ECETOC

Joint Assessment of Commodity Chemicals No. 39

Tetrachloroethylene

CAS No. 127-18-4

European Centre for Ecotoxicology
and Toxicology of Chemicals

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THE ECETOC SCHEME FOR THE JOINT ASSESSMENT OF COMMODITY CHEMICALS

This report has been produced as part of the ECETOC programme for preparing critical reviews of the toxicology and ecotoxicology of selected existing industrial chemicals.

In the programme, commodity chemicals, that is those produced in large tonnage by several companies and having widespread and multiple uses, are jointly reviewed by experts from a number of companies with knowledge of the chemical. It should be noted that in a JACC review only the chemical itself is considered; products in which it appears as an impurity are not normally taken into account.

ECETOC is not alone in producing such reviews. There are a number of organisations that have produced, and are continuing to prepare, reviews with the aim of ensuring that toxicological knowledge and other information are evaluated. Thus a producer, government official or consumer can be informed on the up-to-date position with regard to safety information and standards. Within ECETOC we do not aim to duplicate the activities of others. When it is considered that a review is needed every effort is made to discover whether an adequate review exists already; if this is the case the review is checked, its conclusions summarised and the literature published subsequent to the review assessed. To assist ourselves and others working in this field we have published a summary of international activities incorporating work planned, in hand, or completed on the review of safety data for commodity chemicals. Interested readers should refer to Technical Report No. 71 entitled "Inventory of Critical Reviews on Chemicals", jointly published by ECETOC and UNEP Chemicals.

This document presents a critical evaluation of the toxicology and ecotoxicology of tetrachloroethylene (CAS No. 127-18-4).

Tetrachloroethylene

CAS No. 127-18-4

CONTENTS

1. SUMMARY AND CONCLUSIONS

Tetrachloroethylene (perchloroethylene, PER) is a volatile, non-flammable liquid. Its primary use is as a solvent in the dry-cleaning of textiles, in metal degreasing and as a chemical intermediate. It is produced and used in large quantities (several hundred kt/y) throughout the world. Due to the increased use of control technology and recycling, the production of PER has declined in recent years and will continue to do so in the future.

1.1 ENVIRONMENTAL DISTRIBUTION

Due to its high volatility and pattern of use, the majority of PER released to the environment is distributed to the atmosphere with a minor proportion finding its way into water and soil. Natural production of PER by marine algae may contribute a significant part of the total release to the atmosphere.

The atmospheric half-life of PER is approximately 3 months. In the atmosphere, PER is believed to be degraded mainly to carbon dioxide and hydrogen chloride, with trichloroacetic acid (TCA) as a minor product. The contribution of PER to the TCA levels observed in precipitation is uncertain, but it may be a significant part of the total. It is not transported in significant quantities to the stratosphere and does not contribute appreciably to ozone depletion. It is too unreactive to be a “volatile organic carbon compound (VOC)” and does not contribute to urban tropospheric ozone formation (“photochemical smog”).

In surface waters, PER is removed mainly by volatilisation. Its evaporation half-life varies from a few days to up to one month, depending on the prevailing conditions. When present in sediment or soil, PER is fairly mobile and may leach, unchanged, into groundwater.

PER is not readily biodegradable using standard aerobic test procedures, but biodegradation has been observed under methanogenic conditions. Its bioaccumulation is limited due to its high volatility and depuration rate.

1.2 ENVIRONMENTAL LEVELS

PER has been detected at ppb levels in all environmental compartments, in aquatic organisms and in plants. The background concentrations in air in remote regions is much lower (< 0.1 ppb; < 0.69 mg/m^3) than in urban or suburban air (up to 3 ppb; 21 mg/m^3). PER has been found in indoor air at concentrations up to 1 ppm (6.9 mg/m^3), principally as a consequence of its use in dry-cleaning. PER may also be present in drinking water and foodstuffs.

1.3 ENVIRONMENTAL EFFECTS

The acute toxicity of PER to aquatic organisms has been studied extensively. Validated studies have shown the lowest acute (96-h) LC_{50} for freshwater fish to be 5 mg PER/l. Similar values are found for marine fish. For *Daphnia,* 48-h EC_{50} values from 8.5 mg/l are reported. Acute LC_{50} values for freshwater and marine algae are higher (> 500 mg/l). Thus, the Predicted No-Effect Concentration (PNEC) in the aquatic compartment is estimated to be 0.05 mg PER/l.

In chronic toxicity studies, the lowest No-Observed Effect Concentration (NOEC) for *Daphnia* is 0.5 mg/l (28 days), whereas fish embryo-larval stages were resistant up to a concentration of 1.4 mg/l PER. Studies in ecosystems have demonstrated effects at concentrations of 0.1 mg/l and above in microfauna. In natural ecosystems, *Daphnia* appear to be more sensitive than in laboratory studies, with acute lethal concentrations occurring at around 0.3 mg/l.

Several soil organisms, including micro-organisms, invertebrates and plants, have been used to assess the toxicity of PER after acute or prolonged exposure. Most of these studies have been conducted under non-standard conditions. NOECs are of the order of 1 mg/kg soil (dry weight). Effects have been reported following exposure to PER at concentrations starting from 10 mg/kg for one plant species or 18 mg/kg for terrestrial worms. It is suggested that PER may have an adverse effect on the photosynthetic apparatus of conifers and other higher plants following exposure, for example, to air concentrations of 1.7 ppb PER (12 mg/m^3) for 7 months.

Based on its octanol-water partition coefficient, no significant bioaccumulation of PER is expected. The concentrations of PER in marine algae and plankton have been shown to be up to 180 times higher than in sea-water. Bioconcentration factors in marine species have been estimated to be < 100 in fish liver, birds' eggs and seal blubber. Measured bioconcentration factors for PER in freshwater fish were found to be < 100 (range 26-77). Thus there is no significant evidence of biomagnification of PER along the food chain. Secondary poisoning due to PER is, therefore, not expected to occur.

1.4 MAMMALIAN KINETICS AND METABOLISM

During occupational or environmental exposure, PER is absorbed via the lungs and, to a lesser extent, via the skin and the gastro-intestinal tract. In humans, the majority (approximately 70%) of the inhaled dose is excreted unchanged via the lungs in the first 24 hours post-exposure. The remainder partitions to adipose tissue, from which it is slowly released and either exhaled unchanged (half-life > 10 days) or metabolised. Some accumulation of PER in adipose tissue might be anticipated following repeated daily exposure. The principle metabolic route for PER in all species is via cytochrome P450, the major metabolite being TCA. A secondary metabolic pathway, via glutathione (GSH) S-transferase, has been shown to be present in rats and mice. It may also be present at low

levels in humans; low levels of mercapturic acid metabolites, presumably resulting from the GSH conjugation of PER, have been detected in the urine of exposed volunteers. Significant differences in the kinetics of both pathways have been demonstrated between species, including humans. These metabolic differences are reflected in the toxicity of PER to different species, particularly in their carcinogenic response.

In humans, the total urinary metabolite levels of trichlorinated compounds (trichloroethanol and TCA) correlate well with atmospheric concentrations of PER up to 100 ppm (690 mg/m^3) at which level there is substantial evidence of a saturation of the oxidative pathway (cytochrome P450). Urinary metabolite levels have therefore been used as the basis for the biological monitoring of exposure to PER in the workplace.

A number of kinetic models have been developed for PER which, in general, describe toxicological risk in terms of total metabolised dose. None of these models provides a full description of the kinetic behaviour of PER nor of its metabolism via the GSH pathway. It is judged that these models are not sufficiently developed to allow a reliable prediction of the carcinogenic or other toxicological risks for humans.

1.5 MAMMALIAN TOXICITY

PER has low acute toxicity by all relevant routes of occupational or environmental exposure. The principal target organs for the acute toxic effects of PER are the central nervous system (CNS), and - at higher doses - possibly the heart (sensitisation to catecholamine-induced arrhythmias), the liver and, at even higher doses, the kidney. PER is irritant to the skin under occlusive conditions, this effect being much reduced under non-occlusive conditions due to its volatility. It is a mild eye irritant and may cause irritation of the respiratory tract at high concentrations. It is not a skin sensitiser and no significant effects on immune function have been described.

Target organs following repeated exposure to PER in animals (up to 8 months) are the liver (adaptive changes in rodents not accompanied by histochemical changes) and, at higher concentrations, the kidney (increased weight and histopathological changes) the lungs (dyspnoea) and the CNS (neuro-behavioural effects). Following the administration of PER to rats or mice for 2 years, the principal target organ is the kidney, with adaptive effects in the liver being primarily observed for the mouse. There are no reports of toxic effects in the liver or kidney in humans following repeated occupational exposure to PER.

PER has been shown to be foetotoxic, but not teratogenic, at maternally toxic dose levels in several animal species, with the mouse being the most sensitive species. It is concluded that this effect is associated with the maternal toxicity of either PER or its oxidative metabolite, TCA. PER had no effect

on fertility in rats and mice although there was evidence of aberrant sperm morphology in mice (but not in rats) and lower testicular weight in rats at high exposure levels. In a two-generation inhalation reproductive toxicity study in rats, PER induced pre- and post-natal toxic effects, with a No Observed Effect Level (NOEL) of 100 ppm (690 mg/m^3). PER had no effect in a dominant lethal study in the rat.

There is no substantive evidence from occupationally-exposed human populations that PER leads to infertility or to any significant adverse effects on pregnancy or birth. Reports have been published of adverse effects on fertility and on pregnancy outcome in women employed either in the laundry and/or dry-cleaning industry and assumed to have been exposed to PER. These studies provide inadequate details of the exposure to PER which is important, as mixed exposures are usual in these industries. Furthermore, the studies were inadequate in their design, particularly in the control for confounding factors and, in some instances, claimed effects were not statistically significant. Other studies in the same industries have revealed no evidence of an excess in birth defects in the offspring of exposed women.

PER has been assessed for mutagenic activity in a wide variety of *in vivo* and *in vitro* test systems. It is concluded from an overall assessment of the available data, taking into account the quality of conduct and reporting of the studies, that PER is non-mutagenic.

PER has been shown to cause hepatocellular carcinoma in the mouse and renal tubular cell carcinoma in the male rat.

Studies on the mechanism of tumour formation in rodents lead to the conclusion that the increased incidence of mouse liver tumours is due to the metabolism of PER to TCA (a known peroxisome proliferator, liver growth agent and rodent hepatocarcinogen) via the cytochrome P450 pathway, a route that is not saturated at the highest dose tested in this species. The absence of an increased incidence of liver tumours in the rat can be explained by the fact that the oxidative pathway is saturated at low doses (> 100 ppm; 690 mg/m^3) in this species, which results in a limitation of metabolite (TCA) formation and hence, any resulting toxicity.

It is thus predicted that PER would not induce liver tumours in humans because saturation of the oxidative pathway in humans (following exposure to atmospheric concentrations of PER > 100 ppm; > 690 mg/m^3) leads to insufficiently high blood levels of TCA. In addition, human hepatocytes have been shown not to be responsive to TCA as shown by the absence of peroxisome proliferation and associated biochemical events in human hepatocytes exposed to the metabolite. Thus, there are both kinetic and toxicodynamic reasons for concluding that humans will not be susceptible to PER-induced liver tumours.

Mechanistic studies on the male rat kidney tumours have led to the conclusion that they are the consequence of protein droplet nephropathy, a male rat specific phenomenon, coupled with sustained chronic toxicity. The latter effect is probably due to hepatic GSH conjugation of PER leading to the activation of the resulting cysteine conjugate via renal β-lyase to a genetically active metabolite. Although mercapturic acid derivatives have been detected in the urine of humans exposed to PER, the GSH-conjugation pathway has not be detected in human liver samples in-vitro. Nevertheless, it is reasonable to conclude that this pathway is operative in humans, albeit at a very low level. The large difference in rates of metabolism of PER by this pathway in rats, compared to humans, suggests that humans are not likely to be susceptible to the renal toxicity associated with the resulting metabolites. This conclusion is supported by the lack of the observation of renal toxicity in humans exposed to PER.

The observation of increased incidences of mononuclear cell leukaemia in F344/N rats, but not in the Osborne-Mendel nor Sprague-Dawley rat, exposed to PER is considered to be of no significance for human hazard assessment. This neoplasm is known to be of a high and variable incidence specifically in the F344/N strain of rat.

1.6 CANCER EPIDEMIOLOGY

A number of cohort mortality and proportional mortality studies of workers from the laundry and dry cleaning industry have been published in which exposure to PER may have occurred in the latter group. Cohort mortality studies have also been conducted on groups of workers exposed to PER during its use in metal cleaning. Some case-control studies of various cancers also provide some information regarding exposure to PER. Finally, several studies of cancer incidence in populations exposed to drinking water contaminated by PER are also described in the literature.

Of these, three cohort studies provide the most relevant information for assessing the relationship between exposure to PER and cancer risk in humans. Excesses of various cancers are described in these studies, including oesophageal cancer, cervical cancer, non-Hodgkin's lymphoma and bladder cancer. The incidence of none of these cancers was consistently increased in all studies. All three studies provide only limited information about the extent of exposure to PER. Furthermore, none of the investigators collected data on known determinants of mortality for the various cancers of interest, with the exception of factors such as race, sex and duration of follow-up. A further limitation of all three studies is their low power to detect changes in cancer incidence for specified sites.

Overall, the epidemiological studies of greatest relevance are insufficient in both their design and outcome to demonstrate a relationship between exposure to PER and the occurrence of cancer in humans.

There are reports in the literature of animal studies and of studies in human populations which suggest a relationship between repeated exposure to PER and the occurrence of permanent chronic toxic effects on the CNS. An overall assessment of the data leads to the conclusion that there is no convincing evidence in support of this relationship. However reversible CNS effects of a neuro-pharmacological nature are observed following acute exposure to PER at concentrations of 100 ppm and above.

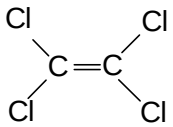
It is concluded that the appropriate effects upon which human health hazard assessment should be conducted are toxic effects on the liver and the kidney. A Lowest Observed Effect Level (LOEL) following repeated inhalation of 100 ppm PER (690 mg/m^3) has been demonstrated in a wide range of species, on the basis of histological criteria for all critical organs in studies of up to 2 years duration.

2. IDENTITY, PHYSICAL AND CHEMICAL PROPERTIES, ANALYTICAL METHODS

2.1 IDENTITY

Name:	Tetrachloroethylene
IUPAC name:	Tetrachloroethene
Synonyms:	Ethene, Tetrachloro- Ethylene tetrachloride PER Perc Perk Perchlor Perchloroethylene Tetrachloroethene 1,1,2,2-Tetrachlorethylene
CAS name:	Ethene, 1,1,2,2-tetrachloro-
CAS registry No.	127-18-4
EEC No.	602-028-00-4
EINECS No.	204-825-9
RTECS No.	KX 3850000
Formula:	C_2Cl_4
Molecular mass:	165.83

Structural formula:



2.2 PHYSICAL AND CHEMICAL PROPERTIES

Tetrachloroethylene (Perchloroethylene, PER) is a clear, colourless, volatile, non-flammable liquid with a characteristic, mild odour that is reminiscent of ether or chloroform. It is miscible with most organic solvents and exhibits a high solvency for organic compounds, but has a very low solubility in water. A peculiar property of PER is its ability to form binary azeotropes with water, certain alcohols and several other organic compounds (Hardie, 1964).

Some important physical and chemical properties of PER liquid and vapour are summarised in Table 1.

At normal temperatures, pure PER is resistant to hydrolysis: corrosion of construction materials is less pronounced than with other chlorinated solvents (Gerhartz, 1986). When exposed to light and air (oxygen), PER will autoxidise to trichloroacetyl chloride and phosgene (Gerhartz, 1986). Stabilisers such as amines or phenols can suppress this autoxidation. Other stabilisers are added to humid PER to prevent corrosion of metals such as aluminium, iron and zinc (Section 3.1.2).

Stabilised PER can be used in the presence of air, water, light and common materials at temperatures < 140°C without decomposition (Hardie, 1964). When heated to temperatures ≥ 150°C in the presence of air (oxygen), PER begins to decompose into chlorine, carbon monoxide and carbon dioxide. In addition, phosgene, carbon tetrachloride, hexachloroethane and hexachlorobutadiene may be formed (Margossian *et al*, 1971; Rinzema, 1971; CEDRE, 1990), and possibly hydrogen chloride (Hardie, 1964). Under inert conditions (in the absence of catalysts, air or moisture) PER usually remains stable at temperatures < 400-500°C, depending on the metals to which it is exposed (Hardie, 1964; Margossian *et al*, 1973; Archer and Stevens, 1977).

Table 1: Physical and Chemical Properties

Parameter, units	Value	Reference
Melting temperature, °C	-22.4 -22	Verschueren, 1983; Gerhartz, 1986; Weast *et al*, 1988 Windholz *et al*, 1976; Neumüller, 1988
Boiling temperature, °C at 1013 hPa	121 121.14 121.2 121.4	Neumüller, 1988 Weast *et al*, 1988 Gerhartz, 1986 Verschueren, 1983
Decomposition temperature, °C in air	>140	CEDRE, 1990
Relative density D_4^{20} (density of water at 4°C = 1,000 kg/m^3)	1.6226 1.6227 1.6230 1.624 1.626	Irish, 1963 Weast *et al*, 1988 Windholz *et al*, 1976; Gerhartz, 1986; Neumüller, 1988 Verschueren, 1983
Viscosity, mPa.s at 20°C	0.880	Hardie, 1964; Gerhartz, 1986

Table 1: Physical and Chemical Properties (continued)

Parameter, units		Value	Reference
Refractive index n_D, at 20°C		1.5053 1.5055	Weast *et al*, 1988 Windholz *et al*, 1976; Gerhartz, 1986
Vapour pressure, hPa at 20°C		18.6 19.0	Verschueren, 1983 Gerhartz, 1986
Relative density (air = 1), at boiling temperature		5.7 5.8 5.83	Irish, 1963 Gerhartz, 1986; CEDRE, 1990 Verschueren, 1983
Saturation concentration in air, kg/m^3 at 1,013 hPa and 20°C		0.126	Verschueren, 1983
Threshold odour concentration, mg/m^3		30 - 470 230 340	Ruth, 1986 Ballschmiter *et al*, 1987 Verschueren, 1983
Odour: ethereal, reminiscent of chloroform			
Surface tension, mN/m	at 20°C	31.3 32.1	CEDRE, 1990 Gerhartz, 1986
Solubility in water, mg/kg	at 20°C at 25°C	160 150	Ballschmiter *et al*, 1987 Horvath, 1982; Gerhartz, 1986; CEDRE, 1990
Solubility of water in PER, mg/kg at 25°C		105	Horvath, 1982; Gerhartz, 1986
Miscible with ethanol, ether, chloroform, benzene and numerous other organic solvents		Yes	Windholz *et al*, 1976; Gerhartz, 1986; Weast *et al*, 1988
Fat solubility, mg/100 g at 37°C		No data	
Partition coefficient, log P_{ow} (octanol/water) at 20°C		2.53 - 2.88	Neely *et al*, 1974; Chiou *et al*, 1977; Hansch and Leo, 1979; Veith *et al*, 1980
Partition coefficient, log K_{oc} (soil-sediment/water) at 20°C		1.9 - 2.56	Chiou *et al*, 1977; Kenaga, 1980; Schwarzenbach and Westall, 1981; Mabey *et al*, 1982; Giger *et al*, 1983; Friesel *et al*, 1984; Seip *et al*, 1986; Abdul *et al*, 1987; Heil *et al*, 1989; Lee *et al*, 1989; Zytner *et al*, 1989a
Henry's law constant, Pa.m^3.mol^{-1} at 20°C		1,303 - 1,429	Yurteri *et al*, 1987 and Ashworth *et al*, 1988, both as cited in BUA, 1994
Flash point, °C		None	
Flammability		None	
Explosive properties		No data	
Auto-flammability		None	
Oxidising properties		No data	

2.2.1 Impurities

Commercial grade virgin PER is 99.9% pure. Typical commercial PER is normally sold with specifications identical or very close to those shown in Table 2. The identity and quantities of organohalogen impurities present depend on the manufacturing process used (Section 3.1).

