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Reproductive hazards related to perchloroethylene

A review

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Summary. The literature of perchloroethylene (PER) was scrutinized to find answers to the following questions: (1) is an effect of PER on reproduction to be expected, and (2) if so, has such an effect actually been shown in animal experiments and/or in epidemiological studies? From this review it can be concluded that the first question should be answered in the affirmative, considering the various mechanisms capable of leading to defects in the reproductive processes and the information about how PER can interact (and in fact does interact) with these mechanisms. The few studies in which the effects of PER exposure on reproductive outcome have been studied are, however, not very conclusive. Some suggest an effect, others do not. In view of the incompleteness of the experimental results and the methodological shortcomings especially of the epidemiological studies, there is a need for a suitably designed epidemiological investigation on the reproductive consequences of exposure to PER. In order to avoid the methodological problems of the above-mentioned studies, the design should be a prospective one.

Key words: Perchloroethylene – Reproductive hazards – Spontaneous abortion – Dry cleaning – Epidemiological studies

Introduction

Per- or tetrachloroethylene (PER) is one of the solvents widely used in industry. A major application of this unsaturated chlorinated hydrocarbon is in dry cleaning establishments. Owing to its high volatility, human exposure to PER may be high. Concentrations in the order of magnitude of 35 ppm (the Dutch MAC-value) in workplaces are not uncommon (Shipman and Whim 1980; WHO 1984). It has also been shown that people living in the neighbourhood of dry cleaning shops may be exposed to considerable concentrations of PER (Verberk and Scheffers, 1979). The general population is exposed to PER at low, but measurable levels through air, drinking water and food (Wallace et al. 1985; Hajimiragha 1986).

Workers are usually exposed to a mixture of solvents. By contrast, in the case of PER in dry cleaning, one may speak of a single exposure which can be measured by means of biological monitoring. By taking samples of breathing-air, the time-weighted average exposure over a whole workweek can be validly estimated (Monster et al. 1983).

With respect to the health hazards of PER exposure, considerable attention has been paid to its acute and chronic toxicity. PER has been shown to depress the central nervous system and to be hepatotoxic and nephrotoxic (WHO 1984). Less attention has been paid, however, to the possible reproductive hazards of PER. Yet such interest is relevant because of the following reasons:

- solvents in general are highly suspected of injurious effects on reproduction processes (Zielhuis et al. 1984; Koskinen and Hemminki 1985)
- in dry cleaning shops many women of reproductive age are exposed to PER.

To examine the possible reproductive hazards of PER exposure two questions have to be answered:

(1) Has an effect of PER on reproduction already been shown in animal experiments or in epidemiologic studies?

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(2) Is an effect of PER on reproduction to be expected in populations which are occupationally exposed to relatively high concentrations?

Potential of PER being a reproductive hazard

Reproduction is a complex and stepwise process, which can be affected at different moments of the reproductive cycle and in different ways (Mattison 1983). Besides hereditary defects, adverse effects of exposure to biologically active exogenous compounds must be taken into account. Injury may be inflicted upon male and female fertility, conception, implantation, embryonic and foetal development, growth and maturation and upon postnatal development. A xenobiotic compound, such as a solvent like PER, may influence each of these stages and more than one mechanism may play a role.

The following general mechanisms have been suggested in recent literature (Sever 1981; Mattison 1983; Kolk 1984):

I. Exposure may cause mutations or other genotoxic damage in the ova or sperm.

II. Exposure may cause injurious effects on parental cells or cell systems, which are essential in the reproductive process (ova, sperm, ovaria, testes, prostate, endometrial tissue, hypothalamus, pituitary, etc.), or it can cause such effects on embryonic or foetal cells, tissues or organs.

III. Exposure may act as an agonist or antagonist of endogeneous hormones relevant to reproduction. An example is the working of oral contraceptives.

IV. Exposure may disturb regulatory mechanisms important in reproduction, e.g. through induction or inhibition of enzyme systems.

