 animals in this group were dead.

Body weight gains by rats were only slightly affected by chronic PCE administration. Males maintained normal weights. For the initial 76 weeks of the study, body weights for the treated animals tended to be less than those of controls. Dosed females maintained normal weights through the first 42 weeks of the study and, while they continued to gain weight through the remainder of the study, their rate of gain was less than that of controls.

**Table 2**

Survival and Weight Gains in Fischer 344 Rats Administered Pentachloroethane for 103 Weeks

<table>
<thead>
<tr>
<th>Dose (mg/kg)</th>
<th>Survival</th>
<th>Weight Gain</th>
<th>Survival</th>
<th>Weight Gain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>41/50</td>
<td>295</td>
<td>38/50</td>
<td>17b</td>
</tr>
<tr>
<td>75</td>
<td>33/50</td>
<td>263 (−10.8%)</td>
<td>36/50</td>
<td>147 (−16.3%)</td>
</tr>
<tr>
<td>150</td>
<td>20/50</td>
<td>257 (−12.8%)</td>
<td>25/50</td>
<td>140 (−20.5%)</td>
</tr>
</tbody>
</table>

Pentachloroethane was mixed with corn oil and administered by gavage 5 days per week.

Number of survivors/number of animals starting the study.

Body weight gains between the first and last days of the study.

Values in parentheses represent percentage difference from control.

*Copies can be obtained from the Public Information Office, National Toxicology Program, P.O. Box 12323, Research Triangle Park, NC 27709.

tumors in rats treated with PCE. However, negative trends were detected among males with respect to subcutaneous tissue fibromas (controls, 5/50; low-dose, 0/49; high-dose, 0/50; p < 0.05) and in both sexes with respect to pituitary adenomas (controls, 23/48; low-dose, 13/46; high-dose, 4/46; p < 0.01 and controls, 27/49; low-dose, 17/46; high-dose, 12/45; p < 0.05 for males and females, respectively).

A chronic, diffuse renal inflammation was observed in a significant (p < 0.001) dose-related incidence among males (controls, 4/50; low-dose, 14/49; and high-dose, 33/50). This nephropathy was characterized by prominent interstitial fibrosis, interstitial accumulation of mononuclear inflammatory cells, and severe tubular dilation in the pars recta (inner cortex) with some dilated tubules containing giant cells and casts. These lesions could be distinguished from those seen in aging nephropathy (Barthold, 1979) where interstitial fibrosis and tubular dilation were not as severe as in lesions observed in the present study. In addition, the giant cells within tubules are not a feature of aging nephropathy. Glomerular hyalinization and mineralization of the renal papilla were also observed.

Chronic study in mice

The effects of PCE on survival and body weight gains in B6C3F1 mice are summarized in Table 3. The chronic administration of PCE produced a significant (p < 0.01) dose-related reduction in the survival of both male and female mice. Among high-dose males, the initial death was during week 18 and only 8/50 animals survived to week 41. These surviving animals were sacrificed during week 41 and 25 control males were killed during week 44 to provide control histological samples. The first death among the low-dose males occurred during week 31 and only 22/50 of these animals survived to the terminal sacrifice. Two low-dose male mice died during the week of final sacrifice (week 104). In the statistical analysis of data on tumor incidence no distinction was made between these animals and those sacrificed during this time period.

Females survived the high-dose treatment slightly better than did males. The first female death occurred during week 38, but all high-dose females were dead by week 74. The initial death among low-dose females did not occur until week 53, but only 9/50 of the animals in this group survived to the end of the study.

Both doses of PCE decreased body weight gains in both sexes of mice with the males being affected earlier. By week 12, the high-dose males had stopped growing appreciably and by week 52 the body weights of the low-dose males were less than those of controls. Between weeks 42 and 104 the mean body weight of the low-dose males decreased by approximately 20%, while that of the controls remained essentially constant. The mean body weights of high- and low-dose females were lower than those of controls after 26 and 72 weeks, respectively.