Table 2: Typical Composition of Commercial Grade PER

Component	% (w/w)
PER	≥ 99.5
Stabilisers[a]	
Normal grade, dry-cleaning	≤ 0.05
Metal cleaning grade	≤ 0.5
Impurities	≤ 0.010
Acid (HCl)	≤ 0.010
Water	≤ 0.005
Evaporation residue	
Other impurities[b]**, not mentioned in the DIN norm**	
Hexachloroethane	≤ 0.006
Pentachloroethane	≤ 0.005
Tetrachloroethane	≤ 0.005
Tetrachloromethane	≤ 0.005
4,1,2 Trichloroethane	≤ 0.005

[a] Depending on the area of application (Tables 3 and 4)
[b] Depending on the manufacturing process

2.3 CONVERSION FACTORS

In this report, the following conversion factors are adopted for PER concentrations in the gas phase at 20°C and 1,013 hPa (760 mm Hg):

1 mg/m^3 = 0.145 ppm
1 ppm = 6.89 mg/m^3

2.4 ANALYTICAL METHODS

The preferred method of analysing for chlorinated hydrocarbons (including PER) involves separation by gas chromatography (GC) and detection by various methods. Standard methods for various media have been developed in several countries (see below).

For low concentrations, GC with capillary columns and electron capture detector (ECD) offers excellent sensitivity down to the pg level. PER can be identified unequivocally in samples of unknown origin by the

use of GC coupled with mass spectrometry (GC-MS) analysis. During routine analysis for higher concentrations, reliable results are obtained using packed columns and a flame ionisation detector (FID).

A concentration step prior to GC analysis is often required for the determination of very low (environmental) PER concentrations. Therefore, it is important to ensure that samples are not contaminated by PER present in the local environment e.g. recently dry-cleaned clothes. Sampling, storage and preparation of samples should be carried out carefully and quickly so as to avoid any contamination, loss or changes of the sample.

2.4.1 Determination in Air

A method for the determination of PER in the sub-ppb range in air by GC-ECD was developed by Sykes *et al* (1980). Air is sampled at a flow rate of 250 ml/min through a standard NIOSH (US National Institute of Occupational Safety and Health) charcoal tube that is subsequently desorbed using a carbon disulphide/methanol (25:75) mixture. The method was comparable to a technique using Tenax as sorbent material, thermal desorption and subsequent GC-MS in the concentration range of 0.1-3.2 ppb (0.69-22 $\mu g/m^3$).

The detection limit can be lowered by prior enrichment, i.e. by passing air over a suitable sorbent, such as active carbon, Tenax or XAD, followed by thermal elution or solvent extraction; a cold trap has also been used. In this way, detection limits of 0.1-5 ppt (0.69-34.5 ng/l) have been achieved (Grimsrud and Rasmussen, 1975; Class and Ballschmiter, 1986, 1987).

Higher concentrations (ppm levels), e.g. at the workplace, can be determined with personal monitoring tubes (Dräger, Auer). Dräger reports useful ranges of 5-50 ppm (34.5-344.5 mg/m^3) 10-500 ppm (69-3,445 mg/m^3) respectively for two different PER detector tubes. There is also a diffusion tube for long-term sampling available from Dräger, which has an application range of 25-200 ppm (172-1,378 mg/m^3). These detector tubes should be used with care, considering possible cross-sensitivities and interferences (Dräger, 1982; Von Düszeln and Thiemann, 1983; Kühn-Birett, 1991). Passive sampling by diffusion on Tenax and thermodesorption has also been used to achieve a lower detection limit (ppm) (Von Düszeln and Thiemann, 1983).

For the purpose of workplace monitoring, various countries have adopted standard methods. The methods reported by the US-NIOSH and the UK Health and Safety Executive (HSE) are summarised below. Although primarily designed for workplace monitoring, the techniques described below may also be useful for stack (emission) monitoring and related environmental measurements with appropriate quality assurance measures.

UK-HSE Methods for the Determination of Hazardous Substances 28 (Rev)

A method for workplace monitoring of a group of halogenated hydrocarbons including PER over periods from 10 minutes to 8 hours is described. It involves collection of the vapours in an activated charcoal tube by means of battery operated pumps. The charcoal is subsequently desorbed in carbon disulphide and analysed by GC-FID. A useful range of 0.2-200 ppm (1.4-1.378 mg/m^3) is reported for a 10-litre air sample (HSE, 1990).

US-NIOSH Projected and Completed Analytical Methods 127 and S335

In NIOSH method 127, a known volume of air (1-25 l) is drawn through a charcoal tube by means of a personal sampling pump to trap any PER vapours present. The charcoal tube is transferred to a test tube and desorbed with carbon disulphide. An aliquot of the desorbed sample is injected into a GC-FID and the peak measured and compared with the area obtained from injected standards. The detection limit is 2.4-60 mg/m^3 air (0.35-8.7 ppm) (NIOSH, 1977a). The US Occupational Safety and Health Administration (OSHA) uses a slightly modified, generalised version of this method (OSHA, 1989).

NIOSH Method S335 is based on the same principles, but using a 3-litre air sample. The method was validated over a range of 655-2,749 mg PER/m^3 (95.0-398.6 ppm) (NIOSH, 1977b).

2.4.2 Determination in Water

Water samples with higher concentrations of PER (e.g. > 1 mg/l) can be injected directly into a capillary GC-ECD (Nicholson *et al*, 1977), but an enrichment step is usually necessary to cope with lower levels. PER is part of the (organic) fraction that may be absorbed on to active carbon or Tenax (AOX), extracted by pentane (EOX) or purge-and-trapped by air (POX); other validated enrichment techniques include closed-loop stripping and the use of headspace and cold trap. The detection limits vary from 0.1 ng/l to 0.5 µg/l (Bauer, 1981a,1990; UBA, 1983; Gruber, 1984; Selenka and Bauer, 1984). The latter limit can also be obtained with a GC-FID combination (Nicholson *et al*, 1977).

2.4.3 Determination in Soils, Sediments and Wastes

A variety of methods for the determination of PER in soils and sediments are available. One method describes the need to grind soil or sediment samples prior to suspension in distilled water followed by extraction into *n*-pentane. The pentane fraction is analysed for PER by direct GC-ECD. The detection limit, with a proviso for matrix effects, is 0.1 µg/kg (Arge Elbe, 1986).

A standard GC method prescribed by the US Environmental Protection Agency (US-EPA) uses the purge-and-trap method for analysing PER in ground water or soils contaminated at low levels. For soils or sediments contaminated at intermediate levels, methanol extraction may be necessary prior to purge-

and-trap analysis. When the GC is equipped with a halogen-specific detector (HSD), the limit of detection is 0.3 µg/l for ground water and soil contaminated at low levels, 15 µg/l for water-miscible liquid waste and 37.5 µg/l for soil contaminated at high levels and sludge or non-water-miscible waste. These limits are highly matrix dependent (US-EPA, 1987-1988).

PER can be determined by GC-MS in nearly all types of soils, regardless of the water content, including ground water and sediments. The sample may be introduced into the GC by the purge-and-trap technique or by direct injection. With a packed column, the detection limits range from approximately 5 µg/kg (w/w) for soil/sediment samples, to 5 µg/l for groundwater samples. With a capillary column, the respective detection limits are 5 mg/kg (w/w) for soils and sediments and 5 mg/l for groundwater. This method is also suitable for various wastes (US-EPA, 1987-1988).

The air in soils can be analysed for PER by direct GC-ECD. Normally 10-100 µl air is taken by means of an injection valve from a sampling tube, which is driven into the soil. A detection limit of 1 µg/m^3 (150 ppt) has been reported (Neumayr, 1981; Walther *et al*, 1985).

2.4.4 Determination in Food and Tissues

PER can be analysed in solid food or tissue samples after they are deep-frozen and ground with sodium sulphate, exposed to nitrogen gas at 80°C to desorb gaseous contents and subsequently adsorbed by a suitable sorbent. Following elution of the sorbent, the eluate is analysed directly for PER (Bauer, 1981a).

PER can be co-distilled from fatty foodstuffs with decane or using a modified distillation with water vapour and *n*-pentane in a Clavenger apparatus. Other validated methods are available. The detection limits depend on matrix effects and, using GC-ECD or GC-MS, range from 0.01-0.02 µg/kg (McConnell *et al*, 1975; Bauer, 1981a; Selenka and Bauer, 1984).

Bauer (1990) reports a standard method for the determination of PER in edible oil.

PER and its metabolites can be determined in blood or urine (20 or 100 µl) by incubation with β-glucoronidase to split the trichloroethanol glucuronide, followed by heating to 100°C to convert TCA to chloroform. The headspace gas is collected after 30 minutes at 90°C, and injected into a GC with capillary column and ECD. The limit of detection varies from 0.01-0.04 mg/ml (Schoknecht *et al*, 1983). GC has also been used in biological monitoring assays (Section 11.3.3).

3. PRODUCTION, STORAGE, TRANSPORT AND USE

3.1 PRODUCTION

Industrial production of PER commenced in Europe in 1914, when it was commercially marketed in Germany and the UK, and in the USA in 1925.

PER may be produced by oxychlorination, chlorination and/or dehydrochlorination reactions of hydrocarbons or chlorinated hydrocarbons. The most common methods of production reported are high-temperature chlorinolysis of propylene and oxychlorination of 1,2-dichloroethane (Brooke *et al*, 1993). Both routes yield a mixture of PER and trichloroethylene. Varying the reaction conditions can alter the proportions of each compound produced. Carbon tetrachloride is also produced via the chlorination of propylene, the amounts produced being dependent upon the reaction conditions employed. Due to reduction in use of carbon tetrachloride, the current reaction conditions are likely to favour the production of PER by the oxychlorination of 1,2-dichloroethane route (ECSA, 1996).

Broadly speaking, four different grades of PER are produced for different uses (Table 3).

Table 3: Grades of PER

Grade	Application
Alkaline/dry-cleaning grade	Dry-cleaning
Alkaline/vapour-degreasing grade	Metal degreasing
Technical	Intermediate, formulations
High purity	Extraction

The production capacity for trichloroethylene and PER currently installed in western Europe is estimated at 450 kt/y. Due to flexible production ratios between PER and its co-products, this figure is not an accurate reflection of actual PER capacity.

The total world production for PER in 1994 was estimated at 245 kt/y (Coopers and Lybrand, 1995). In the EU during the 1990s, the annual production levels of PER have been falling. The production volumes for 1986 to 1994 are shown in Table 5 (Section 3.3).

Small quantities of used PER (approximately 10 kt/y) from a variety of industries are recycled. The recycled product usually re-enters commerce in metal degreasing applications.

3.1.1 Stabilisers

Stabilisers are normally added to PER to prevent its decomposition during storage and use. Due to its relatively high stability, PER is less stabilised than other chlorinated solvents. To be effective during use, the stabilisers must be co-volatile with PER, so that they are present in both the liquid and vapour phase. Four types of stabiliser can be blended with the commercial product, depending on the application:

- epoxides, which neutralise small quantities of acids formed during metal degreasing; they are not normally used for dry-cleaning grade PER;
- secondary or tertiary alcohols, or nitroalkanes to protect the metal surface by de-activation or removal of metal salts by complex formation;
- alkylamines or phenols, as antioxidants to inhibit autoxidation of PER by air (oxygen);
- alkylamines, to prevent corrosion of mild or galvanised steel.

A number of stabilisers that are in common use are listed in Table 4. The total concentration of stabilisers is normally lower than 500 ppm (0.05%) in dry-cleaning grade PER; highly stabilised grades for metal-cleaning applications might include up to 5,000 ppm (0.5%).

Table 4: Chemicals in Use as Stabilisers

Amines	Alcohols, phenols	Epoxides and other compounds[a]
Allylamine	Alkylcresols	Alkylglycidylether
Cyclohexylamine	Alkylphenols	
Diisobutylamine	Butanol	Cyclohexene oxide
Diisopropylamine	Ethanol	Cyclo-octatriene
Morpholine	Methanol	
n-Alkyl-morpholines	Propanol	Isopropylacetate
n-Alkyl-pyrrenes	Tetrahydrofuran	Nitroalkanes
Triethylamine	Thymol	

[a] Butylene oxide, epichlorhydrin and propylene oxide are not currently used

3.2 STORAGE AND HANDLING

PER is normally stored in bulk storage or drums made of a grade of steel suitable for the storage of chlorinated solvents. Bulk storages are vented to prevent the build up of PER vapours. Drums should be stored in a dry, freshly aerated place, in a catchment area capable of holding the total volume of the largest tank involved. Small laboratory quantities may be stored in fully-closed brown glass bottles. Further details are given in Section 11.3 and ECSA (1989).

3.3 USE

PER is widely used as a solvent for fats, oils, greases, waxes, rubber, gums, tar, soot, and several synthetic materials (Hardie, 1964; Verschueren, 1983). Its use in the extraction of non-edible fats from animal waste is now negligible.

The principal use of PER is as a solvent in the dry-cleaning industry because of its high solvency and high solute-carrying capacity, low capacity to inflate hydrophilic textile fibres and above all its non-flammability and low toxicity, when compared with other potential dry-cleaning solvents. Another major use is in vapour-phase metal degreasing in the engineering industry (ECSA, 1995).

PER is also used as an intermediate in the manufacture of TCA and fluorocarbons, including both chlorofluorocarbons (CFCs; production already phased out in developed countries) and their partially hydrogenated substitutes, hydrofluorocarbons (HFCs). Other minor uses include various applications in the textile industry and as a solvent during fabrication of industrial glues and rubber formulations.

In western Europe, the quantities of PER sold have declined from 290 kt/y in 1974 to 162 kt/y in 1986 and further to 78 kt/y in 1994 (ECSA, 1995) (Table 5). These figures exclude amounts of recycled PER, currently estimated at 10 kt/y, and uses for the production of fluorocarbons. It is expected that both the pattern of use and the total amount of product used (virgin and recycled) will change, due to the future decrease in consumption. This decrease in consumption is due to evolving techniques to further improve the capture of emissions and the recycling of residues. Use in the production of CFCs (not HFCs) has fallen significantly in western Europe the 1990s as a consequence of the controls introduced by the Montreal Protocol.

Table 5: PER Production and Consumption (kt/y) in Western Europe 1986-1994
(Midgley and Place, 1992; ECSA, 1995)

	1986	1987	1988	1989	1990	1991	1992	1993	1994
Production	340.8	322.8	342.9	317.1	279.8	219.8	ND	ND	164.0
Sales[a]	161.6	151.8	144.1	131.3	122.6	113.4	88.7	78.0	77.9

[a] Excludes amounts exported from or imported into western Europe, recycled or used as a chemical intermediate
ND No data

An analysis of the production, sales and use patterns for PER in western Europe during 1994 concluded that of the 164 kt produced, 56 kt were exported outside the EU, 30 kt were consumed as a chemical intermediate and 78 kt were sold for downstream solvent applications (ECSA, 1996).

An approximate analysis of the use pattern of PER in solvent uses (% of sales) in western Europe is given in Table 6. The pattern may vary from country to country although dry-cleaning is the dominant use in most countries.

Table 6: Use Pattern of PER (% of Sales)
(ECSA, 1995)

Application	Usage (%)
Dry-cleaning	80
Metal degreasing	18
Others	2

4. ENVIRONMENTAL DISTRIBUTION AND TRANSFORMATION

4.1 ENVIRONMENTAL DISTRIBUTION

Most of the known sources of PER are anthropogenic. However, synthesis by marine macro and micro algae has been detected in the laboratory (Abrahamsson *et al*, 1995a,b). Aucott (1997) has estimated the oceanic source of PER to be of the order of 100 kt/y (Appendix A).

Because of its physico-chemical properties and the large number of consumers (dry-cleaning shops and degreasing in workshops), the potential for release of PER in the environment is high. Owing to its high Henry's Law constant (Table 1), the majority will ultimately partition into the air (ECETOC, 1988). The ambient air levels are higher in areas of concentrated industry and population, where most dry-cleaning establishments and engineering workshops are located; the values found in rural and remote areas are lower. These levels reflect the relative magnitude of sources, and are usually in the ppt to ppb range.

4.1.1 Emissions during Production, Storage and Handling

Losses of PER to the atmosphere were reported to be 2.5 t/y from a German company in 1990 (BUA, 1994). Accidental release of vapours and spillage of liquid will occur during the manufacturing process itself and also during blending and filling operations. Two European producers reported general emissions for 1994 around 0.02% of PER production mainly coming from tank respiration (ECSA, 1996). Based on a total production of 164 kt/y for the EU, this would lead to a total release of approximately 32 t/y in 1994.

PER occurs in waste-water for a variety of reasons, including washing organic phases during production, rinsing during cleaning operations of tanks used in bulk storage and transport, leakage during filling, vent scrubbing and its dissolution in rainwater. Contaminated effluents are normally collected in basins where most of the PER settles by gravity. Small quantities of PER which remain in solution can be removed by stripping, by adsorption or by biological treatment with adapted micro-organisms. A removal efficiency of > 95% is normally obtained (Section 4.2.4).

Two German producers reported, respectively, total emissions of 0.12 and 0.15 t of PER in water for the year 1991 (BUA, 1994). From 1994, European producers were expected to comply with Directive 76/464/EEC, i.e. water emissions to be < 2.5 g/t of PER produced (ECSA, 1996). Based on a total production of 164 kt/y for the EU, this would lead to a total release to water of a maximum of 410 kg/y.

4.1.2 Emissions during Use

There is no significant emission of PER during its use as a chemical intermediate: data from one European company show air releases being 0.04% of the total quantity of PER used for intermediate production (ECSA, 1996). Emissions of PER to air, to water and via solid waste occur during use of the product as a solvent in dry-cleaning and metal degreasing. The average releases to the environment in western Europe in 1994, based on sales figures for 1994, were 90% (70.2 kt/y) to air and 10% (7.8 kt/y) to water (ECSA, 1996).

The current trend in the dry-cleaning industry is a stringent reduction of the total (mainly airborne) emissions. This is achieved by the increasing use of closed-system machines. Total losses, estimated in the past to be up to 7 kg of solvent per 100 kg of cleaned clothes, are decreasing substantially and now amount to only one kg per 100 kg of cleaned clothes. Similar efforts undertaken in the metal-degreasing industry are leading to reduced air emissions from their workshops.