Each of these mechanisms should be considered as a potential agency for PER to interfere with reproduction. Obviously these mechanisms may act simultaneously.

I. Genotoxicity

There is some evidence that PER may exert a genotoxic effect. The biotransformation of PER appears to involve an epoxide as intermediate (Yllner 1961; Henschler and Bonse 1977). This intermediate, however, is rather stable and therefore unlikely to be mutagenic (Bonse and Henschler 1976). Recently thioethers were demonstrated in the urine of six women occupationally exposed to PER in dry cleaning shops (Lafuente and Mallol 1986), suggesting the possibility of a genotoxic effect (Henderson et al. 1984). This suggestion finds support in some positive results in mutation tests (Cerná and Kypenová 1977; Callen et al. 1980; Beliles et al. 1982; Vainio et al. 1985). However, in other studies no mutagenic effect has been detected (Bartsch et al. 1979; Greim et al. 1975; Henschler and Bonse 1977; Bronzetti et al. 1983; Connor et al. 1985).

PER did not induce unscheduled DNA synthesis in isolated hepatocytes from rats treated with phenobarbital (Costa and Ivanetich 1980). It was not active in a BALB/c 3T3 cell transformation assay (Tu et al. 1985). No chromosomal aberrations were found in bone-marrow cells after single, repeated or long-term exposure of mice and rats to PER (Cerná and Kypenová 1977; Rampy et al. 1978). Walles (1986) observed in male mice a linearly dose-dependent increase of single strand breaks in kidney and liver DNA, but not in lung DNA, one hour after i.p. injection of 4 to 8 mmol PER/kg b.wt. This damage was repaired in 24 h. Covalent binding of PER to DNA in vivo could not be verified (Reitz et al. 1980). Ikeda et al. (1980) investigated the lymphocytes of ten workers, who had been exposed to PER in concentrations between 30 and 220 ppm during periods from 3 months to 18 years. They did not find any significant dose-related changes in chromosome aberrations, SCEs rate, the proportion of M2 + M3 or mitotic index.

Studies of carcinogenicity of PER are relevant, because if PER is a genotoxic carcinogen, it might also have a genotoxic effect on germ cells. There are only two positive animal studies. A study by NCI (1977) resulted in a significantly increased incidence of hepatocellular carcinoma in both male and female B6C3F1 mice after oral exposure to PER during 17 months, 5 days a week. The average dosages were 536 or 1072 mg/kg/day for male mice and 386 or 772 mg/kg/day for females. After administration of PER in a similar way and in similar dosages to rats of both sexes no significant incidence of neoplastic lesions was observed (NCI 1977). No effect was found in inhalation studies with rats (Rowe et al. 1952; Rampy et al. 1978; Bolt et al. 1982) or with guinea pigs, rabbits and monkeys (Rowe et al. 1952). Mennear (1985), however, observed some positive effects in inhalation studies with F344/N rats and B6C3F1 mice after inhalation of 200 or 400 ppm PER for the rats and 100 or 200 for the mice, 6 h/d, 5 d/wk for 2 years. The incidence of mononuclear cell leukemia was greater in exposed rats of both sexes. Male rats exhibited renal tubular cell adenomes and adenocarcinomas, but no renal neopasms were detected in female rats. In mice of both sexes a greater incidence of hepatocellular carcinomas was found. Repeated application of PER with or without a tumour-promotor on the shaved

skin of rats did not induce dermal tumours (Van Duuren et al. 1979).

There are five retrospective epidemiological studies based on the death certificate records of American laundry and dry cleaning workers. Only Blair et al. (1979) found an overall excess of cancer deaths, mainly caused by an excess of lung cancer, skin cancer and cancer of the cervix uteri. Katz and Jowett (1981) observed an increase of genital and kidney cancer; Duh and Asal (1984) an increase of lung cancer and kidney cancer. Brown and Kaplan (1987) found an increase of cancer of the urinary organs in dry cleaning workers who had been exposed for at least one year to PER. Blair et al. (1986) noted excesses for larynx cancer, bladder cancer and lymphoma in a cohort mortality study. In this study no overall excess of cancer deaths was observed. These studies are not very conclusive because they are all biased by the fact that the occupational code includes both laundry and dry cleaning workers. Another point is that the workers had been exposed to other solvents apart from PER as well. Moreover, there were no data about the level and the duration of exposure or about other risk factors, such as cigarette smoking.