Pathological evaluation of tissue samples revealed evidence of increased incidences of hepatic lesions in mice treated with PCE. The incidences of these lesions, hepatocellular adenoma, and hepatocelelular carcinoma, are summarized in Table 4.

The markedly reduced survival observed in the high-dose male mice and the killing of 25 male controls at week 44 precluded the use of the usual statistical methods for the primary tumor data. Observed tumor incidences in male mice were compared at 0-52 weeks, 53-103 weeks and 104 weeks. The individual time interval comparisons were then combined by Mantel-Haenszel (1959) methods to obtain an overall result. The analyses of primary tumors in female mice were carried out by the procedure previously described. However, because there was little overlapping survival in the high-dose and control groups, it was not feasible to compare these two groups by the incidental tumor test.

The administration of PCE significantly increased the incidence of hepatocellular carcinoma in both sexes of mice. While both dosage levels produced significant increases, overall dose-response relationships were not apparent, possibly due to the early deaths associated with the administration of the high-dose. These hepatocellular carcinomas had areas of trabecular formations and had metastasized to the lung in one low-dose female, two low-dose males and one control male.

A significant increase in the incidence of hepatocellular adenoma was observed among female mice. This effect was dose-related despite the shortened survival of the high-dose animals. Increases in the incidence of this lesion in male mice were not observed. Also, fatty metamorphosis was found in the livers of treated mice, but the effect was minimal and may reflect variability in nutritional status rather than a direct effect of PCE. A complete listing of individual animal pathology and survival data has been published elsewhere (NTP, 1981).

DISCUSSION

Despite a relatively cautious approach to the selection of dosage levels for the chronic studies, the maximum tolerated dose of PCE for both rats and mice was exceeded. Neither gross nor microscopic pathological examinations revealed consistent changes that could account for the decreased survival among treated animals. Since PCE is a chlorinated hydrocarbon one might suspect hepatic and/or renal lesions to be causative factors but the evidence does not support this. Among the high-dose male mice, 42/50 were dead within 41 weeks but only 6 had hepatocellular carcinoma (the seventh hepatocellular carcinoma was detected in an animal killed during week 41) and other hepatic lesions were not remarkable. While renal lesions which could have contributed to decreased survival were detected in male rats, there were none among females and the survivals of the two sexes at the higher dose level were similar. Further, the lesion, although its incidence was dose-related, was not detected in all males that died before the end of the experiment.

<table>
<thead>
<tr>
<th>Table 3 Survival and Weight Gains in B6C3F1 Mice Administered Pentachloroethane for from 41 to 103 Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily Gavage</td>
</tr>
<tr>
<td>--------------</td>
</tr>
<tr>
<td>Control</td>
</tr>
<tr>
<td>250</td>
</tr>
<tr>
<td>500</td>
</tr>
</tbody>
</table>

Pentachloroethane was mixed with corn oil and administered by gavage 5 days per week.
Number of survivors/number of mice starting the study.
Body weight gains between the first and last days of the study.
A total of 50 male mice started the study but 25 were sacrificed during week 44.
Values in parentheses represent percentage difference from control.
The chronology of PCE effects on body weight gains and survivals during the chronic studies is suggestive of a cumulative effect in these species. A cumulative effect is consistent with the PCE metabolism and excretion data presented by Ylner (1971). After a large subcutaneous dose, NMRI mice excreted only 55\%, chronic bioassays of chlorinated ethanes and ethylenes in that metabolites) in 24, 48, and 72 hours, respectively.

The results of the present study are similar to those of earlier chronic bioassays of chlorinated ethanes and ethylenes in that the previous studies were also confounded by treatment effects on survival (Weisburger, 1977; IARC, 1979). This class of compounds appears to present special problems in the selection of maximum tolerated doses. Further, the use of more than two dosage related agents, metabolism and excretion studies should be considered prior to the selection of treatment regimens. Further, the use of more than two dosage levels should be considered. Such experimental approaches could minimize the risk of generating equivocal data.

The daily administration of PCE did not result in an increased incidence of primary tumors in rats. In fact, negative trends were detected for subcutaneous tissue fibromas (males) and pituitary adenomas (both sexes). Statistical analyses revealed that these negative trends were not due entirely to shortened survival times, but an alternate explanation is not obvious.