The residues from dry-cleaning and metal-degreasing operations contain, typically, 10% of PER. Sometimes the content of PER may be as high as 50%, which makes recycling technically and economically viable in specialised recycling plants. Alternatively, residues may be incinerated (ECSA, 1996).

4.2 BIOTRANSFORMATION AND ENVIRONMENTAL FATE

4.2.1 Atmospheric Fate

A detailed discussion of the fate of PER in the atmosphere, with references to the relevant literature, is given in Appendix A. The conclusions may be summarised as follows:

The atmospheric degradation of PER occurs mainly in the troposphere and is initiated principally by reaction with hydroxyl ($^{\cdot}OH$) radicals and possibly to some extent by reaction with chlorine atoms. Reaction with other reactive trace species and direct photolysis are believed to make only a very minor contribution to the degradation of PER. Physical removal of PER from the troposphere by “rainout” or uptake by the oceans is negligible compared to chemical destruction.

The overall atmospheric lifetime of PER, derived either from the rate constant of the reaction of PER and the known concentration of $^{\cdot}OH$, or from “budget” calculations, is approximately 4 to 5 months (corresponding to a half-life of roughly 3 months). This lifetime is long enough for transport to occur to regions far removed from the emission sources, but it is short enough for only a small fraction of the PER emitted at a given location to cross the equator into the other hemisphere.

The atmospheric photochemical reactivity of PER is too low for it to make any significant contribution to local urban tropospheric ozone formation and the related “photochemical smog”. The US-EPA has therefore exempted PER from being regarded as a “VOC” (Volatile Organic Carbon).

Current global anthropogenic emissions of PER, deduced from audited production and sales data, are estimated to be approximately 300 kt/y and to occur essentially (> 98%) in the northern hemisphere. Broadly speaking, the observed atmospheric background concentrations and their geographical distribution (much higher levels are observed in the northern hemisphere than in the southern hemisphere) are consistent with these emissions data and with the assumption that reaction with the ·OH radical in the troposphere is the dominant atmospheric sink for PER. A recent modelling study suggests that there may be a natural oceanic source of approximately 100 kt PER/y.

In the northern hemisphere there is a marked seasonal variation of the background PER concentrations. These are lowest after a period of high “oxidising power” of the atmosphere (high ·OH concentrations), which occurs in the summer months.

A number of laboratory studies carried out under “simulated atmospheric conditions” have enabled various reaction products to be identified: phosgene, trichloroacetyl chloride (TCAC), dichloroacetyl chloride, tetrachloroethylene epoxide, carbon oxides, formic acid, hydrogen chloride, chlorine, carbon tetrachloride and chloroform. Of these products, phosgene and TCAC are the most commonly reported ones. Such studies should, however, be interpreted with great caution and deviations from actual tropospheric conditions should be taken into account when postulating likely breakdown pathways in the real atmosphere.

Thus, experiments carried out in the presence of chlorine scavengers demonstrate that TCAC is the product of the chlorine-atom initiated oxidation pathway (which also gives rise to phosgene in 15% yield), while the degradation initiated by the ·OH radical leads exclusively to one-carbon products, including phosgene.

From the known rate constants for reaction of PER with ·OH and with Cl, and from available data on the tropospheric abundances of these two reactive species, it is concluded that the reaction of PER with Cl represents approximately 13% of the overall atmospheric degradation of PER. The TCAC thus formed will be partly photolysed (giving phosgene) and partly taken up by cloud, rain and ocean water and hydrolysed to TCA. The best estimate of the overall atmospheric yield of TCA from PER is 5%, but there is considerable uncertainty and the value might conceivably be as low as 0.1% or as high as 33%. The concentrations of TCA observed in rainwater over Europe are broadly consistent with the assumption that the atmospheric degradation of PER, at background concentrations, is the main source of TCA (with a yield of 5%). However, over other parts of the globe (in particular at high

latitudes of both hemisphere), observed TCA levels in precipitation appear to be either too high or too low for them to be consistent with this assumption.

Simulated atmospheric degradation experiments carried out in 1975 led to the conclusion that carbon tetrachloride (CCl_4), an ozone-depleting substance, could be formed from PER, with a yield of approximately 8%. More recent laboratory studies have confirmed the formation of CCl_4, albeit in much lower yields. They have demonstrated that CCl_4 is a secondary and/or tertiary oxidation product, arising from the photolysis of TCAC or its hydrolysis product TCA, largely through heterogeneous reactions occurring on the walls of the reactor. CCl_4 is thus a minor product of the Cl-atom initiated degradation pathway. From information provided by the laboratory studies and the estimate of the importance of the Cl-atom pathway in the troposphere (up to 13% yield), it is concluded that the overall atmospheric yield of CCl_4 from PER is unlikely to exceed 0.03%.

It is not meaningful to calculate an Ozone Depleting Potential for a substance with an atmospheric lifetime as short as that of PER, the tropospheric concentration of which varies greatly with latitude, being much higher in the northern hemisphere, where it is emitted, than in the southern hemisphere. Nevertheless, PER contributes only approximately 1% of total current atmospheric chlorine loading and hence plays only a minor part in ozone depletion. Part of the small fraction of PER that does reach the stratosphere (estimated at approximately 1.6% of ground-level emissions) is degraded to phosgene and returned to the troposphere where it is destroyed by hydrolysis. Thus not all the chlorine contained in the PER entering the stratosphere is actually converted into ozone-depleting species. Furthermore, the tropospheric breakdown products arising from PER (phosgene and possibly some TCAC) contribute considerably less to stratospheric chlorine loading than PER itself.

The contribution of PER to the acidity of precipitation (“acid rain”) is less than 0.1% of the global total.

4.2.2 Aquatic Fate

A detailed discussion of the fate of PER in aquatic media, with references to the relevant literature, is given in Appendix B. The conclusions may be summarised as follows:

The abiotic processes which may be expected, a priori, to contribute to the removal of PER from aqueous media are: volatilisation, chemical (or photochemical) reaction and sorption. However, in confined groundwater, neither volatilisation nor photodegradation will occur.

Owing to its high Henry's Law constant, any PER present in surface waters will partition preferentially into the ambient air. Application of a Mackay Level 1 model leads to the conclusion that 99.45% of PER partitions to the air compartment.

Volatilisation from water to air is a fairly rapid process. Very short evaporation half-lives (< 1 h) have been observed in laboratory studies. Nevertheless, it is recognised that the rate-limiting process is diffusion in the liquid phase, so the volatilisation rate is highly dependent on mixing conditions, which are often much more vigorous in laboratory experiments than in the real environment. In surface waters, mixing is determined by water flow-rate and depth as well as wind speed. The evaporation half-life of PER derived from actual field observations is of the order of 2-10 days for rivers and 1 month for lakes or ponds.

Volatilisation is nevertheless expected to be by far the dominant process for removal of PER from surface waters, since known chemical or photochemical reactions of PER in the aquatic environment (such as direct photolysis or hydrolysis) appear to be exceedingly slow compared to evaporation.

However, it has not been possible, for lack of reliable data, to assess the significance of reactions of PER in aquatic media with various reactive species of photochemical origin such as hydrated electron, ·OH radical, alkylperoxy or alkoxy radicals, excited molecular oxygen, superoxide ion, etc.).

The removal of PER from aqueous media by sorption onto soils, sediments or suspended matter is discussed in Section 4.2.3 and in Appendix B (Section B.3).

4.2.3 Fate in Soils and Sediments

Due to its high vapour pressure and moderately low soil adsorption (K_{oc} is 79 to 360, Table 1), PER on the soil surface will evaporate rapidly (Wilson *et al*, 1981).

In soil and sediment with a partition coefficient of the order of 200 (Table 1, log K_{oc} = 1.9 - 2.56), PER is considered to be fairly mobile and to have the potential to contaminate large areas of groundwater when leached by rainwater.

PER can leach rapidly through sandy soil into groundwater. Its retardation is 2.5 times that of water (Wilson *et al*, 1981). In a bank filtration system tested in Switzerland (Schwarzenbach *et al*, 1983) and in the Netherlands (Zoeteman *et al*, 1980), PER was rapidly transported to groundwater. It was estimated that only 0.01% was adsorbed to particulate matter.

Soil/water partition coefficients for PER have been established following exposure of Agawan soil (fine sandy loam) to aqueous solutions of 4.18-68.2 µg/l. Coefficients of 6.5 (24 h) and 7.3 (72 h) were determined (Pignatello, 1990a,b).

Sorption capacity was established experimentally in a closed system. Twenty-two percent of a 1 µg/l solution of PER was absorbed by bentonite clay (750 mg/l) after 30 minutes. No further sorption was

noted. Peat moss (500 mg/l) absorbed 40% of a 1 µg/l solution of PER in 10 minutes (Dilling *et al*, 1975).

Measured adsorption of PER to soil appears to be higher than would be predicted from the soil organic carbon/water partition coefficient (log K_{oc}, Table 1), suggesting some form of adsorption to the non-organic component of the soil (Mokrauer and Kosson, 1989; Piwoni and Banerjee, 1989).

In a study designed to simulate field conditions it was concluded that the sorption of PER to aquifer materials was reversible at concentrations typical in natural waters (Schwarzenbach and Westall, 1981).

Once it is present in groundwater, PER can no longer be removed by volatilisation and photochemically-driven degradation processes are not operative.

4.2.4 Biodegradation

Aerobic Conditions

PER was not biodegraded in a shake-flask, closed-bottle biodegradation procedure after a 21 day acclimation period (adaptative transfers after 48 or 72 h) both with and without lactose. No biodegradation was observed in a river die-away study after a 21 days of acclimation without co-metabolite (Mudder, 1982).

Under aerobic conditions, in column experiments, no biodegradation of PER was observed over 25 weeks at 20°C, or over 2 years at 22-23°C, using a bacterial inoculum from a primary sewage effluent (Bouwer *et al*, 1981a; Bouwer and McCarty, 1982).

PER was shown to be significantly biodegradable after 7 days of incubation at 25°C in the dark or using a static-culture biodegradation test in closed vials with an enriched domestic waste. Gradual adaptation was observed in three weekly subcultures, with degradation increasing from 30-45% to 84-87% over 7 days. The volatilisation loss from the glass-stoppered vials was 16-23% over 10 days at 25°C (Tabak *et al*, 1981).

Wilson *et al* (1983a,b) did not find evidence of degradation of PER (initial concentration 600-800 µg/l) in a static microcosm made up with aerobic subsurface material sampled from subsurface positions immediately above and below a shallow water-table aquifer at sites in Oklahoma and Los Angeles.

In several studies using pure cultures of propylene-grown *Xanthobacter* sp. and ammonia-oxidising bacteria or using mixed-cultured methane-utilising microbes, degradation of several chlorinated

ethenes (trichloroethylene, dichloroethylene, vinyl chloride) was observed; PER, however, did not degrade under these conditions (Ensign *et al*, 1992; Fogel *et al*, 1986; Vannelli *et al*, 1990).

Different results were obtained by Phelps *et al* (1991) who claimed a 60% decrease in initial PER concentration within 21 days in an aerobic packed-bed column. The results could not be explained by the investigators, who suggested the presence of anaerobic "microniches" in the column bed.

Schwarzenbach *et al* (1983) studied the concentration profile of micropollutants during infiltration of river water to groundwater. They found no degradation of PER during the mostly aerobic process. During the monitoring time of one year one of the sampling wells had oxygen concentrations of 1-2 mg/l for approximately 2 months. These low oxygen concentrations were probably still too high to create the appropriate anaerobic degradation conditions. On the other hand, a slow rate of aerobic degradation of PER has been demonstrated in 3 different soil types (Loch *et al*, 1986).

Anaerobic Conditions

Under methanogenic, strictly anaerobic conditions, PER is dechlorinated to trichloroethylene, 1,2-*cis*- and 1,2-*trans*-dichloroethylene and vinyl chloride. Theoretically, the reduction of PER can proceed to ethane. In addition, PER was partially mineralised to carbon dioxide (Table7).

Several sources for active inocula are mentioned in the literature; contaminated aquifer, sub-surface soil, sediment and anaerobic sludge from waste-water treatment plants. Anaerobic bacteria of two *Methanosarcina* strains and strain DCB-1 have been shown to be effective in PER dechlorination during methanogenesis, in the presence of an additional carbon substrate. It is assumed that electrons are transferred to PER via an electron carrier involved in the biosynthesis of methane (Fathepure and Boyd, 1988).

The dechlorination of PER is promoted by different factors:

- the presence of methanogenic and acetogenic bacteria
- adaptation time of several months
- incubation over several months at 25 - 35°C
- redox potential below –150 mV (methane producing, sulphate reducing conditions)
- concentrations of intermediates (lower chlorinated ethylenes and ethylene) which do not suppress methanogenic activity
- cofactors such as electron donors, co-pollutants and carbon source.

Conclusion

Anaerobic conditions appear to be essential for the biodegradation of PER, given the fact that almost all studies under aerobic conditions, including microcosms of subsurface soil and methane utilising bacteria, failed to demonstrate biodegradation.

Methanogenic bacteria are an important class of anaerobic bacteria for the biodegradation of PER by virtue of their extreme diversity of habitat and the fact that they are likely to be present in a variety of environments where PER occurs as a contaminant.

Table 7: Anaerobic Biodegradation Tests

Inoculum	Concentration of PER		Degradation	Duration	Result	Degradation products[b]	Reference
	(mmol/l)	(mg/l)[a]	(%)	(d)			
Activated sludge, adapted, industrial	-	16.23	> 99	10	Inherently biodegradable	TCE; *cis*-DCE	Kästner, 1991
Activated sludge, adapted	-	91	> 99	2	Inherently biodegradable	TCE trace; DCE trace; VC; ethene	DiStefano *et al*, 1991
Activated sludge, adapted, river sediment/granular	9	1.5	> 95	5	Inherently biodegradable	TCE; *cis*-DCE; VC; ethene; ethane	De Bruin *et al*, 1992
Activated sludge, adapted		91	> 99	5	Inherently biodegradable	TCE; DCE; VC 20%; ethane 80%	DiStefano *et al*, 1992
Anaerobic micro-organisms	4.9	0.81	80	50	Inherently biodegradable	TCE	Fathepure *et al*, 1987
Anaerobic micro-organisms with methanogenic bacteria	4.9	0.81	> 99	7	Inherently biodegradable	TCE	Fathepure *et al*, 1987
Anaerobic micro-organisms	-	3	20	13	Inherently biodegradable	TCE	Fathepure and Boyd, 1988
Anaerobic micro-organisms	-	0.13	80	37.5 h	Inherently biodegradable	TCE trace; DCE trace	Fathepure and Vogel, 1991
Anaerobic micro-organisms	4	0.7	> 99	5	Inherently biodegradable	TCE; DCE; VC; ethene	Freedman and Gossett, 1989
Anaerobic micro-organisms	200	33.2	> 99	54	Inherently biodegradable	TCE; DCE; VC; ethene	Holliger *et al*, 1993

Table 7: Anaerobic Biodegradation Tests (continued)

Inoculum	Concentration of PER (mmol/l)	(mg/l)[a]	Degradation (%)	Duration (d)	Result	Degradation products[b]	Reference
Anaerobic micro-organisms	0.36	0.060	> 98	2	Inherently biodegradable	TCE; DCE; VC	Vogel and McCarty, 1985
Anaerobic micro-organisms from contaminated aquifer	60.3	10.0	23 - 51	7	Inherently biodegradable	TCE; *trans*-DCE; VC	Liang and Grbic-Galic, 1993
Anaerobic micro-organisms from sulphate-reducing aquifer	-	NS	Yes	NS	Biodegradable	Sequential reductive dehalogenation	Suflita *et al*, 1988
Soil	-	11.5 mg/ kg	> 99	332	Biodegradable	NS	Pavlostatis and Zhuang, 1993
Column/culture							
Mixed-film methanogenic	-	0.060	24	4	Biodegradable	TCE; DCE isomers; VC	Vogel and McCarty, 1985
Mixed-film methanogenic	-	0.300	100	10	Biodegradable	VC	Vogel and McCarty, 1985
Methanogenic biofilm	-	0.130 0.032 0.010	86	9-12 wk[c]	Inconclusive	NS	Bouwer *et al*, 1981b
Static microcosm, groundwater sediment	-	4.2	Yes	16 wk	Biodegradable	*cis*-DCE; *trans*-DCE trace	Parsons *et al*, 1985

[a] Concentrations originally reported as mmol/l were recalculated to µg/l
[b] TCE, trichloroethylene; DCE, 1,2-dichloroethylene (*cis* and *trans* isomers); VC, vinyl chloride
[c] Not clearly stated
NS not stated

4.2.5 Bioaccumulation

Given the octanol-water partition coefficient of 2.53-2.88 (log P_{ow} in Table 1), no significant bioaccumulation of PER is expected. Its volatility and high depuration rate will reduce the probability that bioaccumulation will occur.

There are only few experimental data concerning the bioconcentration of PER. In freshwater fish, bioconcentration factors ranged from 40 in rainbow trout (*Oncorhynchus mykiss*) (Neely *et al*, 1974) to 49 in bluegill sunfish (*Lepomis macrochirus*) (Barrows *et al*, 1980). The depuration rate ($t_{1/2}$) in the bluegill sunfish was < 1 day (Barrows *et al*, 1980). In carp (*Cyprinus carpio*) exposed to 0.1 mg PER/l, a bioconcentration factor (BCF) of 26 to 77 was determined after 56 days (CITI, 1992). Kenaga (1980) proposed a theoretical BCF of 31 predicted from the water solubility.

Bioconcentration factors for PER in sea-water have been estimated to be < 100 in different biota such as fish liver, bird's eggs and seal blubber. The concentration found in the liver of dabs was 40-60 times higher than in the flesh (Pearson and McConnell, 1975).

PER concentrations in marine algae and plankton have been shown to be up to 180 times higher than in sea-water (Bauer, 1981a).

There is no evidence of biomagnification of PER along the food chain.

4.2.6 Evaluation

The half-life of PER in the atmosphere is approximately 3 months.

The major degradation product is believed to be phosgene, which will be taken up by cloud, rain or ocean water and hydrolysed to CO_2 and HCl. TCAC may be a minor breakdown product. If formed, it will be hydrolysed to TCA and HCl. The contribution of PER to the TCA levels observed in precipitation is highly uncertain, but it may be a significant part of the total. The acids (HCl and possibly TCA) arising from the degradation of PER will end up in rain or sea-water, but the contribution of PER to "acid rain" will be negligible. Photolysis of TCAC may lead to extremely low overall yields of carbon tetrachloride.

PER does not contribute significantly to tropospheric ozone formation or stratospheric ozone depletion.

In surface water, the evaporation half-life of PER varies from a few days to 1 month, depending on water movement, depth and wind speed. Degradation, either through hydrolysis or photochemically induced reactions, is believed to be limited.

In sediment and soil PER is fairly mobile and can leach into ground-water. Under these conditions no physico-chemical breakdown has been observed.

PER is not readily biodegradable under standard test conditions. Study results on the aerobic degradation of PER are ambiguous and seem to demonstrate that PER is refractory to aerobic degradation. Under methanogenic, strictly anaerobic conditions, dechlorination and partial mineralisation has been observed.

Bioaccumulation of PER is limited due to its high volatility and high depuration rate. Concentrations in aquatic organisms, with the exception of marine algae and plankton, do not exceed water concentrations by a factor of > 100.

5. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

5.1 ENVIRONMENTAL LEVELS

Present analytical techniques have allowed a more detailed evaluation of the presence and fate of chemicals in the environment and improved controls of emissions over the last decade have led to lower environmental levels of PER. This chapter has therefore concentrated on the more recent publications. Details of environmental PER levels in the USA and Canada can be found in Delzell *et al* (1994).

5.1.1 Atmosphere

Ambient Air

From measurements carried out in all parts of the world it appears that PER is ubiquitous in the troposphere. Global background concentrations range from below the detection limit (0.002 ppb) to 0.01 ppb (0.014 - 0.069 μg/m^3) over the oceans in the Southern hemisphere and from 0.007 to 0.128 ppb (0.048 - 0.882 μg/m^3) over oceans and remote land surfaces in the Northern hemisphere. In rural areas in the Northern hemisphere background concentration range from 0.02 to 0.3 ppb (0.14 - 2.1 μg/m^3). In urban and suburban areas concentrations were found between 0.02 and 3.3 ppb (0.14 - 23 μg/m^3) (Table 8).

Table 8: Background Concentrations in Air

Area	Year of measurement	Average or median concentration (ppb)	Average or median concentration (μg/m^3)[a]	Reference
Remote				
Atlantic ocean (Bermuda)	1985	< 0.002 - 0.003	< 0.014 - 0.021	Class and Ballschmiter, 1986
Atlantic ocean				Class and Ballschmiter, 1986, 1987
Northern hemisphere	1985	0.015 - 0.030	0.10 - 0.207	
Southern hemisphere	1985	0.005 - 0.010	0.034 - 0.069	
Atlantic ocean				Koppmann *et al*, 1993
45 °N	1989	0.013	0.090	
30 °S	1989	0.0027	0.186	
Eastern Pacific ocean				Singh *et al*, 1982
0 - 40 °N	1981 (winter)	0.029[b]	0.20[b]	
0 - 40 °S		0.005[b]	0.034[b]	
Pacific ocean				Atlas *et al*, 1993
15 °N	1990	0.0078	0.054	
10 °S		0.0026	0.018	

Hokkaido (Japan)	1979-1986	< 0.025	< 0.17	Makide *et al*, 1987

Table 8: Background Concentrations in Air (continued)

Area	Year of measurement	Average or median concentration (ppb)	($\mu g/m^3$)[a]	Reference
Northern hemisphere 30 - 90 °N 0 - 30 °N	1982-89	 0.021 0.007	 0.145 0.05	Wiedmann *et al*, 1994
Southern hemisphere 0-90 °S	1982-89	0.002	0.014	Wiedmann *et al*, 1994
Arctic ocean (Norway)	1981-1983	0.075 - 0.081	0.52 - 0.56	Khalil and Rasmussen, 1983; Hov *et al*, 1984
Point Barrow (Alaska)	1981	0.056 - 0.128	0.386 - 0.882	Khalil and Rasmussen, 1983
Subarctic central and eastern Canada	1990	0.012	0.083	Wofsy *et al*, 1994
Madeira, remote oceanic site	1988	0.043	0.296	Frank *et al*, 1991
Rural				
South Germany, Asch	1985	0.029 - 0.26	0.20 - 1.8	Güthner *et al*, 1990
Germany, Berchtesgaden	1990	0.022 (summer)	0.15	Frank *et al*, 1990
Germany, Black Forest	1990	0.15 ($\leq$ 1.5)[b]	1.0 ($\leq$ 10)[b]	Frank *et al*, 1990
Germany, unknown	< 1989	0.1 - 0.3	0.69 - 2.1	UBA, 1989
Germany, Hochgrat Alps, 860 m altitude	1982	0.016[b]	0.11[b]	Kirschner and Ballschmiter, 1983
Netherlands, Isle of Terschelling	1980-1981	0.1 (0.6)[b]	0.69 (4.1)[b]	Guicherit and Scholting, 1985
Netherlands, countryside	1991	0.02 - 0.06	0.14 - 0.41	RIVM, 1993
France, Bretagne	1985	0.02 - 0.027	0.14 - 0.186	Ballschmiter *et al*, 1987; Hecht *et al*, 1987
France	< 1992	0.0004	0.003	Bouchereau, 1992
Finland, countryside	1987	Not detectable	-	Kroneld, 1989a
Madeira	1982	0.09 - 0.027	0.62 - 0.186	Kirschner and Ballschmiter, 1983
Azores, Sao Miguel, 510 m altitude	1982	0.014	0.096	Kirschner and Ballschmiter, 1983
USA, 577 sites	< 1986	0.16	1.1	Eichler and Mackay, 1986

Table 8: Background Concentrations in Air (continued)

Area	Year of measurement	Average or median concentration (ppb)	Average or median concentration ($\mu g/m^3$)[b]	Reference
Urban and suburban				
West Germany, suburban cities	1980-1988	0.029 - 1.1	0.20 - 7.6	Bauer and Gregorzik 1982; Von Düszeln *et al*, 1982; Kubin *et al*, 1989; Frank, 1989
Germany, cities	1986-1987	0.1 - 3.3	0.69 - 23	UBA, 1989; Bruckmann and Kersten, 1988; Kirschmer and Gerlach, 1989; Güthner *et al*, 1990
Netherlands, cities	1979 - 1983	0.1 - 0.38	0.69 - 2.62	Thijsse, 1983; Guicherit and Scholting, 1985
Netherlands, cities	1991	0.06 - 0.11	0.41 - 0.76	RIVM, 1993
France, cities	< 1992	0.22	0.15	Bouchereau, 1992
Italy, Turin (summer) (winter)	1988	0.7 1.97	4.8 13.6	Gilli *et al*, 1990
Belgium, cities	1989	0.19 - 0.29 (1.03)[b]	1.3 - 2.0 (7.10)[b]	Ministerie van Volksgezondheid en Leefmilieu, 1990
Belgium, Tessenderlo	1988-1989	0.14 (0.72)[b]	0.96 (4.96)[b]	Wauters and Verdun, 1989
Portugal, Fonte (near Lisbon)	1988	0.029 - 0.14	0.20 - 0.96	Frank *et al*, 1991
Finland, suburb (Turku city)	1987	11.6	79.9	Kroneld, 1989b
Switzerland	1984	0.02	0.14	Fahrni, 1985
Japan, cities	1979-1986	0.4 - 0.78	2.8 - 5.4	Dohdoh *et al*, 1985; Goto *et al*, 1987; Urano *et al*, 1988
USA, cities	1980-1987	0.06 - 0.68	0.41 - 4.7	Ligocki *et al*, 1985; Sullivan *et al*, 1985; Harkov *et al*, 1985; Singh *et al*, 1982; Wallace, 1991
USA, Southern California	1987-1990	1.74 (2.9)[b]	12.0 (20)[b]	Hisham and Grosjean, 1991

[a] Converted values

[b] Maximum concentration

Makide *et al* (1987) observed seasonal variations in PER concentration in remote areas, with high levels in winter and low levels in summer. The authors suggested that these variations were related to seasonal differences in photochemical activity or differences in longitudinal transport of air masses. Similar findings in urban and suburban areas were reported by Gilli *et al* (1990).

Emissions from industrial production or use of PER may give rise to higher local ambient air concentrations. Average levels of 12 ppb (83 µg/m^3) have been measured in industrial areas in the former West Germany (Bauer and Gregorzik, 1982). In Finland, a level of 20 ppb (138 µg/m^3) of PER was measured in industrial air (Kroneld, 1989b). In the immediate surroundings of a production plant in England in the 1970's, levels were 15 - 40 ppb (103 - 276 µg/m^3) (Pearson and McConnell, 1975). Concentrations of 2.9 - 6.0 ppb (20 - 41 µg/m^3) and 0.15 - 0.75 ppb (1.0 - 5.2 µg/m^3) were measured near production sites in Germany (Selenka and Bauer, 1984) and in Belgium (Wauters *et al*, 1989), respectively.

Relatively high ambient air levels of PER have been measured in the vicinity of waste disposal sites. For example, in New Jersey (USA) levels > 7 ppb (> 48 µg/m^3) were found close to such a site (Harkov *et al*, 1985).

Measurements in the Netherlands showed that under unfavourable climatological and various operating conditions of a dry-cleaning shop, the closest neighbours could be exposed to an average level of up to 23 ppb (158.5 µg/m^3) PER during the hours of maximum processing activity (Monster and Smolders, 1984). PER levels were reported to be as high as 300 - 1,000 ppb (2,067 - 6,890 µg/m^3) near dry-cleaning shops in the former West Germany (Czaplenski *et al*, 1988; Reinhard *et al*, 1989). During working hours, the average concentration of PER measured immediately outside 8 dry-cleaning shops in Essen (Germany) during 1987-88 was 45 ppb (range 4 - 145 ppb) (310; range 28 - 999 µg/m^3) and 11 ppb (range 1 - 49 ppb) (76; range 6.9 - 338 µg/m^3) at the opposite side of the street (Beier *et al*, 1989). In the USA (New York State), average concentrations of 940 µg/m^3 (136 ppb) were measured outside dry-cleaning shops using an (open) transfer system,. Outside dry-to-dry cleaners (closed), the average concentration was 240 µg/m^3 (34.8 ppb) (Schreiber *et al*, 1993) (Table 9).

Table 9: Ambient Air Concentrations near Dry-Cleaning Shops

Area	Year of measurement	Average concentration (ppb)	(µg/m^3)[a]	Reference
Netherlands, closest neighbourhood	1981-1984	≤ 23	160	Monster and Smolders, 1984
Germany	< 1988	300 - 1,000	2,067 - 6,890	Czaplenski *et al*, 1988
Germany, Köln	1987-1989		3 - 138	Reinhard *et al*, 1989
Germany, Essen,	1987-1988			Beier *et al*, 1989
Outside: 8 dry-cleaning shops		4 - 145	28 - 999	
Opposite side of the street:		1 - 49	6.9 - 338	
New York State	1991			Schreiber *et al*, 1993
outside transfer cleaner:		136	≤ 940	
outside dry-to-dry cleaner:		34.8	≤ 240	

[a] Converted values

Precipitation

Rainwater and snow in general contain PER at concentrations of < 0.001 - 0.115 µg/l (Table 10). Concentrations up to 0.15 µg/l PER were found in rainwater collected close to an industrial site with organochlorine manufacture (Pearson and McConnell, 1975).

Table 10: Background Concentrations in Rainwater

Area	Year of measurement	Average concentration (µg/l)	Reference
UK, rainfall	1980	< 0.01	James *et al*, 1980
Germany, rural rainwater	1987-1989	< 0.001 - 0.024	Herrmann, 1987; Kubin *et al*, 1989; Renner *et al*, 1990
Germany, mist	1988	0.080	Kubin *et al*, 1989
Netherlands, 4 locations	1983	< 0.005	Van de Meent *et al*, 1986
Switzerland, Dübendorf, rainwater	1985-1986	< 0.01 - 0.115	Czuczwa *et al*, 1988
Japan, Kobe area	1982	0.050	Tamaoki *et al*, 1983
USA, Los Angeles, rain/snow	1982	0.021	Kawamura and Kaplan, 1983

5.1.2 Surface Water

PER is a common contaminant of surface waters, with average background concentration levels of the order of 0.0001 - 0.0021 µg/l in the open ocean and up to 0.43 µg/l in sea-water near the coast (up to 1.4 µg/l in Japan). Concentrations of PER in rivers may be higher, e.g. in western Europe levels of 0.004 - 2.5 µg/l were found (Table 11).

Table 11: Background Concentrations in Surface Waters

Area	Year of measurement	Average or medium concentration (µg/l)	Reference
Seawater - remote locations			
Gulf of Mexico, open ocean	NS	0 - 0.001 (≤ 0.040)[a]	Sauer, 1981
Eastern Pacific Ocean			
13 - 30 °N	1981	0.0010 - 0.0021	Singh *et al*, 1983
0 - 11 °N	1981	0.0003 - 0.0005	
9 - 39 °S	1981	0.0001 - 0.0004	
North Atlantic	NS	0.00012 - 0.00080	Murray and Riley, 1973; Pearson and McConnell, 1975
Antarctic (Terra Nova Bay)	1990	0.0007	Zoccolillo and Rellori, 1994
Coastal Waters and Estuaries			
Germany, Ostsee	1983	< 0.010 - 0.16	Hellmann, 1984
Germany, Nordsee	1983	0.16 - 0.43	Hellmann, 1984
Germany, Unterweser, lower part	1985-1987	0.050	Bohlen *et al*, 1989
The Netherlands, Rhine-Meuse estuary	1983-1984	0.009 (≤ 0.090)[a]	Van de Meent *et al*, 1986
The Netherlands, Rhine estuary	< 1993	0.0013 - 0.047	Krijssel and Nightingale, 1993
UK, North Sea	1986	< 0.002 - 0.16	Hurford *et al*, 1989
UK, Humber estuary	< 1993	0.00087 - 0.0017	Krijssel and Nightingale, 1993
UK, Humber estuary	1992	0.051 - 0.274	Dawes and Waldock, 1994
UK, Tees estuary	1992	< 0.010 - 0.175	Dawes and Waldock, 1994
UK, Tyne estuary	1992	< 0.025 - 0.0425	Dawes and Waldock, 1994
UK, Poole, Southampton coasts	1992	< 0.025	Dawes and Waldock, 1994
UK, Solent estuary	< 1991	< 0.01 - 0.34	Bianchi *et al*, 1991
Sweden, Arctic sea	1980	0.0069	Fogelqvist, 1985
Sweden, Stenungsund	1988	0.002 - 0.0036	Abrahamsson *et al*, 1989
France, Rhone, delta	1984	0.15 - 0.25	Marchand *et al*, 1988
France, Rhone, delta (surroundings)	1984	0.026 - 0.0006	Marchand *et al*, 1988
France, Lyon, gulf	Unknown	< 0.0005 - 0.0008	Marchand *et al*, 1988
France, Provence, Côte d'Azur	Unknown	0.0011	Marchand *et al*, 1988

Table 11: Background Concentrations in Surface Waters (continued)

Area	Year of measurement	Average or medium concentration (µg/l)	Reference
France, Loire estuary	1983	0.012 - 0.060	Marchand *et al*, 1986
Greece, Thermaikos and Kavala gulf	1984	0.00027 - 0.003	Fytianos *et al*, 1985
Japan, Shizuokaden coastal zone	1985-1987	0.2 - 1.4	Watanabe *et al*, 1989
Freshwater			
Germany, Rhine	1982-1984	0.1 - 0.5	Rippen, 1992
Germany, Emscher, Main	1982-1984	1.3 - 2.5	Rippen, 1992
Germany, Elbe	1988	0.14 - 0.87	Malle, 1990
Germany, Rhine, Main, Lippe, Ruhr, Wupper	1989-1990	0.2 - 2.5	Wittsiepe, 1990
The Netherlands, Rhine, Lobith	1991	0.05	RIVM, 1993
The Netherlands, Meuse, Eijsden	1993	0.3	RIWA, 1995
The Netherlands, Meuse, Keizersveer	1993	0.05	RIWA, 1995
France, Loire	1983-1984	0.004 - 0.02	Marchand *et al*, 1988
Belgium, Meuse, Tailfer	1993	0.1	RIWA, 1995
Finland, Aura river	1985	0.1[a]	Kroneld, 1986
Switzerland, 155 samples river water	1981-1983	0.274	Fahrni, 1985
Switzerland, Glatt, Chimlibach, Chriesbach	< 1984	0.06 - 0.88	Ahel *et al*, 1984

[a] Maximum concentration

Local concentrations of PER may be higher, e.g. in Germany up to 16 µg/l was measured in the River Saale which is contaminated with industrial effluents (Wittsiepe, 1990). Older data show average PER concentrations of 55 µg/l (maximum 120 µg/l) in the River Main near Rüsselsheim (Kußmaul and Mühlhausen, 1981); in Emilia-Romagna (Italy) 48 - 168 µg/l and in the Rhône river (France) 150 - 250 µg/l) (Aggazzotti and Predieri, 1986; Marchand *et al*, 1988). In the USA, PER was found at a level of > 10 µg/l at one out of 204 monitoring sites in 14 heavily industrialised river basins (HSDB, 1987).

PER was found in European sewage treatment plants at levels of 1 - 23 µg/l in the influent and 0.01 - 8.5 µg/l in the effluent. In the USA, levels in the effluent from sewage treatment plants may be higher due to the practice of effluent chlorination (Table 12).

Table 12: Concentrations in Municipal Sewage Treatment Plants

Country, municipality	Year of measurement	Average concentration (µg/l)		Reference
		Influent	Effluent	
France, Toulon	1985	19.8	8.5	Marchand, 1989;
Morlaix		2.0	0.41	Marchand *et al*, 1989
Nantes Nord		7.8 - 18.1	ND	
Nantes Sud		1.05 - 23	0.01 - 0.39	
Germany, Seehausen	1987	NS	0.23 - 3.1	Bohlen *et al*, 1989
Delmenhorst			0.010 - 3.1	
Osterholz			0.220[a]	
Farge, Unterweser			0.03 - 0.08	
Bremerhaven			0.02 - 5.9	
Klockner-Werke, Unterweser			0.09[a]	
Switzerland	1982-1984	NS	0.03 - 6.4	Ahel *et al*, 1984; Fahrni, 1985
UK	NS	NS	2.81	Wilson *et al*, 1994
USA, Baltimore	NS	NS	8 - 129	Helz and Hsu, 1978
USA, STORET database	NS	NS	1 - 10	Staples *et al*, 1985

[a] Maximum
[b] 0.093 mg/kg (dry weight) in digested sewage sludge
[c] Before and after chlorination
ND Not detected
NS Not stated

Industrial effluents (1,390 individual data points) in the STORET database (USA) showed a median concentration of 5 µg PER/l (Staples *et al*, 1985). Industries in which the mean or maximum PER levels exceeded 1,000 µg/l in raw waste-water were dry-cleaning, aluminium forming, metal finishing, organic chemical and plastics manufacturing, and paint and ink formulation. After treatment, all effluents contained < 1,000 µg/l PER (Callahan *et al*, 1979).

In Japan, effluents of factories handling PER contained > 300 µg/l PER in 30% of the samples taken cases (Magara and Furuichi, 1986).

5.1.3 Soil and Sediment

Significant contamination of the soil with PER is a local phenomenon. Median levels of < 5 µg PER/kg soil were reported for soils and sediments in the USA, calculated from 359 data points of the EPA STORET Data Base (Staples *et al*, 1985). In soil samples from rural areas in Germany 0.004 - 0.010 µg PER/kg was found (Renner *et al*, 1990).

In Germany, soil-air concentrations of PER of 0.7 - 4.4 ppb (4.8 - 30 µg/m^3) were found in industrial areas with an ambient air concentration of 4.4 - 44 ppb (30 - 303 µg/m^3) (Neumayr, 1981).

Concentrations of 0.3 - 0.7 ppb (2.1 - 4.8 µg/m^3) PER were measured in soil-air in forest areas in southern Germany; similar levels were found in the ambient air (Frank *et al*, 1989a).

The levels of PER found in groundwater are discussed in Section 5.2.2.

Concentrations of PER ranging from 30 to 6,000 µg/kg were found in the sediment of Liverpool Bay (Pearson and McConnell, 1975) and 18 to 50 µg/kg in the sediment of harbours along the river Rhine (Alberti, 1989) (Table 13).