In two case-control studies about the role of occupation in the etiology of bladder cancer, no effects of dry cleaning work were found (Chapman et al. 1981; Smith et al. 1985). McLaughlin et al. (1987) found no increase of renal cancer risk for laundry and dry cleaning workers when linking the data of the Swedish Cancer Registry to industrial and occupational codes for all employed individuals in Sweden. Like some of the cohort studies, these studies are biased by the fact that laundry (not exposed) and dry cleaning workers were regarded as one group. Furthermore, the sample size of these studies was too small to show an increased risk for cancer of workers exposed to PER. In a fourth case-control study an increased risk (RR 2.50, 95% CI 1.02, 6.14) of primary liver cancer was found in male workers in laundries and dry cleaning establishments (Stemhagen et al. 1983). The amount of exposure to PER of the workers is not specified in this study, however.

II. Cytotoxicity

In a review of the health effects of exposure to PER from the WHO (1984), adverse effects on the central and autonomic nervous system, liver, kidney, skin and adrenal glands were listed. In the studies reviewed, changes of enzyme concentrations and macroscopic and microscopic lesions were observed. In studies with labeled PER, an irreversible binding of PER to hepatic macromolecules was demonstrated (Bonse et al. 1975; Pegg et al. 1979; Schumann et al. 1980). Because they did not find radioactivity bound to DNA, Schumann et al. (1980) doubted whether the carcinogenic effect of PER observed in mice (NCI 1977) is caused by a genotoxic mechanism. They suggested that this might be an epigenetic effect due to recurrent cytotoxic effects in longterm exposure to PER.

PER might have injurious effects on different cell types and organs, and it cannot be ruled out that PER may affect reproduction by toxic effects on essential cells and cell systems. Such an effect is suggested to explain the reduced fertility of women exposed to trichloroethylene (Pries 1981). Laham (1970) demonstrated in human studies and Helliwell and Hutton 1950) in experiments with sheep and goat that trichloroethylene readily passes through the placenta. A similar property has been demonstrated for some other halogenated hydrocarbons in rats (Vosovaya 1977) and in human cord blood (Dowty and Laseter 1976). These findings are suggestive for the possibility that PER too can pass through the placenta and can exert some direct influence on foetal tissue.

III. Structural similarity

Several xenobiotics that are absorbed by the hypothalamus or pituitary are known to affect the reproduction by steroid hormone agonism or antagonism (Matisson 1983). Such an effect of PER has not been investigated. Taking into account the marked effects of PER on the central nervous system, an influence on the hypothalamus or the pituitary gland is possible. The association of dry cleaning work with an increased risk of feminine hormonal disturbances and delayed conception and with sperm abnormalities (Rachootin and Olsen 1983) might be an indication for such an effect of PER exposure.

IV. Enzyme modification

PER does induce hepatic microsomal enzyme systems in mice (Bronzetti et al. 1983) and rats (Costa and Ivanetich 1980). Especially the cytochrome P450-system is affected (Moslen et al. 1977; Costa and Ivanetich 1980; Bronzetti et al. 1983). A toxic effect of the metabolites of PER on cytochrome P450 is suggested (Callen et al. 1980). Bronzetti et al. 1983). Because PER does modify hepatic enzyme systems there may be an effect on the biotransformation of hormones or other endogeneous compounds important for reproduction. This might reduce fertility or affect pregnancy.

It is also possible that the combined destruction and induction of essential enzyme systems due to exposure to PER may interfere with the metabolism of other endogeneous or exogeneous compounds, possi-

bly resulting in the formation of metabolites which affect the reproductive processes. Compounds, which are not active as such, may have a negative role through such an interaction (Bronzetti et al. 1983).