Although the survival of the treated mice was compromised by the chronic dosage levels employed, the hepatocarcinogenicity of the treatment in this species was clearly established. The times to the occurrence of first and second hepatocellular carcinomas were only 35 and 39 weeks, respectively. By week 41, when the 8 surviving high-dose males were sacrificed, 7(15)\% of the animals in this group had the lesion. None of the 25 control males killed at week 44 had hepatocellular carcinoma. The conclusion regarding the hepatocarcinogenicity of PCE in mice was strengthened by the significantly increased incidences of the lesion in the low-dose male group as well as both treated groups of females.

Pentachloroethane has been shown to be metabolized to tri- and tetrachloroethylene (18 to 48\% and 12 to 31\% of the dose, respectively) by NMRI mice (Ylner, 1971). These estimates are based on the excretion of the two chloroethylenes as well as their major metabolites. Both of these chloroethylenes have been shown to produce hepatocellular carcinoma in B6C3F1 mice but not Osborne-Mendel rats (NCI, 1976a; NCI, 1977). Although the earlier studies were somewhat confounded by the presence of epichlorohydrin (0.09\%) in the test material, a more recent study (to be published by NTP) has confirmed the hepatocarcinogenicity of epichlorohydrin-free trichloroethylene in B6C3F1 mice. Assuming a similar metabolic pattern for NMRI and B6C3F1 mice, the mice in the present study could have been indirectly exposed to as much as 240 and 155 mg/kg/day of tri- and tetrachloroethylene, respectively. Therefore, it is possible that the carcinogenic action of PCE in mice was mediated through the biotransformation of the parent chemical to these metabolites which were then converted to the ultimate carcinogens. Sufficient data do not exist at present to adequately assess this possibility. The hepatocarcinogenic doses of the chloroethylenes used in the earlier studies were approximately four times higher than the possible indirect doses received by the mice in this study.

Hexachloroethane, the major contaminant in the PCE sample used in the chronic study, has also been shown to produce hepatocellular carcinoma in B6C3F1 mice but not Osborne-Mendel rats (NCI, 1976b). The low-dose mice in the present study were exposed to 10.5 mg/kg/day of hexachloroethane. This dose can be contrasted with a carcinogenic dose of 590 mg/kg/day of hexachloroethane in the earlier study. Because lower doses of hexachloroethane per se have not been studied for carcinogenicity, it is impossible to assess the potential impact of the contaminant on the outcome of the present study. While it seems unlikely that the relatively low doses of hexachloroethane encountered in this study could account for the high incidence of hepatocellular carcinoma observed, an additive or potentiating interaction between the contaminant, the chloroethylene metabolites, and/or the parent compound can not be dismissed as a potential mechanism of carcinogenicity.

The possibility that PCE induces hepatocellular carcinoma in B6C3F1 mice through an epigenetic mechanism must also be considered. As a class, chlorohydrocarbons are generally negative in tests for genotoxic activity (Weisburger and Williams, 1978 and 1980; for exceptions see IARC, 1979 and Simmon, 1978). The lack of consistent genotoxic effects for these compounds was noted in the previous chronic studies with pentachloroethylene. The results of the present study provide no evidence that pentachloroethylene is genotoxic to B6C3F1 mice.
pounds has led Weisburger and Williams (1980) to suggest that the selective induction of hepatocellular carcinoma in mice could be mediated through a promoting action. The nature of the initial genetic change at the level of the hepatocyte remains to be determined, but it could be an heritable trait. This is an attractive hypothesis when one considers that far greater than it is in either Osborn-Mendel and PCE. like other chlorohydrocarbons, induces hepatocellular activity of absence of a similar effect in F344 rats suggests a species difference in sensitivity, the decreased survival of treated rats of a carcinogenic effect in this species.


REFERENCES


National Cancer Institute (1978c). Bioassay of 1,1,2-Tetrachloroethane for Possible Carcinogenicity. DHEW Publication No. (NIOSH) 78-827, Washington, D.C.