Table 13: Background Concentrations in Sediments

Country, area	Year of measurement	Average concentration (µg/kg wet weight)	Reference
Germany, sediment			
Rhine, Hitdorf Hafen	1987-1988	18	Alberti, 1989
Rhine, Wesel Hafen	1987-1988	50	Alberti, 1989
UK, Liverpool bay (172 sampling points)	1973	30 - 6,000	Pearson and McConnell, 1975
UK, Solent estuary	<1991	0.085 - 20	Bianchi *et al*, 1991
USA, STORET database (359 data points [a])	< 1985	< 5	Staples *et al*, 1985
Scandinavia	1989-1990	< 10	Pedersen *et al*, 1994

[a] Soils and sediments together

5.1.4 Aquatic Organisms

Molluscs and fish caught in the Irish Sea contained 0 - 176 µg PER/kg and up to 43 µg/kg dry body weight, respectively. PER levels did not exceed 41 µg/kg wet body weight in marine organisms collected from Liverpool Bay and Mersey estuary adjacent to an area with major industrial organochlorine production and use. The PER levels were similar to or only slightly higher than concentrations found in marine organisms of the Thames estuary.

In Finland in 1987, fish for consumption contained average PER levels of 0.3 µg/kg.

PER was found in fish sampled in the river Rhine in 1981; a level of > 100 µg/kg was measured in 4% of the samples.

The available data are detailed in Table 14.

Table 14: Background Concentrations in Marine Biota

Country, area	Year of sampling	Nature of sample	Average concentration (µg/kg wet weight)	Reference
UK, Liverpool Bay and Mersey estuary	1972-1973	Fish	≤ 41	Pearson and McConnell, 1975
UK, Thames estuary	1972-1973	Algae Invertebrates Crab Fish	13 - 22 1 - 9 8 - ≤ 9 0.3 - 41	Pearson and McConnell, 1975
UK, Irish sea	< 1976	Mollusc bodies and organs (3 species) Fish organs (5 species)	0 - 176[a] ≤ 43	Dickson and Riley, 1976
Finland	1987	Fish for consumption	0.3	Kroneld, 1989a,b
Germany, Rhine	1981	69% fish samples 13% fish samples 4% fish samples	 >1 25 - 100 > 100	Binnemann *et al*, 1983
Norway	1981	Fish, 9 marine species	36	ECETOC, 1988
USA, Lake Pontchartrain	1980	Oysters	10	Ferrario *et al*, 1985

[a] Dry weight

5.1.5 Plants

In spruce needles sampled in the Black Forest and the city of Tübingen (Germany) up to 3.5 µg PER/kg was found. In a similar study in UK, needles of conifers were reported to contain 12 to 26 µg PER/kg (Table 15).

Table 15: Background Concentrations in Conifers

Country, area	Year of sampling	Nature of sample	Average concentration (µg/kg dry weight)	Reference
Germany, Black Forest and city of Tübingen	< 1989	Spruce needles	≤ 3.5[a]	Frank and Frank, 1989
UK, Ponsonby and Devilla forests	1993	Pine (*Pinus sylvestris)* needles, top of canopy Needles, middle of canopy	 < 15 - 26 12, 16	Brown *et al*, 1993

[a] Wet weight

5.2 HUMAN NON-OCCUPATIONAL EXPOSURE

5.2.1 Indoor Air

Average indoor-air levels of PER measured in 1985-1990 in some 500 houses in Germany were 2 ppb (range 0.1 - 136 ppb) (14; range 0.69 - 937 µg/m^3) (Seifert, 1990). In northern Italy, mean indoor

levels of 2.6 ppb (range 0.4 - 7 ppb) (18; range 2.8 - 48 µg/m^3) were measured (De Bortoli *et al*, 1986). In the USA in 1990, indoor air average PER concentrations of 28 µg/m^3 (range 6.7 - 103 µg/m^3) (4.1; range 0.97 - 14.9 ppb) were measured (Schreiber *et al*, 1993). In the autumn of 1981 in New Jersey (USA), indoor levels of PER were found to be 3 to 10 times higher than in outdoor air (Wallace *et al*, 1984).

Indoor air levels of PER have been reported to be 2 ppb (14 µg/m^3) in a classroom near a factory and 0.2 - 1.3 ppb (1.4 - 9.0 µg/m^3) in a residential home near a former chemical waste dump site. Alveolar air measurements of the children and residents were 3.6 ppb (controls 0.4 ppb) and 0.3 - 1.1 ppb (25 controls 2.8; and 2.1 - 7.6 µg/m^3), respectively (Monster and Smolders, 1984).

Several studies have evaluated the impact of dry-cleaned clothes on indoor-air quality. Depending on the conditions in the house and the amount of dry-cleaned clothes present, 7-d average concentrations of 23 - 200 µg/m^3 PER (3.3 - 29 ppb) were measured (Table 16). In dry-cleaned clothes, residual PER can be present in concentrations up to 13,600 mg/kg cloth, depending on the type of fibre (Jensen and Ingvordsen, 1977; Kawauchi and Nishiyma, 1989).

Table 16: Indoor Air Concentrations in Homes Resulting from Off-gassing of Dry-cleaned Clothes

Area	Year	Average concentration (µg/m^3)	Average concentration ppb[a]	Remark	Reference
Japan	NS	≤ 7.4[b]	≤ 1.07		Kawauchi and Nishiyma, 1989
USA		200	29.0	7 d	Howie and Elfers, 1981
		740	107.3	Day 1	
		43	6.2	Day 7	
USA	NS	47	6.8	7 d, bedroom	Tichenor *et al*, 1990
		23	3.3	7 d, den	
USA	NS	≤ 100	≤ 14,5		Thomas *et al*, 1991

[a] Converted values
[b] ≤ 13.6 µg PER/g dry-cleaned clothes

Higher indoor concentrations of PER were found in buildings situated close to dry-cleaning shops. When open (transfer-type) cleaners were being operated, average concentrations of 7,700 µg/m^3 (1,117 ppb) were measured. When closed systems were in use (dry-to-dry cleaners), the indoor air level were only 250 µg/m^3 (36.3 ppb) (Table 17).

Table 17: Indoor Air Concentrations in Homes Near Dry-Cleaning Shops

Country, area	Year	Average concentration (ppb[a])	(µg/m^3)	Remark	Reference
USA, New York State	1990	1,117 36.3	7,700 250	Above transfer cleaners Above dry-to-dry cleaners	Schreiber *et al*, 1993
Germany, Köln	≤ 1989	2.5 - 333	17 - 2,296	7 d, 5 homes	Reinhard *et al*, 1989
Switzerland	≤ 1991	14.5	100	1 apartment	Grob *et al*, 1991

[a] Converted values

In Italy, levels of PER ranging from 25 to 9,600 µg/m^3 (3.6 - 1,392 ppb) have been found in 25 private homes of dry-cleaners living far away from their dry-cleaning shops (Aggazzotti *et al*, 1994a,b). In 6 homes of dry-cleaning workers in the USA, indoor concentrations of 21 to 560 µg/m^3 (3.0 - 81.2 ppb) have been reported (Thompson and Evans, 1993).

Consumer exposure to PER may occur through the use of coin-operated Laundromats. The concentration of PER in the air of the customer area of dry-cleaning shops equipped with coin-operated dry cleaning machines was in the range of 36 - 39 ppm (248 - 269 mg/m^3) (NIOSH, 1976; Jensen and Ingvordsen, 1977). In another study in the USA, the average PER concentration was 9,000 µg/m^3 (1,305 ppb) during the summer in 4 coin-operated laundry facilities (Michigan Department of Public Health, 1979). In 6 coin-operated facilities in the USA, PER concentrations (average over 7 days) ranged from 900 to 10,350 µg/m^3 (130.5 - 1,500 ppb) in 5 facilities and were as high as 59,340 µg/m^3 (8,600 ppb) in the remaining facility (Howie and Elfers, 1981).

5.2.2 Drinking Water

A survey of all German water works from 1985-1986 showed that PER was present in 49% of the drinking water supplies. The survey also showed that 14% of groundwater sources were contaminated (Bauer, 1990). An older survey of 230 Dutch groundwater sources revealed that 37.5% were contaminated; the concentration of PER had reached levels above 100 mg/l in 2 cases (Trouwborst, 1981).

Groundwater used for drinking water in Switzerland and Italy contained concentrations of PER at 0.8 µg/l and 7.8 µg/l, respectively (Fahrni, 1985; Aggazzotti and Predieri, 1986).

PER was detected in 30% of shallow or deep drinking-water wells in urban areas of Japan; 4% showed levels of PER in excess of 10 µg/l (Magara and Furuichi, 1986).

Details of the above studies and other data are presented in Table 18.

Table 18: Concentrations in Groundwater and Drinking Water Supplies

Country, area	Year of measurement	Average concentration (µg/l)	Remarks (% of sources)	Reference
Groundwater				
Germany, survey of water works (90% coverage)	1985-1986	> 1 > 10	10% 4%	Bauer, 1990
Germany, Düsseldorf	Around 1986	0.9, 370[a]		Sagunski *et al*, 1987
Netherlands, survey of 230 drinking water sources	< 1981	< 10 > 10 > 100 > 1,000 > 100,000	64.3% 28% 5.2% 1.7% 0.8%	Trouwborst, 1981
Netherlands, Heemstede	1983	0.35	Below flower field at 15 m depth	Teekens, 1985
UK, Birmingham aquifer	1988-1989	NS, max 460	59 samples, 44% positive	Rivett *et al*, 1990
UK, 4 areas, 209 supply boreholes	1984-1985	> 1 > 100	17% 2 samples	Folkard, 1986
France, Val de Marne	1983 1983	ND - 3,300 ND - 63.3	10 m depth 40 m depth	Penverne and Montiel, 1985
Switzerland, 84 sites	1981-1983	0.8, 17.5[a]	-	Fahrni, 1984
Italy, Emilia-Romagna	1983-1984	7.8	-	Aggazzotti and Predieri, 1986
Hungary, water wells	1988	0.18	-	Laszlo, 1989
USA, 51 states	1981-1982	0.35 - 69	945 samples, 79 positive	Westrick *et al*, 1984
USA, Texas, Edward aquifer	1987	0.02 - 0.09	70%	Buszka *et al*, 1990
Japan, urban areas	1982	> 0.2 > 10	30% 4%	Magara and Furuichi, 1986
Japan	1989	< 1	-	Inamori *et al*, 1989
USA, water wells	Unknown	≤ 0.5[b] > 5	97% 0.7 %	US-EPA, 1985

Table 18: Concentrations in Groundwater and Drinking Water Supplies (continued)

Country, area	Year of measurement	Average concentration (µg/l)	Remarks (% of sources)	Reference
Drinking Water				
Germany, survey of water works (90% coverage)	1985-1986	< 0.001[b] 0.001 - 0.5 > 0.5	51% 40% 9%	Bauer, 1990
Italy, Milan	1984	2 - 68		Ziglio *et al*, 1985
Austria, Vienna, 23 areas	1984	0.1, 18[a]		Pfannhauser and Thaller, 1985

[a] Maximum concentration
[b] Detection limit
ND Not detected, detection limit not stated
NS Not stated

5.2.3 Foodstuffs

In the UK, Germany, Finland and USA, average concentrations of PER in dairy products ranged from 0.2 to 13 µg/kg; in lean meat from 0.9 to 5 µg/kg and in edible oils and fats from 0.01 to 7 µg/kg. Foodstuffs such as sauce and jelly and beverages contained < 3.6 µg/kg (Table 19).

Table 19: Background Concentrations in Foodstuffs and Beverages

Area	Year of measurement	Foodstuff	Concentration (µg/kg)	Reference
UK	< 1975	Dairy products Meat Oils, fats Beverages Fruit, vegetables Fresh bread	0.3 - 13 0.9 - 5 0.01 - 7 2 - 3 0.7 - 2 1	McConnell *et al*, 1975
Germany, Hamburg	1987	Butter	0.3 - 0.6	Gulyas *et al*, 1988
Finland, city on south coast[a]	1987	Dairy products Beverages Meat	0.2 0.01 - 0.3 1.1	Kroneld, 1989b
USA, Washington DC[b]	NS	Meats Oils, fats Beverages Dairy products	< 4.6[c] < 13[c] < 0.5[c] < 2.3[c]	Entz and Hollifield, 1982
USA, Washington DC	NS	Chinese style sauce Quince jelly Crab apple jelly Grape jelly Chocolate sauce	2 2.2 2.5 1.6 3.6	Entz and Hollifield, 1982

[a] Ambient air concentration of 0.01 ppb
[b] Seven market baskets
[c] Detection limit

In a market basket survey in the former West Germany, the total daily intake was approximately 90 µg PER from food and beverages (Von Düszeln *et al*, 1982).

In Switzerland, Zimmerli *et al* (1982) observed seasonal variations in the PER concentration in milk between 2.5 and 20 µg/kg during summer and winter, respectively.

Certain surveys of foodstuffs in Germany and Switzerland have shown high levels of PER in meat and eggs. These levels were attributed to the animals having been fed on PER-contaminated forage and the use of PER in animal feed processing (Bauer and Gregorzik, 1982; Zimmerli *et al*, 1982; Vieths *et al*, 1987).

PER was detected in foodstuffs located in houses or supermarkets situated close to poorly operated dry-cleaning shops where ambient air concentrations of PER were high (Reinhard *et al*, 1989). Foodstuffs with a high fat content stored for several weeks under such conditions showed levels of up to 98,000 µg/kg (Vieths *et al*, 1987).

Further details of these studies and other data are presented in Table 20.

Table 20: Concentrations in Foodstuffs and Beverages due to Contamination

Country, area	Year of measurement	Foodstuff	Average concentration (µg/kg)	Remark	Reference
Due to contaminated animal feed					
Germany, various regions of former Western Germany	NS	Lard Butter Milk Eggs Sausage	1,370 50 80 670 260	-	Bauer and Gregorzik, 1982
Switzerland, Bern	1981	Milk Butter and cheese Eggs Meat	10 120 - 500 380 3,500	-	Zimmerli *et al*, 1982
Germany	1981	Dairy products Meat Oils, fats Eggs	2 - 1,200 36 - 319 2 - 44 139	-	Vieths *et al*, 1987
Near dry-cleaning shops					
Germany, Köln (5 houses)	NS	Butter Cream	175 - 1,651 25 - 117	Stored for 7 days 7 days	Reinhard *et al*, 1989
Germany	1981	Coconut butter Margarine Nougat spread Flower Cheese[a] Chocolate Milk Eggs	98,000 ≤ 33,000 21,000 1,370 2,670 4,700 790 440	Stored for several weeks 2 weeks 1 week Several weeks 1 week 3 days 3 days Several days	Vieths *et al*, 1987
UK	1990	Lard, butter	< 10 - 763 < 10 - 75 < 10 < 10 - 16	Adjacent to shop Close Distant Remote	Williams, 1991

[a] Parmesan

5.2.4 Total Exposure

The average total human daily intake of PER from air, food and water in the former West Germany has been estimated to be 113 - 260 µg/person (Bauer 1981b; Bauer and Selenka, 1982; Von Düszeln *et al*, 1982).

When individual human exposure to PER was assessed by measuring its concentration in whole blood, levels ≤ 2.1 µg/l were found in 95% of the population studied (inhabitants of Düsseldorf), suggesting that the actual body burden was lower than that indicated by market basket surveys (Hajimiragha *et al*, 1986). A survey of 250 persons in the USA showed PER levels of 0.7 - 23 µg/l in whole blood (Antoine, 1986). Blood levels of PER in a group of inhabitants of Milan were 57 ± 32 µg/l (controls 27 ± 10 µg/l), the main intake coming from contaminated drinking water which contained > 50 µg PER/l (Ziglio, 1981).

In two studies of persons living close to dry-cleaning shops, blood levels of 7 - 65 µg/l and 20 - 2,500 µg/l PER have been reported (Czaplenski *et al*, 1988; Ohde and Bierod, 1989).

Breath samples from a group of 83 persons of different ages and exposed to a wide range of indoor air concentrations of PER (0 - 108 µg/m^3; 0 - 15.7 ppb) contained 9 ± 5 µg PER/m^3 (1.31 ± 0.73 ppb) (Selenka and Bauer, 1984).

A survey of several hundred residents of New Jersey (USA) showed a median concentration of 14 µg/m^3 (2 ppb) (Wallace *et al*, 1984) or 2 to 30 µg/m^3 (0.29 - 4.4 ppb) (Thomas *et al*, 1991) PER in alveolar air. In some cases, the alveolar air concentration rose to 61 µg/m^3 (8.8 ppb) after dry-cleaned clothes had been brought home.

Analysis of alveolar air of residents living near dry-cleaning shops showed PER concentrations up to 5 mg/m^3 (0.73 ppb) (Table 21).

Table 21: Alveolar Air Concentrations in Humans Living Close to Dry-Cleaning Shops (Verberk and Scheffers, 1980)

Subject location	Geometrical mean concentration	
	(ppb)[a]	(mg/m^3)
Above dry-cleaning shop	0.73	5
Adjacent	0.15	1
Two houses away	0.029	0.2
Across the street	< 0.015	< 0.1

[a] Converted values

The alveolar air of children in a school near a small chemical factory contained 24 µg PER/m^3 (3.5 ppb). The alveolar air of residents living near a former chemical waste dump contained 7.8 µg/m^3 (1.13 ppb) (Monster and Smolders, 1984).

The presence of PER in alveolar air of family members of dry-cleaners suggests that non-occupational exposure exists; the levels measured at home were 272 µg/m^3 (39.4 ppb) for those not attending the premises and 4,111 µg/m^3 (596 ppb) in those who were dry-cleaners (Aggazzotti *et al*, 1994a,b).

Human tissue samples from people living in the areas described in the study of Kroneld (1989b) and Bauer (1981a) were analysed for PER. Kidney, liver, lung adipose and muscle tissues showed average PER concentrations of 0.09 - 0.6 µg/kg in Finland and 3.5 - 14.1 µg/kg in the former West Germany. In a further study conducted in England, somewhat higher levels of PER (0.5 - 29 µg/kg) were found, especially in human fat tissue (McConnell *et al*, 1975).

In the USA, as part of the National Human Adipose Tissue Survey of 1982, a level of > 3 µg PER/kg was found in 62% of the samples (Stanley, 1986).

Concentrations of PER in breast milk have been shown to vary between 0.1 and 4.3 µg/l (Erikson *et al*, 1980; Pellizzari *et al*, 1982). A sample of breast milk taken from a mother one hour after a visit to a dry-cleaning shop contained 10,000 µg PER/l, decreasing to 3,000 µg/l after 24 hours (Jensen and Ingvordsen, 1977).

5.2.5 Environmental and Public Health Standards

The following information on environmental and public health standards is derived from environmental and public standards (Table 22).