"Repro-toxic" properties of PER demonstrated

Reproductive effects of (occupational) exposure to PER has been investigated in some animal experiments and in some epidemiological studies.

Animal studies

The only study in the literature of the effects of PER on fertility (Carpenter 1937) is not conclusive because statistical analysis is lacking.

The effects of exposure to PER during gestation have been examined in a few studies. Exposure of 17 rats and 17 mice to 300 ppm PER (7 h/d) on Days 6 to 15 of gestation caused a slight, but statistically significant, increase of the incidence of resorptions of the rat foetuses and a decrease of the foetal body weight of the mice. Among the new-born of the exposed mice the incidence of subcutaneous oedema was significantly larger. In this group an increase of the incidence of delayed ossification of skull-bones and split sternebrae was found (Schwetz et al. 1975). In a study with exposure of 30 rats and 30 rabbits to 500 ppm PER (6 to 7 h/d) during the whole period of gestation no effects on foetal development and no externally visible malformations were found (Hardin et al. 1981). After injection of 100 µmol PER in the air chamber of chicken eggs, the survival of embryos decreased in comparison with the controls. There was a slight decrease in embryonic weight and length. Treatment of 67 eggs with PER (5, 25, 50 or 100 µmol/egg) caused more macroscopic malformations than treatment with olive oil (Elovaraa et al. 1979). Nelson et al. (1979) exposed 40 rats to 900 ppm PER during either gestation Days 7 to 13 or Days 14 to 20. No effects

Table 1. Results of animal studies concerning reproductive effects after exposure to PER

Parameter	Species	*N*	Dose	Duration/ period	Route	Results	Reference
Fertility	Rat	e:3 × 12 c:10	70, 230, 470 ppm	8 h/d/7 months	Inhalation	70 ppm: reduced fertility; 240, 470 ppm: increased fertility	Carpenter 1937
Intra uterine development	Chicken egg	e:10 c:14	100 µmol/egg	6th day of life	Injection	Decreased survival	Elovaraa et al. 1979
	Mouse	e:17 c:30	300 ppm	7 h/d/Days 6–15 of gestation	Inhalation	Decreased fetal body weight	Schwetz et al. 1975
	Rat	e:17 c:30	300 ppm	7 h/d/Days 6–15 of gestation	Inhalation	Increase of resorption of fetuses	Schwetz et al. 1975
	Rat	e:15, 40 c:15, 32	100, 900 ppm	7 h/d/Days 7–13 or 14–20 of gestation	Inhalation	No effects	Nelson et al. 1979
	Rat	e:30 c:?	500 ppm	7 h/d/Days 1–19 of gestation	Inhalation	No effects	Hardin et al. 1981
	Rabbit	e:20 c:?	500 ppm	7 h/d/Days 1–24 of gestation	Inhalation	No effects	Hardin et al. 1981
Malformations	Chicken egg	e:61 c:56	5–100 µmol/ egg	Days 2–6 of life	Injection	More macroscopic malformations	Elovaraa et al. 1979
	Mouse	e:17 c:30	300 ppm	7 h/d/Days 6–15 of gestation	Inhalation	Subcutaneous oedema and ossification	Schwetz et al. 1975
	Rat	e:30 c:?	500 ppm	7 h/d/Days 1–19 of gestation	Inhalation	No effects	Hardin et al. 1981
	Rabbit	e:20 c:?	500 ppm	7 h/d/Days 1–24 of gestation	Inhalation	No effects	Hardin et al. 1981
Postnatal behaviour	Rat	e:15, 40 c:15, 32	100, 900 ppm	7 h/d/Days 7–13 or 14–20 of gestation	Inhalation	900 ppm: differences on behavioural tests, decreased neurotransmitter levels 100 ppm: no effects	Nelson et al. 1979

were found on the number and proportion born alive, on birth weight or on growth. Several behavioural tests showed differences between pups of exposed dams and their controls. The exposed group scored less well on one of the test days, but on all later tests its performance was superior to that of the controls. In the same study decreased levels of neuro-transmitters (acetylcholine and dopamine) were observed in 21-day-old pups of the exposed group. After exposure to 100 ppm PER during Days 14 to 20 of gestation, no significant differences were observed in any of the behavioural tests between the offspring of 15 exposed animals and the litters of controls (Nelson et al. 1979). The results of these animal experiments are summarized in Table 1.