Table 22: Environmental and Public Health Standards

Compartment / Country or region	Maximum concentration Mean (unit)	Period	Legal status	Reference
Indoor air	(mg/m^3)			
Europe	5	24 h	Advisory	WHO, 1987[a]
Germany (Federal Republic)	0.1	7 d	Regulatory	Bundesgesetzblatt, 1991[a]
Ambient air	(mg/m^3)			
Japan	0.230	-	Advisory	Government of Japan[a]
Exhaust air	(mg/m^3)			
Germany (Federal Republic)	20[b]	7 d	Regulatory	Bundesgesetzblatt, 1991[a]

Table 22: Environmental and Public Health Standards (continued)

Compartment / Country or region	Maximum concentration Mean (unit)	Period	Legal status	Reference
Food	(µg/kg)			
Germany (Federal Republic)	100		Regulatory	Bundesgesetzblatt, 1989[a]
Drinking water	(µg/l)			
EU	10	-	Regulatory	EC, 1980
Germany (Federal Republic)	10[c]	-	Regulatory	Bundesgesetzblatt, 1993[a]
Czech Republic	10	-	Regulatory	Statni Norma, 1989[a]
USA	5	-	Regulatory	US-EPA, 1991[a]
Japan	10	-	Regulatory	Waterworks Law of Japan, 1992[a]
World	40	-	Advisory	WHO, 1993
Surface water	(µg/l)			
EU	10	-	Regulatory	EC, 1975
Japan	10		Regulatory	Government of Japan[a]
Russia	20		Regulatory	Ministry of Health USSR, 1988[a]
Waste water	(mg/l)			
EU	0.1[d] 0.2[d] 0.5 - 1.25[e] 1 - 2.5[e]	1 month 1 d 1 month 1 d	Regulatory	EC, 1990
USA	0.7	-	Regulatory	US-EPA, 1993
Czech Republic	1[b,d]	-	Regulatory	Sbirka Zakonu CR, 1992[a]
Japan	0.1	-	Regulatory	Government of Japan[a]
Groundwater	(mg/l)			
Netherlands	0.01[f] 40[g]	- -	Regulatory	Veul *et al*, 1997
Soil	(mg/kg)			
Netherlands	0.01[f] 4[g]	- -	Regulatory	Veul *et al*, 1997
	(µg/l)			
Japan	10[f,h]	-	Regulatory	Government of Japan[a]

[a] As cited in IRPTC, 1997
[b] Total volatile halogenated hydrocarbons
[c] Total of 4 chlorinated solvents
[d] From metal degreasing
[e] During PER production, depending on the manufacturing process
[f] Target
[g] Intervention
[h] In eluate from leaching test

5.3 OCCUPATIONAL EXPOSURE

5.3.1 Production and Intermediate Use

Occupational exposure to PER can occur during the manufacture, packing and recycling of the product, its use in dry-cleaning, as a chemical intermediate, in metal degreasing and during its other minor uses, and disposal.

The main route of occupational exposure to PER is via inhalation. A summary of the data available on airborne exposure levels measured in the workplace during various conditions of handling is presented in Table 23. The data suggest that, in general, exposure during manufacture and use as a chemical intermediate is lower than during recycling and disposal.

Table 23: Occupational Exposure Concentrations During Manufacture and Processing
(OECD, 1996)

Process	Number of samples	Mean (ppm)	Range (ppm)	Mean[a] (mg/m^3)	Range[a] (mg/m^3)	Country
Manufacture	837	0.3[b]	ND - 158	2.1	ND - 1,089	UK
	1,408	0.3	0.04 - 0.9	2.1	0.28 - 6.2	Belgium, Germany, Italy, UK
Packing	298	0.5[b]	ND - 274	3.4	ND - 1,888	UK
	501	0.5	< 0.2 - 0.9	3.4	< 1.4 - 6.2	Belgium, Germany, Italy, UK
Recycling	48[c]	2.9 - 11	ND - 35	20 - 76	ND -241	UK
Chemical intermediate	203	0.2	ND - 7.4	1.4	ND - 51	UK
Disposal	7	7.2	-	49.6	-	Finland

[a] Converted values
[b] Geometrical mean
[c] 4 sets of data
ND Not detectable

5.3.2 Dry-Cleaning

Exposure levels of PER in dry-cleaning shops can be found in Table 24 below (most data are taken from epidemiological studies discussed in Section 9.5).

Recent data (1982-94) from Belgium, Finland, Germany, Italy, Switzerland and UK show mean exposure levels of less than 30 ppm PER (207 mg/m^3). Older data (before 1980) from the Netherlands and the UK show higher levels of up to 60 ppm (413.4 mg/m^3) and up to 100 ppm (689 mg/m^3) respectively. In the USA, Ludwig *et al* (1983) and Materna (1985) determined atmospheric concentrations in dry-cleaning shops to be 30 to 1,000 mg/m^3 (4.4 - 145 ppm) time weighted average (TWA) although during loading and unloading short-term (peak) concentrations of 1,000 to 3,500 mg/m^3 (145 - 507.5 ppm) were recorded.

Table 24: Exposure Concentrations in Dry-Cleaning Shops

Country	Year of measurement	No. of shops	No. of workers	No. of samples	Type of sample	Mean (ppm)	Range (ppm)	Mean[a] (mg/m^3)	Range[a] (mg/m^3)	Remark	Reference
Belgium	NS	6	26	NS	Personal	21	9 - 38	145	62 - 262	TWA	Lauwerys *et al*, 1983
Finland	1982-85	6	NS	10	Area	13	3 - 29	89.6	21 - 200	TWA	Rantala *et al*, 1992
France	NS	26	NS	> 100 /shop	NS	NS	0 - 100	-	0 - 689		Davezies *et al*, 1983
Germany	NS	NS	19	55	Personal	9.0 6.2	2.3 - 97.4	62 43	16 - 671	End of week Monday after	Pannier *et al*, 1986
Germany	NS	NS	NS	101	Personal	30	NS	207	NS	TWA	Seeber, 1989
Germany	1987-89	15	NS	75	Area	NS	> 50 > 100 > 200	-	> 344.5 > 689 > 1,378	45% 33% 9%	Gulyas and Hemmerling, 1990
Germany	1993-94	21	NS	100		1	< 0.003 - 4	6.9	< 0.021 - 27.6		Klein and Kurz, 1994
Italy		47	143	NS	NS	11.3	1 - 80.8	78	6.9 - 557		Missere *et al*, 1988
Italy	1992-93	28	60	NS	Personal Area	NS 5.2	0.4 - 32 0.03 - 45	- 36	2.8 - 220.5 0.21 - 310		Aggazzotti *et al*, 1994a,b
Italy	NS	22 13		NS NS	NS	7.3 4.9	0.4 - 31 0.5 - 11	50 34	2.8 - 214 3.4 - 76		Cavalleri *et al* ,1994
Netherlands	1976	1	5	48	NS	6.7	3.7 - 25.9	46	25.5 - 178.5		Van der Tuin and Hoevers, 1977a
Netherlands	1977	1	10	86	NS	41.3	11 - 101	284.6	76 - 696		Van der Tuin and Hoevers, 1977b
Netherlands	1978	1	9	80	NS	59.7	10.0 - 250	411.3	68.9 - 1,723		Van der Tuin, 1979

Table 24: Exposure Concentrations in Dry-Cleaning Shops (continued)

Country	Year of measurement	No. of shops	No. of workers	No. of samples	Type of sample	Mean (ppm)	Range (ppm)	Mean[a] (mg/m^3)	Range[a] (mg/m^3)	Remark	Reference
Netherlands	NS	3	23	46	Personal	7.2 - 51.7[b]	4.6 - 158.7[c]	49.6 - 356[a]	32 - 1,093.4[b]		Monster *et al*, 1983
Switzerland	NS	10	NS	(1 week)	NS	18.5	NS	127.5	-		Boillat *et al*, 1986
Switzerland	NS	1	NS	NS	NS	1.5	NS	10	-		Grob *et al*, 1991
UK	NS	5	NS	14	NS	< 20 < 30 < 100	2.7 - 245	< 138 < 207 < 689	18.6 - 1,688	43% 64% 79%	OECD, 1996
UK	1990-91	81	NS	405	Personal	22.5	0 - 360	155	0 - 2,480		Edmondson and Palin, 1989
UK	NS	90	NS	333	Personal	< 30 < 50 < 100	NS	< 207 < 344.5 < 689	-	74% 88% 97%	Shipman and Whim, 1980
UK	NS	41	NS	160	Personal	< 30 < 50 < 100	NS	< 207 < 344.5 < 689	-	53% 76% 93%	Shipman and Whim, 1980
USA	NS	44	NS	323	Personal	5.7 – 76	0.1 - 366	39 - 523.6	0.69 - 2,522	TWA	Ludwig *et al*, 1983
USA	1982	37	NS	37	Personal	28.2 - 86.6	3.0 - 303	194.3 - 597	20.7 - 2,088	TWA	Materna, 1985

[a] Converted values
[b] Reported as 300 - 2,150 µmol/m3
[c] Reported as 190 - 6,600 µmol/m3
TWA Time-weighted average
NS Not stated

5.3.3 Metal Degreasing

Few data are available on exposure to PER from metal degreasing in Europe. Measurements made in Finland between 1982-85 in five plants manufacturing printing plates showed an average exposure level of 9.6 ppm (66 mg/m^3) with concentrations ranging from 3 to 19 ppm (21 - 131 mg/m^3). In three other plants where PER was used for metal degreasing the average exposure level was 3 ppm, range 1.8 - 5 ppm (21; 12.4 - 34.5 mg/m^3) (Rantala *et al*, 1992).

Exposure levels of 5.2 ± 4.8 ppm (36 ± 33 mg/m^3) and 10.1 ± 6.3 ppm (69.6 ± 43.4 mg/m^3) PER have been reported in two metal cleaning operations in Finland (OECD, 1996).

Monster *et al* (1983) conducted a survey in a Dutch metal cleaning shop where 9 male workers were exposed to a TWA concentration of 2 ppm (14 mg/m^3) of PER dissolved in 1,1,1-trichloroethane (5:95). The authors found a good correlation between the concentration of PER in blood and exhaled air, and TWA exposure. The correlation with other parameters (metabolites in blood and urine) was influenced by the presence of 1,1,1-trichloroethane.

5.3.4 Occupational Exposure Limits

The occupational exposure limits adopted by different countries are presented in Table 24. The TWA concentration in almost all countries varies from 170 - 340 mg/m^3 (25 - 50 ppm) for an 8-h working day, except for Denmark, Sweden and Egypt where limit values of 70 mg/m^3 (10 ppm) and 35 mg/m^3 (5 ppm) have been adopted.

Table 25: Occupational Exposure Limits

Country	8-h TWA		STEL			Reference
	(ppm)	(mg/m^3)[a]	(ppm)	(mg/m^3)[a]	Duration (min)	
Australia	50	335	150	1,005	NS	IARC, 1995
Austria	50	345	-	-	-	DFG, 1997
Belgium	25	170	100	685	15	ACGIH, 1996
Brazil	-	525	-	-	-	IARC, 1995
Canada (Saskatchewan)	50	335	54	420	5	IARC, 1995
Chile	-	536	-	-	-	IARC, 1995
China	100	610	-	-	-	IARC, 1995
Czech Republic	-	250	-	1,250	NS	IARC, 1995
Denmark	30	200	-	-	-	Arbejdstilsynet, 1988

Table 25: Occupational Exposure Limits (continued)

Country	8-h TWA		STEL			Reference
	(ppm)	(mg/m^3)[a]	(ppm)	(mg/m^3)[a]	Duration (min)	
Egypt	5	35	-	-	-	ACGIH, 1996
Finland, 1987	50	335	75	520	15	ACGIH, 1996
France	50	340	-	-	-	INRS, 1993
Germany	50	345	100	690	30	BMA, 1995
Hungary	-	-	-	50	-	ACGIH, 1996
Indonesia	-	670	-	-	-	IARC, 1995
Italy	25	170	100	100	15	ACGIH, 1996
Japan, 1989	50	340	-	-	-	IARC, 1995
Mexico	100	670	200	1,340	15	SSA, 1984
Netherlands	35	240	-	-	-	Arbeidsinspectie, 1995
Norway	20	130	-	-	-	Arbeidstilsynet, 1995
New Zealand	25	170	100	685	15	ACGIH, 1996
Poland	-	60	-	-	-	IARC, 1995
Romania	-	400	-	500	NS	IARC, 1995
Russian Federation	50	340	-	10	NS	IARC, 1995
Singapore	25	120	100	685	15	ACGIH, 1996
USA	25	170	100	685	15	ACGIH, 1996
USA (OSHA)	100	678	200[b]	1,356[b]	170	IARC, 1995
Sweden	10	70	25	170	-	AFS, 1996
Switzerland	50	345	100	690	30	Suva, 1997
Thailand	100	-	200	-	NS	ACGIH, 1996
UK	50	335	150	1,000	-	HSE, 1995
Venezuela	-	670	-	1,000	NS	IARC, 1995

[a] Official values, some countries use different conversion factors and/or other ambient temperature
[b] Ceiling value
TWA Time-weighted average concentration (8-h working period)
STEL Short-term exposure limit
NS Not Stated

5.3.5 Biological Monitoring

Exposure to PER is mainly by inhalation, but it has been shown that dermal absorption can contribute. As it is excreted partly unchanged, PER may be measured directly in exhaled air and in blood. The main metabolites, TCA and trichloroethanol, can also be traced in blood or urine (Chapter 7).

PER has a long half-life in humans. It is therefore recommended to sample at least 2 days after exposure and before the shift. Influences such as heavy workload, obesity or high physical activity have to be taken into account (ACGIH, 1996).

Data on biological monitoring in exhaled air, blood or urine of workers occupationally exposed to PER can be found in Table 26, 27 and 28.

The US ACGIH and German MAK Commission (Table 29) have recommended biological Exposure Indices (BEI) and Tolerance Values (BAT).

Table 26: Biological Monitoring of PER in Exhaled Air

Workplace air					Exhaled air (breath)					Reference
Number of samples	Mean (ppm)	Range (ppm)	Mean[a] (mg/m^3)	Range[a] (mg/m^3)	Number of samples	Mean (ppm)	Range (ppm)	Mean[a] (mg/m^3)	Range[a] (mg/m^3)	
26	20.8	8.9 - 37.5	143	61 - 258.4	26	1.9[b] 5.1[c]	0.1 - 5.5[b] 0.2 - 10[c]	13[b] 35[c]	0.69 - 38[b] 1.4 - 69[c]	Lauwerys *et al*, 1983
7	NS	48 - 629	-	331 - 4,334	7	NS	6.3 - 50.4[c]	-	43.4 - 347.3[c]	Ohtsuki *et al*, 1983

[a] Converted values
[b] Pre-shift
[c] Post-shift
NS Not stated

Table 27: Biological Monitoring of PER in Blood

Number of subjects	Concentration in air				Concentration in blood		Reference
	Median (ppm)	Range (ppm)	Median[a] (mg/m^3)	Range[a] (mg/m^3)	Median (µmol/l)	Range (µmol/l)	
50	14.8	0 - 85	102	0 - 585.7	0.86	0.05 - 5.4	Mutti *et al*, 1992
18	NS	33 - 53	-	227.4 - 365	8.93	4.76 - 79.97	Skender *et al*, 1991
26	20.8[b]	8.9 - 37.5	143[b]	61 - 258.4	2.4[c] 7.2[d]	0.6 - 4.8[c] 2.4 - 8.7[d]	Lauwerys *et al*, 1983
27	NS	1.6 - 20.9	-	11 - 144	NS	0.6 - 8.5	Kostrzewski and Jakubowski, 1985
35	NS	0.1 - 31	-	0.69 - 214	NS	0.06 - 7.8	Triebig and Schaller, 1986

[a] Converted values
[b] Average concentration
[c] Pre-shift
[d] Post-shift
NS Not stated

Table 28: Biological Monitoring of PER and Its Metabolites in Urine

Number of subjects	Concentration in air (range) (ppm)	(mg/m^3)[a]	Concentration (µmol/l) of PER in urine	Trichloroethanol in urine (µmol/l)	TCA in urine (µmol/l)	Reference
34	0 - 400	0 - 2,756	-	0 - 394	0 - 624	Ikeda *et al*, 1972
18	33 - 53	227.4 - 365	-	- 0.73[b]	0.81 - 10.81[b]	Skender *et al*, 1991
40	0 - 7	0 - 48	0 - 1.3	-	-	Ghittori *et al*, 1987
61	629 max	4,334	-	-	Up to 1.114[c]	Ohtsuki *et al*, 1983
26	8.9 - 37.5	61 - 258.4	-	-	0	Lauwerys *et al*, 1983
35	0.1 - 31	0.69 - 214	-	-	0.1 - 6.2[b]	Triebig and Schaller, 1986

[a] Converted values
[b] mmol/mol creatinine
[c] µmol/ total trichloro compounds

Table 29: BEI and BAT Recommended Biological Action Levels

Biological Media	Biological exposure Index (BEI)	Biological tolerance value (BAT)	Sampling strategy	Reference
Concentration in end-exhaled air	10 ppm (69 mg/m^3)		Prior to last shift of work week	ACGIH, 1996
Concentration in blood	1 mg/l (6 µmol/l)		Prior to last shift of work week	ACGIH, 1996
TCA in urine	7 mg/l (42 µmol/l)		At end of work week	ACGIH, 1996
Concentration in alveolar air		9.5 ppm (65.5 mg/m^3)	Beginning of next shift	DFG, 1997
Concentration in blood		1 mg/l (6 µmol/l)	Beginning of next shift	DFG, 1997

5.4 SUMMARY OF EXPOSURE DATA

PER is widely dispersed in all environmental compartments. In the air, it has been found up to 0.1 ppb over oceans and remote areas and up to 3 ppb (21 µg/m^3)in suburban or urban air. In the proximity of areas of production and dry-cleaning facilities, concentrations up to 40 ppb (275.6 mg/m^3) and from 300 to 1,000 ppb (2,067 - 6,890 mg/m^3) have been reported.

In the water compartment, background levels of PER are of the order of 0.0001 µg/l in oceans and 2.5 µg/l in fresh water (urban areas). Concentrations greater than 10 µg/l PER have been found in water in industrialised areas as well as in municipal waste-water treatment plants.

In soils and sediments, levels reported are generally lower than 5 µg/kg but may be higher in contaminated areas. Concentrations of PER in aquatic organisms and plants are generally below 40 µg/kg.

Average measured concentrations of PER in indoor air of the order of 10 to 20 µg/m^3 (1.5 - 2.9 ppb) have been reported. Levels up to 7,100 µg/m^3 have been measured in buildings situated close to dry-cleaning facilities. Also, customers of dry-cleaning establishments, who are potentially exposed to PER by entering the shop and handling fabrics containing residual PER, may be exposed to concentrations up to 700 µg/m^3 (101.5 ppb).

A survey of drinking waters showed that levels were generally lower than 10 µg/l for both surface and ground water. In some cases following environmental releases, significantly higher levels up to 1,000 µg/l (mainly in ground water) have been reported. Average concentrations of PER in foodstuffs are reported to range from 0.2 to 13 µg/kg, although levels as high as 98,000 µg/kg have been reported in certain circumstances, especially in products with a high fat content. A market basket survey estimated a total daily intake of 90 µg PER/person. Estimates of the average total daily intake of PER range from 113 to 260 µg/person.

Concentrations of PER in workplace air during its production and use as a chemical intermediate are relatively low (0.3 to 11 ppm; 2.1 - 76 mg/m^3, TWA). In dry-cleaning facilities, TWA concentrations of PER up to 30 ppm (mean value; 207 mg/m^3) have been reported.

In most industrialised countries, an occupational exposure limit for PER in the range of 25 - 50 ppm (170 - 345 mg/m^3) (8-h TWA) is recommended. In some countries, biological exposure indices (BEI) have been proposed in order to evaluate workplace exposure.

6. EFFECTS ON ORGANISMS IN THE ENVIRONMENT

6.1 MICRO-ORGANISMS

The EC_{10} for growth inhibition of the bacteria *Pseudomonas putida* was 51 mg PER/kg soil (wet weight) after exposure for 16 hours (Knie *et al*, 1983).

Soil respiration in the presence of added glucose was inhibited by 45% following treatment with 2,000 mg/kg PER (wet weight). Nitrification was slightly affected after 28 days following treatment with > 40 mg PER/kg (wet weight) (Vonk *et al*, 1986).

Treatment of brown soil with PER decreased the adenosine triphosphate (ATP) content. While there was no effect at a concentration of 0.1 mg PER/kg soil (dry weight), there was a significant effect at 1 mg/kg and 10 mg/kg soil (dry weight). Recovery from these effects took 2 months (Kanazawa and Filip, 1987).

Danneberg (1993) studied the effect of PER on the dehydrogenase activity in soil micro-organisms. Two concentrations were tested: 0.5 and 5 mg/kg soil (dry weight). On day 0 an increase (42 - 62%) of the dehydrogenase activity was found; on day 14 there was a decrease (11 - 18%) and on day 28 a further increase (6 - 13%). The data show that no consistent effect was observed.

6.2 AQUATIC ORGANISMS

6.2.1 Acute Toxicity

The high volatility of PER presents experimental difficulties in conducting aquatic toxicity tests. Flow-through systems or closed static systems are necessary to maintain exposure concentrations and conduct adequate toxicity studies. These conditions have not always been met (for details see tables below).

Growth inhibition has been observed in methanogenic bacteria; the EC_{50} was 22 mg PER/l. Other bacteria are less sensitive with an EC_{50} of 89 to 1,904 mg/l. Exposure of certain protozoa, rotatoria and oligochaeta to PER revealed effects on growth when exposed to 13 mg/l and higher. PER was lethal when tested on midge larvae (*Tanytarsus dissimilis*) at 31 mg/l (Table 30).

Table 30: Acute Toxicity to Lower Aquatic Organisms

Description	T (°C)	pH	Dissolved O_2 (mg/l)	Hardness (mg $CaCO_3$/l)	Test system	Time (h)	Effect/ Parameter	Concentration (mg/l)	Reference
Bacteria							**Growth inhibition**		
Nitrosomas sp.	NS	NS	NS	NS	NS	24	EC_{50}	112	Blum and Speece, 1991
Aerobic heterotrophic sp.						24	EC_{50}	1,904	
Methanogenic sp.						24	EC_{50}	22	
Photobacterium phosphoreum	10	NS	NS	NS	Microtox	10 min	EC_{10}	89	Bazin *et al*, 1987
Protozoa									
Tetrahymena pyriformis	30	NS	NS	NS	Static, closed	24	EC_{50}	100	Yoshioka *et al*, 1986
Colpoda sp. (activated sludge)	20	NS	NS	NS	Static, closed	NS	EC_{50}	64	Inamori *et al*, 1989
Rotatoria									
Philodina erythrophthalma (activated sludge)	20	NS	NS	NS	Static, closed	NS	EC_{50}	33	Inamori *et al*, 1989
Oligochaeta									
Aelosoma hemprichi (activated sludge)	20	NS	NS	NS	Static, closed	NS	EC_{50}	13	Inamori *et al*, 1989
							Lethality		
Insects									
Midge larvae (*Tanytarsus dissimilis*)	20	7.5	9 - 10	46.4	Static	48	LC_{50}	31	US-EPA, 1980

NS Not stated

The acute toxicity of PER to *Daphnia magna* has often been studied. The EC_{50} values ranged from 3.2 to 147 mg/l. No observed effect concentrations (NOECs) were determined between 0.5 and 10 mg/l. Intermediate EC_{50} values were determined in two other crustaceans (Table 31).

Barnacle larvae (*Elminius modestus*) appeared to be particularly sensitive to the effects of PER, with an LC_{50} of 3.5 mg/l (Table 32). The LC_{50} values of PER for various fish species range from 5 mg PER/l for dab (*Limanda limanda*) and rainbow trout (*Oncorhynchus mykiss*) to 130 mg/l for golden orfe (*Leuciscus idus*).

In a flow-through test with fathead minnow (C*yprinodon variegatus*), the 96-h LC_{50} was 18.4 mg PER/l. The results were similar to those obtained with a static system, where the LC_{50} was 21.4 mg/l (nominal concentration). The observed effects (loss of equilibrium, melanisation, narcosis, swollen and haemorrhaging gills) were reversible at a sublethal level. The 96-h EC_{50} for these effects was 14.4 mg/l (Alexander *et al*, 1978). Other authors reported 96-h LC_{50} values of 13.5 and 23.8 mg PER/l for the same species (Table 32).

Table 31: Acute Toxicity to Crustacea

Species	T (°C)	pH	Dissolved O_2 (mg/l)	Hardness (mg $CaCO_3$/l)	Test system	Time (h)	Effect/ Parameter	Concentration[a] (mg/l)	Reference
Crustacea							**Immobility**[b]		
Water flea (*Daphnia magna*)	NS[c]	NS[c]	NS[c]	NS[c]	Static, nominal concentration	24	EC_{50}	3.2	Bazin *et al*, 1987; Devillers *et al* , 1987
Water flea (*D. magna*)	22 ± 1	8.0	6.5 - 9.1	173	Static, nominal concentration	48 48	LC_{50} NOEC	18 10	Le Blanc, 1980; Hermens *et al*, 1985 US-EPA, 1980
Water flea (*D. magna*)	20 - 22	7.6 - 7.7	> 2	70	Static	24 24	EC_0 EC_{50}	65 147	Bringmann and Kühn, 1982
Water flea (*D. magna*)	20	7.1 - 7.7	7.9 - 9.9	43.5 - 47.5	Static	48 48 48	LC_{50} EC_{50} NOEC	9 - 18 7.5 - 8.5 0.5	Richter (unpublished data) as quoted in Walbridge *et al*, 1983
Water flea (*D. magna*)	NS[d]	NS[d]	NS[d]	NS[d]	Static	48 48	EC_0 EC_{50}	7 22	Knie *et al*, 1983
Water flea (*D. magna*)	NS	NS	NS	NS	NS	24	EC_{50}	8.5	Call *et al*, 1983
Moina macrocopa	20	NS	NS	NS	Static	3	EC_{50}	63	Yoshioka *et al*, 1986
Mysid shrimp (*Mysidopsis bahia*)	22 ± 1	NS	NS	NS	Static, closed, nominal concentration	96	EC_{50}	10.2	US-EPA, 1980

[a] Calculated using the analytically determined concentration in the water
[b] Some papers refer to IC_{50} (immobilisation concentration)
[c] Carried out according to AFNOR T90-301 (1974)
[d] Carried out according to DIN 38412 (1982)

Table 32: Acute Toxicity to Fish and Shellfish

Species	T (°C)	pH	Dissolved O_2 (mg/l)	Hardness (mg $CaCO_3$/l)	Test system	Time (h)	Effect/ Parameter	Concentration[a] (mg/l)	Reference
Fish							**Lethality**		
Sheepshead minnow (*Cyprinodon variegatus*)	25-31	NS	NS	10 - 31	Static, open	96 96	LC_{50} NOEC	29 - 52 29	Heitmuller *et al*, 1981[i]
Rainbow trout (*Oncorhynchus mykiss*[b])	12	7.1	8.2	44	Flow-through (1x/2 h)[c]	96	LC_{50}	5	Shubat *et al*, 1982
Fathead minnow (juvenile) (*Pimephales promelas*)	25±1	6.7 - 7.6	7.6 - 9.2	45	Flow-through[d] (10x/d)	96	LC_{50}	13.4 13.5	Walbridge *et al*, 1983 Veith *et al*, 1983
	25±0.5	7.6±0.2	> 8	45	Flow-through[d] (1x/2-4 h)	96	LC_{50}	23.8	Broderius and Kahl, 1985
Fathead minnow (adult)	12	7.8 - 8.0	> 5	> 5.0	Semi-static[e] Flow-through[e], nominal concentration	96 96	LC_{50} LC_{50}	21.4 18.4	Alexander *et al*, 1978
American flagfish (*Jordanella floridae*)	NS[f]	NS[f]	NS[f]	NS[f]	Static[f] Flow-through[g]	96 96	LC_{50} LC_{50}	24 8.4	Smith *et al*, 1991
Bluegill sunfish (*Lepomis macrochirus*)	21 - 23	6.5 - 7.8	7.0 - < 8.8	32 - 48	Static[h], open, no aeration, nominal concentration	96	LC_{50}	13	Buccafusco *et al*, 1981
Golden orfe (*Leuciscus idus*)	NS[j]	NS[j]	NS[j]	NS[j]	NS	96 96	LC_{50} LC_{50}	130 81	Knie *et al*, 1983
Red killifish (*Oryzias latipes*)	20	NS	NS	80	Static, nominal concentration	48	LC_{50}	39.8	Yoshioka *et al*, 1986

Table 32: Acute Toxicity to Fish and Shellfish (continued)

Species	T (°C)	pH	Dissolved O_2 (mg/l)	Hardness (mg $CaCO_3$/l)	Test system	Time (h)	Effect/ Parameter	Concentration[a] (mg/l)	Reference
Mussel							**Lethality**		
Barnacle larvae (*Elminius modestus*)	NS	NS	NS	NS	Static, control of volatility	48	LC_{50}	3.5	Pearson and McConnell, 1975
	NS	NS	NS	NS	Flow-through, no aeration	96	LC_{50}	5	Pearson and McConnell, 1975

[a] Calculated using the analytically determined concentration in the water
[b] Formerly *Salmo gairdneri*
[c] Lake Superior water with and without dimethylformanide as carrier solvent
[d] Lake Superior Water
[e] Dechlorinated, sterilised Lake Huron water. Methyl- or ethyl alcohol was used as the carrier solvent.
[f] Carried out according to US-EPA, 1975
[g] Dechlorinated Lake Superior Water
[h] De-ionised, reconstituted freshwater
[I] No aeration. Nominal concentrations. Juvenile fish.
[j] Carried out according to DIN 38412 (1982)
NS Not Stated

The lowest 72-h EC_{50} value for growth of freshwater algae (*Chlamydomonas reinhardii*) was found to be 3.64 mg PER/l (Brack and Rottler, 1994). The uptake of carbon dioxide by *Phaeodactylum tricornutum* became affected from 10.5 mg/l (EC_{50}). A decrease of 13% in ^{14}C-uptake as a measure for photosynthetic activity was seen in estuarine phytoplankton exposed to 2 mg/l PER, but not at 1 mg/l (Table 33).

Table 33: Acute Toxicity to Algae

Species	Method	Time (h)	Effect/ Parameter	Concentration (mg/l)	Reference
			Growth inhibition		
Marine					
Phaeodactylum tricornutum	CO_2 uptake	NS	EC_{50}	10.5	Pearson and McConnell, 1975
Skeletonema costatum	Chlorophyll-*a* content Cell number	96	EC_{50}	500	US-EPA, 1980
Estuarine phytoplankton[a]	^{14}C uptake	48 48	LOEC NOEC	2.0[b] 1.0[c]	Erickson and Hawkins, 1980
Freshwater					
Selenastrum capricornutum	Chlorophyll-*a* content Cell number	96	NOEC	816	US-EPA, 1980
Haematococcus pluvialis	O_2 production inhibition	4	EC_{10}	> 36	Knie *et al*, 1983
Chlamydomonas reinhardii	Cell number	72 72	EC_{50} LOEC	3.64 1.77	Brack and Rottler, 1994

[a] Including *Chlorophyceae, Cyanophyceae* and *Bacillariophyceae* (23 - 37 mg/l dry weight or suspended solids)
[b] Flow-through (1 x/h)
[c] Nominal concentration
NS Not Stated

6.2.2 Chronic Toxicity

In a 28-d reproduction study in *Daphnia magna* effects of exposure to PER were seen at 1.1 mg/l; the NOEC was 0.5 mg/l. Marked differences in growth of nauplii of the brine shrimp (*Artemia salina*) were observed, compared to controls, when exposed to 0.25 to 25 mg PER/l (Table 34).

In tests with larvae, fry and adults of various fish species, the lowest observed effect concentration (LOEC) ranged from 0.1 to 5.83 mg PER/l; the LC_{50} for the guppy (*Poecilia reticulata*) was 17.8 mg/l (Table 34).

The chronic toxicity of PER towards two species of algae and one triclad was relatively low, with EC_{50} values from 8 to > 16 mg/l (Table 34).

Testing over the life cycle of the mysid shrimp (*Mysidopsis bahia*) resulted in a NOEC of 0.45 mg PER/l. In the same study, a LOEC of 0.84 mg/l was reported for embryos to juveniles of the fathead minnow (*Pimephales promelas*). Insufficient details are available to allow an evaluation (US-EPA, 1980).

Table 34: Chronic Toxicity to Aquatic Organisms

Species	T (°C)	pH	Dissolved O_2 (mg/l)	Hardness (mg $CaCO_3$/l)	Test system	Time (d)	Effect/ Parameter	Concentration (mg/l)	Reference
Crustacea							**Reproduction**		
Water flea (*Daphnia magna*)	20	6.6 - 7.9	5.4 - 8.9	43 - 48	Semi-static	28	LOEC NOEC	1.1 0.5	Call *et al*, 1983; Richter *et al*, 1983
							Growth inhibition		
Brine shrimp, nauplii I-III (*Artemia salina*)	25	NS	NS	NS	NS	1 - 2	Teratogenic effect	0.25 - 25	Kerster and Schäffer, 1983
Tricladida							**Lethality**		
Dugesia japonica	20	NS	NS	NS	Static	7 7	EC_{50} LC_{50}	8 25	Yoshioka *et al*, 1986
Fish									
Fathead minnow, larvae (*Pimephales promelas*)	NS	NS	NS	NS	NS	NS	MATC[a]	1.4 - 2.8	Walbridge *et al*, 1983
American flagfish, larvae (*Jordanella floridae*) fry	25	6.95	> 9	44.9	Flow-through, closed	10 10 28 28	LOEC NOEC LOEC NOEC	4.85 1.99 5.82 2.34	Smith *et al*, 1991
Guppy (*Poecilia reticulata*)	22	NS	> 5	25	Semi-static	7	LC_{50}	17.8[b]	Könemann, 1981
Black molly (*P. sphenops*)	NS	NS	NS	NS	Semi-static, nominal concentration	60	LOEC	1.6	Loekle *et al*, 1983
Goldfish *(Carassius auratus)*	NS	NS	NS	NS	Static	180	LOEC	0.1	Loekle, 1987

Table 34: Chronic Toxicity to Aquatic Organisms (continued)

Species	T (°C)	pH	Dissolved O_2 (mg/l)	Hardness (mg $CaCO_3$/l)	Test system	Time (d)	Effect/ Parameter	Concentration (mg/l)	Reference
Algae							**Growth inhibition**		
Skeletonema costatum	NS	NS	NS	NS	NS	7	EC_{50}	>16	Erickson and Freeman, 1978
Scenedesmus subspicatus	NS	NS	NS	NS	NS	7	EC_3	> 250	UBA, 1986

[a] Maximum acceptable toxicant concentration, i.e. geometric mean of NOEC and LOEC
[b] 30.9 calculated following QSAR
NS Not stated

6.2.3 Ecosystems

A study was designed to determine the effects of PER on the phyto- and zooplankton community of two experimental freshwater ponds at measured initial concentrations of 0.44 and 1.2 mg/l. A residual concentration of 0.1 mg/l was reached after 5 days in the low-dose pond and after 36 to 38 days in the high-dose pond. Small differences in toxic effects were seen between the low and high dose levels.

At both concentrations, a lethal effect on *Daphnia* was observed, the effect occurring within 4 days (low dose) and within 3 hours to 2 days (high dose). The phytoplankton community showed an increase in relative abundance and a decrease in species diversity. The autotrophic species, *Spirogyra* sp., *Microcystis flos aquae*, *Stichococcus bacillaris* and *Nitzschia acicularis,* showed either a direct or an indirect sensitivity to PER, whereas the heterotrophic and/or mixotrophic species, *Chilomonas paramecium* and *Actinophrys* sp., increased in total numbers (Lay *et al*, 1984).

PER was tested for approximately 11 weeks at average measured concentrations of 0, 0.8 and 1.6 mg/l in a 1,000-litre enclosure within a natural pond. The overall biomass of plankton, algae and microfauna increased, but populations of individual species (certain green algae, *Culex*, crustacea and rotifers) decreased when compared to the control enclosure. The mean LC_{50} values for certain individual species were lower than in laboratory tests. For example, the LC_{50} for *Daphnia pulex* and *Cryptomonas* was 0.3 mg/l after 12 to 15 hours, effects being seen at concentrations as low as 0.01 mg/l. The productivity of phytoplankton, expressed as ATP, chlorophyll and primary production per cell, was also significantly reduced when compared to the control population (Lay and Herrmann, 1989).

A decrease of 13% in ^{14}C-uptake as a measure for photosynthetic activity was seen in estuarine phytoplankton exposed to 2 mg/l PER, but not at 1 mg/l (Table 34, Erickson and Hawkins, 1980).

6.2.4 Sewage Treatment Plants

PER has been found to inhibit the anaerobic fermentation of sewage sludge by up to 50% at 3 g/kg sludge (dry weight) (Schefer, 1981a,b) and, in a second study, up to 20% at 70 g/kg (Benson and Hunter, 1977).

6.3 TERRESTRIAL ORGANISMS

6.3.1 Invertebrates

Two different studies were conducted with the earthworm, *Eisenia foetida*. The respective LC_{50} values were 945 mg/kg (Römbke *et al*, 1991) and 100 - 320 mg/kg soil (wet weight) (Vonk *et al*, 1986) (Table 33). The lower LC_{50} values in the latter study can be explained by the renewal of the soil (and

test substance) and the use of closed systems, which resulted in a higher exposure to PER. In the study by Vonk *et al* (1986), the effect on the production of cocoons occurred at concentrations ≥ 18 mg PER /kg soil, although the appearance of the worms was not affected. Römbke *et al* (1991) also reported the toxicity of PER to the carrabid beetle (*Poecilus cupreus)* which had a 14-d NOEC of 5 mg/kg and to the spring tail (*Folsomia candida*) which had a 1-d LC_{50} of 113 mg/kg and a NOEC of 10 mg/kg soil. The overall NOEC for soil organisms is considered to be approximately 5 mg/kg soil.