Epidemiological studies

The association between infertility and delayed conception on the one hand and a number of occupations and occupational exposures on the other hand was examined in a case control study based on data collected from mailed questionnaires and medical records of an infertility clinic (Rachootin and Olsen 1983). A comparison of case and control couples showed that females reporting exposure to dry cleaning chemicals experienced an increased risk of idiopathic infertility. After adjustment for women's age, education, residence and parity, an odds-ratio of 2.7 (95% CI 1.0, 7.1) was found. The odds-ratios for the reported occupations of females and their spouses also showed an association of subfecundity with dry cleaning work. For men, dry cleaning work was associated with an increased risk of sperm abnormalities, and for females, an association was found with medical evidence of hormonal disturbances and of delayed conception. It is difficult to interpret these associations, because there were no data on actual exposure to PER (or other dry cleaning solvents) or on any other factor in this particular occupation. In addition, the last presented findings were based on such small numbers that it was not possible to adjust for potential confounders as parity and age.

In four Finnish studies the occurrence of spontaneous abortion was analysed from records of the hospital discharge registry of the National Board of Health (Hemminki et al. 1980a, b; Hemminki et al. 1984; Lindbohm et al. 1984). This registry contains information on all women who have been hospitalized with spontaneous abortion, amounting to about 90% of all spontaneous abortions in Finland. These data were analysed according to occupations. For washerwomen, who may be exposed to PER, the risk of spontaneous abortion was higher than for all women. In the study of Lindbohm et al. (1984) an adjusted relative risk of 1.48 (95% CI 1.09, 2.02) was found for laundry workers. It is not clear, however, whether occupational exposure to PER or some other factors related to laundry work explain this observed risk. An important shortcoming of these studies is the lack of data about the intensity of exposure to PER or other chemicals, and about confounding factors such as smoking, use of alcohol, medication, previous abortions, maternal illness, etc. Furthermore, induced abortions are included in the denominators of the rates in the two compared populations. It has not been shown that the rate of induced abortions in laundry workers was similar to that in the total population of Finland. Another shortcoming is that there were no data on the 10% of women with a spontaneous abortion, which were treated as outpatients. The main difference between these patients and the hospitalized ones seems to be the shorter duration of gestation of the first group (Niemi et al. 1985). Moreover, there were no data available about early abortions, which do not come to the attention of physicians at all. Therefore the studies reviewed above do not give any information about occupational effects leading to early abortion. McDonald et al. (1986, 1987) did not find an excess of spontaneous abortion in more than 200 current and previous pregnancies of women working in laundry or dry cleaning shops. They interviewed them in a large survey in 11 Montreal maternity departments as soon as possible after delivery or treatment for a miscarriage. An essential failure in this study is that more than 25% of the women admitted for spontaneous abortion were not reached for an interview during their brief stay in hospital. Besides a high proportion of early and complete abortions were not recorded because not all women who miscarry go to hospital (McDonald et al. 1986). Another limitation is that there were no exposure data. In a retrospective study among 67 women working in dry cleaning shops in Rome, 102 reported pregnancies were compared; 56 occurred to these women during the period when they were employed in dry cleaning shops and 46 while they did not work outside their home (Bosco et al. 1987). No indication of an adjusted risk of spontaneous abortion was found. However, the small sample size of this study does not permit any firm conclusion.

Only in three of the former reviewed epidemiological studies have other possible adverse effects than spontaneous abortion been examined. Hemminki et al. (1984), McDonald et al. (1987) and Bosco et al. (1987) did not observe any higher prevalence of still birth, low birth weight ($\leq$ 2500 g) or malformation in the children of women who were working as dry cleaners. The results of the epidemiological studies are summarized in Table 2.

Table 2. Results of epidemiological studies concerning reproductive effects after occupational exposure to PER

Parameter	Design	*N*	Results	References
Fertility	Case-control study	927 subfecund couples/ 3728 fertile couples		Rachootin and and Olsen 1983
Women				
– Idiopathic infertility			Odds-ratio 2.7 (95% ID 1.0, 7.1)	
– Hormonal disturbance			Positive association	
– Delayed conception			Positive association	
Men				
– Sperm abnormalities			Positive association	
Spontaneous abortion	Registry based study	217975 pregnancies	Positive association	Hemminki et al. 1980a
	Registry based study	280614 pregnancies	Positive association	Hemminki et al. 1980b
	Registry based study	? pregnancies	No association	Hemminki et al. 1984
	Registry based study	294309 pregnancies	Odds ratio 1.98 (95% ID 1.09, 2.02)	Lindbohm et al. 1984
	Cross-sectional study	160716 pregnancies	No association	McDonald et al. 1986, 1987
	Retrospective cohort study	e: 56 pregnancies c: 46 pregnancies	No association	Bosco et al. 1987
Still birth	Cross sectional study	160716 pregnancies	No association	McDonald et al. 1986, 1987
	Retrospective cohort study	e: 56 pregnancies c: 46 pregnancies	No association	Bosco et al. 1987
Birth weight ≤ 2500 g	Cross sectional study	160716 pregnancies	No association	McDonald et al. 1986, 1987
	Retrospective cohort study	e: 56 pregnancies c: 46 pregnancies	No association	Bosco et al. 1987
Birth defects	Registry based study	? pregnancies	No association	Hemminki et al. 1984
	Cross sectional study	160716 pregnancies	No association	McDonald et al. 1986, 1987
	Retrospective cohort study	e: 56 pregnancies c: 46 pregnancies	No association	Bosco et al. 1987

Discussion

PER is widely used as a solvent, especially in dry cleaning shops. The acute and chronic toxicity of PER has been documented fairly well. Little is known, however, about the possibly hazardous effects of this chemical on reproduction. From this review it may be concluded that such effects are not to be ruled out, considering the different mechanisms for defects in the reproduction process and the information on how PER might interact (and indeed interacts) with these mechanisms. Further fundamental research is necessary, however, to affirm or exclude inference of PER by way of the mechanisms that have been mentioned in this article.

There are only a few studies in which the effects of PER exposure on reproductive outcome have actually been investigated. The results of these studies are not conclusive. Some suggest an effect of PER exposure on the reproductive outcome; others do not. A main problem is the incompleteness of the experimental results. The possible reproductive effects of PER exposure have not been studied systematically. The effect on male fertility, for example, has not been studied at all. In addition, especially the epidemiological studies, necessary for an estimate of the actual risk for human populations, have several methodological shortcomings. The only way to come to a more definitive estimation of the reproductive effects of PER is by means of epidemiological investigations

on PER exposure and reproductive outcomes with a proper design. In order to overcome the methodological problems of earlier studies, such a design should of necessity be prospective. Only then can good estimates be made of actual exposure in the relevant periods before and during the reproductive process. Only in a prospective design can the possible effects on fertility, gestation and reproductive outcome (spontaneous abortions, miscarriages) be established validly. Such studies, which can be organized in small samples (say 50 exposed and 50 as a reference group), will give more evidence of the reproductive toxicity of PER than large-scale epidemiological studies based on abortion records, with little information on occupation of the women who have had spontaneous abortions. The large-scale studies are meaningful because they may lead to new hypotheses. This review shows that the stage of hypothesis generation has been left behind. At the moment there is a need for follow-up studies to confirm or reject the central hypothesis of PER being a reproduction hazard in working populations.

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