Table 35: Toxicity to Terrestrial Organisms

Species	Parameter (effect)	Time (d)	Concentration (mg PER/kg soil)	Reference
Eisenia foetida	LC_{50} (lethality)	14	100 - 320[a]	Vonk *et al*, 1986
	NOEC (production of cocoons)	28	≤ 18	
	NOEC (appearance of worms)	28	18 - 32	
E. foetida	LC_{50}	14	945	Römbke *et al*, 1991
	NOEC (mortality, weight and behaviour)	14	577	
Folsomia candida	LC_{50} (lethality)	1	113	Heimann and Harle, 1993
	NOEC (lethality)	1	10	
Poecilus cupreus	NOEC (lethality)	14	5.0[b]	Römbke *et al*, 1993
	NOEC (lethality)	17	3.0[c]	
Avena sativa	EC_{50} (growth)	16	580	Bauer and Dietze, 1992
	NOEC (growth)	16	100[d]	
	NOEC (sublethal effects)	16	1[e]	

[a] Wet weight
[b] One application. A reduction of the feeding rate of 18% was found
[c] Six applications. A reduction of the feeding rate of 14% was found
[d] The ratio between the concentrations was 10
[e] Dry weight

6.3.2 Plants

Frank and Frank (1986) suggested that, upon exposure to light, halogenated hydrocarbons might damage the photosynthetic apparatus of conifers. They reported that, within 2 days of exposure to 40 μg/m^3 PER (5.8 ppb) under intensive UV radiation, the needles of *Picea abies* were bleached. Similar effects were also reported for the sun-exposed leaves of a hornbeam shrub (*Carpinus betulus* and also the spruce (*Picea omorica*), exposed to 1.72 ppb PER (11.85 mg/m^3) over a 7-month period, in which bleaching of chlorophyll in the *in-situ* sunlit twigs was reported to occur. The authors attributed the damage to the herbicidal action of TCA formed by the transformation of PER exposed to UV radiation. Alternatively, the authors have suggested that TCA is formed in the leaves after absorption of the lipophilic PER by the cuticle.

Further studies by Schröder and Weiss (1991) with *Picea abies* under normal light conditions and exposure to 25 ppb PER (172 mg/m^3) for 24 hours showed reversible effects on photosynthesis as well as on respiration and transpiration. The pigment content of the needles was not affected.

Bauer and Dietze (1992) studied the early development of lettuce (*Avena sativa*, Table 33) exposed to PER for 16 days to concentrations ranging from 1 to 1,000 mg/kg soil (dry weight). The NOECs for growth and sublethal effects were respectively of 100 and 1 mg/kg and the 16-d EC_{50} (growth) as 580 mg/kg soil (dry weight).

6.4 SUMMARY

In the aquatic environment, all trophic levels show similar sensitivity to the acute toxic effects of PER, with the lowest acute LC_{50} and EC_{50} values occurring in the range of 1 to 10 mg/l. In validated studies, the lowest LC_{50} for freshwater fish (rainbow trout, *Oncorhynchus mykiss*) is 5 mg/l (96-h LC_{50}), similar values being obtained for marine fish species. LC_{50} values for *Daphnia magna* are reported from 8.5 mg PER/l. EC_{50} values for freshwater and marine algae are reported at higher levels (> 500 mg/l).

In fish, chronic exposure to PER does not increase its toxicity significantly. In a study with guppies (*Poecilia reticulata*), the 7-d LC_{50} was 17.8 mg/l (estimated to be 30.9 mg/l by means of QSAR). The survival rates of black mollies (*Poecilia sphenops*) exposed to 1.6 mg PER/l for 60 days was 17%. Studies with embryos and larvae of the fathead minnow (*Pimephales promelas*) and American flagfish (*Jordanella floridae*) resulted in effects at concentrations of 1.4 and 1.99 mg PER/l and above, respectively.

In ecosystems in natural ponds, *D. magna* proved to be more sensitive to PER than under laboratory conditions, with acute lethal concentrations around 0.3 mg/l. Chronic exposure of crustacea to PER induced effects on reproduction at concentrations of 0.25 mg/l and above. The NOEC for PER in a validated 28-d study in *D. magna* was 0.5 mg/l.

At concentrations ranging from 0.1 to 1.6 mg/l, the effects of PER on aquatic phytoplankton are limited to a decrease in species diversity and productivity. No adverse effects on the aquatic ecosystem have been reported at concentrations of PER below 0.1 mg/l.

Several soil organisms, including micro-organisms, invertebrates and plants, have been used to assess the toxicity of PER after acute or prolonged exposure. Most of these studies have been conducted in non-standard conditions. NOECs are of the order of 1 mg/kg soil (dry weight). Effects have been reported following exposure to PER at concentrations starting from 10 mg/kg for one plant species or 18 mg/kg for earthworms (*Eisenia foetida*). It is suggested that PER may have an adverse

effect on the photosynthetic apparatus of conifers and other higher plants following exposure, for example, to 1.7 ppb PER for 7 months.

Based on its octanol-water partition coefficient, no significant bioaccumulation of PER is expected. Measured bioconcentration factors for PER in freshwater fish were found to be < 100 (range 26 - 77). Bioconcentration factors in sea-water have been estimated to be < 100 in fish liver, bird's eggs and seal blubber. Concentrations of PER in marine algae and plankton have been shown to be < 180 times higher than the concentrations in sea-water. Thus, there is no evidence of biomagnification of PER along the food chain.

7. KINETICS AND METABOLISM

7.1 IN HUMANS

7.1.1 Oral

Human volunteers received 330 μg PER orally by eating 5 eggs fried in oil containing PER. Measurement of the PER concentration in alveolar air showed that the PER was exhaled with a half-life of approximately 6.5 hours (Selenka and Bauer, 1984).

7.1.2 Dermal

Healthy volunteers were exposed via the dermal route by immersing one thumb for 30 minutes in a beaker of PER closed by a membrane. The concentration of PER in samples of exhaled air taken during and up to 5 hours after exposure, was determined by means of GC; a peak concentration of 0.30 ppm (2.1 mg/m^3) was measured 1 hour after exposure (Stewart and Dodd, 1964). The authors concluded that, under the conditions of the experiment, no toxicologically significant amount of PER could have been absorbed through the skin.

The percutaneous absorption of PER vapour was studied by exposing ten healthy volunteers to a vapour concentration of 600 ppm (4,134 mg/m^3) for 3.5 hours in a dynamic exposure chamber. Pulmonary absorption was prevented by the use of respiratory protection. Peak PER concentrations of approximately 800 μg/l in blood and 8 mg/m^3 (1.16 ppm) in expired air were determined by GC immediately after exposure. Exhalation kinetics were similar to those observed following inhalation exposure (Section 7.1.3), with a three-phase elimination curve and half-lives of 1, 6 and 72 hours. Based on the assumption that 98% of the absorbed PER is exhaled, the authors calculated an overall percutaneous absorption of 284 pmol, i.e. 47.1 mg/person after 3.5 hours (Riihimäki and Pfäffli, 1978).

7.1.3 Inhalation

There are only limited data on the uptake and distribution of PER in humans following inhalation. An experimental study was conducted in 17 volunteers exposed (7 h/d) by inhalation to 100 ppm PER vapour (689 mg/m^3) for 5 days (Stewart *et al,* 1970). The kinetic behaviour was analysed by measuring concentrations of PER in expired air. The authors claimed that a state of equilibrium, in which the amount of PER excreted or metabolised was equal to the absorbed amount, was not achieved during the 5 days of exposure. Monitoring of the concentration in expired air showed that PER was predominantly excreted unchanged via the lungs, approximately 70% of the inhaled amount being excreted in the first 24 hours after exposure. Accumulation of PER in the body was indicated by the fact that it took more than 14 days for the remaining 30% of inhaled PER to be excreted via the lungs. Skender *et al* (1991) measured levels of PER and TCA in blood, and TCA in urine, of 18 dry-

cleaning workers exposed to between 33 and 53 ppm PER (227.4, 365 mg/m^3). Samples were taken before work on Monday and after work on Thursday. The most reliable biological indicator of exposure was considered to be PER in blood since TCA levels remained almost constant throughout the working week.

The toxicokinetic behaviour of PER in humans following inhalation exposure under experimental conditions has been studied using a simplified two-compartment model. The two compartments were defined as (i) well perfused tissues (e.g. liver, heart) with rapid blood flow and (ii) well perfused splanchnic tissues with slower blood flow. The duration of exposure ranged from 1 to 60 minutes and the concentration of PER in inhaled air from 0.5 - 10 ppm (3.4 - 68.9 mg/m^3). The kinetic behaviour was recorded by measuring the concentration of PER in exhaled (alveolar) air, during and immediately after exposure, and during a subsequent period of 10 days. Analysis of the data showed biphasic kinetic behaviour with a rapid initial drop of alveolar PER concentrations (half-life in the order of minutes), followed by a slow concentration decrease (half-life in the order of days). The authors suggested that the second, slow, phase was due to PER accumulation in deeper compartments, such as adipose tissue. Further examination revealed that the fast initial kinetic phase is again divided into two subphases with an initial decrease of the alveolar concentration (half-life: 15 - 25 s), followed by a stationary phase (approximately 1 - 3 min) and a subsequent concentration decrease at a slower rate (half-life not determined). The authors claimed that this behaviour was caused by large differences in blood circulation times for the two compartments of their model (Opdam and Smolders, 1986, 1987).

Personal monitoring of human beings exposed to atmospheric PER, by means of analysis of their urine for total trichlorinated compounds (trichloroethanol and TCA), showed that urinary metabolite levels increased linearly with external PER concentrations < 100 ppm (< 689 mg/m^3). A plateau in metabolite excretion in humans was apparent when the external exposure was high, indicating that metabolic saturation occurs at approximately 100 ppm (Ikeda *et al,* 1972; Ohtsuki *et al*, 1983). Ohtsuki *et al* (1983) calculated that, at the end of an 8-h shift with exposure to 50 ppm PER (344.5 mg/m^3), approximately 38% of the inhaled dose would have been exhaled unchanged and < 2% transformed to urinary metabolites; the remaining 60% would be eliminated later. Following inhalation, the mean half-life of exhaled PER was 79 min (Benoit *et al*, 1985). The half-life of TCA in urine and blood was 65-90 hours (Monster *et al,* 1983).

The excretion of urinary metabolites has been studied in one male and one female dry-cleaning worker exposed to PER at a mean concentration of 50 ppm (344.5 mg/m^3) for at least 8 h/d, 5 d/wk and in 2 females exposed to the same concentration for 4 h/d, 5 d/wk. Urine samples were taken at the end of the work shift on a Monday afternoon and again at the end of the workshift on the following Friday. PER was detected in urine from all 4 individuals, day 1 levels ranging from 18.7 to 26.9 nmol/mg creatinine. TCA was only detected in the urine of those exposed to PER for at least 8 h/d, day 1 levels being 21.7 and 40.7 nmol/mg creatinine. In addition, the mercapturic acid derivative,

N-acetyl-*S*-(1,2,2-trichlorovinyl)-L-cysteine, was detected in the urine of all 4 individuals on day 5. The levels detected ranged from 2.2 to 6.0 pmol/mg creatinine in those exposed for 4 h/d and from 10.4 to 14.6 pmol/mg creatinine in those exposed for at least 8 h/d. It is believed that the mercapturic acid derivative is the consequence of the metabolism of PER by GSH transferase, as has been seen in the rat (Birner *et al*, 1998).

7.2 IN EXPERIMENTAL ANIMALS

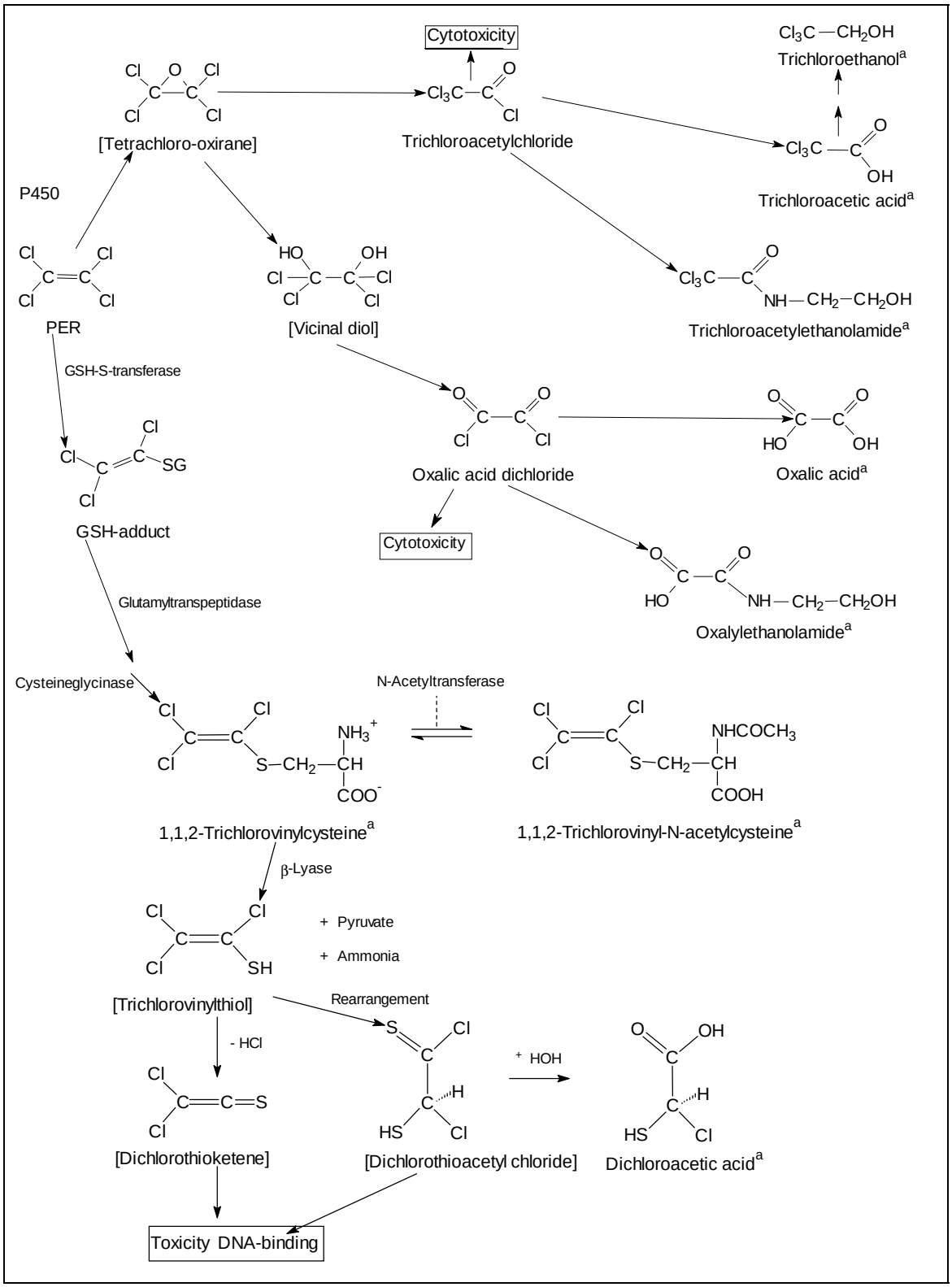
7.2.1 Dermal

The whole-body dermal absorption of PER has been investigated in rats. Animals with closely-clipped fur were exposed to vapour concentrations of 12,500 ppm (86,130 mg/m^3) for 4 hours, while breathing fresh air through a mask. Peak blood concentrations, determined by GC, were approximately 35 µg/l at the end of the 4-h exposure period. A physiologically-based pharmacokinetic (PBPK) model was used to predict a dermal permeability constant of approximately 0.67 µg/cm^2/h for PER, consistent with the experimental blood concentration (McDougal *et al,* 1990). The authors compared the animal data with the data on human percutaneous absorption from the study by Riihimäki and Pfäffli (1978) (Section 7.1.2). Using the PBPK-model, a permeability constant of 0.17 µg/cm^2/h for absorption of PER through human skin was calculated. The authors concluded that, for a range of chemicals including PER, rat skin permeability constants were consistently 2 to 4 times greater than constants for human skin, probably due to physiological differences in the skin of the two species.

7.2.2 Inhalation

PER is metabolised in rodents by cytochrome P450 enzymes, predominantly to TCA. A number of minor metabolites arising from this pathway have also been identified. A second, minor, pathway has been described in the rat involving conjugation of PER with GSH and processing through the mercapturic acid pathways leads to the excretion of mainly *N*-acetyl-*S*-(1,1,2-trichlorovinyl)-L-cysteine in urine. Further details of the pharmacokinetics and metabolism of PER via these pathways have been reviewed earlier (ECETOC, 1990); the metabolic pathways are shown in Figure 1.

Figure 1: Review of the Oxidative and Reductive Biotransformation of PER
(after DFG, 1988)



[a] Identified urinary metabolites
[ ] Theoretical intermediates
GSH Glutathione

Since the ECETOC (1990) review, the following studies have been published. Exposure of rats to PER has been shown to result in the formation of dichloro- and trichloro-acetyl adducts at the lysine residues of renal and hepatic proteins (Birner *et al*, 1994). The *N*-trichloroacetyl adduct is presumed to be derived from trichloroacetyl chloride, an intermediary metabolite in the cytochrome P450 metabolism of PER. The *N*-dichloroacetyl adducts, which occurred predominantly in the kidney, were also found following intravenous administration of the PER metabolite, *S*-(1,1,2-trichlorovinyl)-L-cysteine, suggesting that these adducts are formed by the action of renal β-lyase. *N*-acetyl-*S*-(1,2,2-trichlorovinyl)-L-cysteine has been shown to undergo S-oxidation in liver fractions from male, but not female rats (Werner *et al*, 1996). The resulting sulphoxide is reported to be cytotoxic to rat renal epithelial cells *in vitro* without further metabolic activation. However, at the present time, this metabolite has not been observed *in vivo* and a possible contribution towards the renal toxicity of PER in the rat has not been established.

7.3 KINETIC MODELS

Guberan and Fernandez (1974) developed a PBPK model based on the division of the body into 4 physiological compartments, i.e. a blood vessel-rich group corresponding to brain, heart etc., a muscle group corresponding to muscles and skin, a fat group corresponding to adipose tissue and a blood vessel-poor group composed of connective tissue. The authors predicted that an 8-h exposure of humans to 100 ppm PER would result in a body burden of 1,000 mg of the solvent for a 70 kg person, of which 50% would be distributed to the fat tissue. More recent multi-compartment models which include metabolism have used the PBPK approach to describe the uptake, metabolism and elimination of PER in a number of species (Rao and Brown, 1993; Dallas *et al*, 1994a,b,c).

A significant number of models of this type have been developed for cancer risk assessments (Hattis *et al,* 1986; Reitz and Nolan, 1986; Bogen and McKone, 1987; Ward *et al*, 1988; Travis *et al;* 1989), including two (Hattis *et al,* 1986; Travis *et al*, 1989) which include risk calculations (Appendix C). Several publications have considered the precision and sensitivity of these models (Farrar *et al*, 1989; Hattis *et al*, 1990; Bois *et al*, 1990; Gearhart *et al*, 1993). A further use of this type of model has included a description of the lactational transfer of PER in rats (Bysczkowski and Fisher, 1994; Bysczkowski *et al*, 1994) and humans (Bysczkowski and Fisher, 1995).

All these models have used data from the published literature to derive metabolic constants for either rodents or humans. The models provide an estimate of the dose metabolised by the cytochrome P450 pathway but do not include a description of the GSH pathway that is now known to exist in rodents. They have concentrated on the calculation of total metabolised dose from applied dose, by gavage or inhalation, and on extrapolation between species based on differences in physiology. None of them yet provide a full description of the pharmacokinetic behaviour of PER, its metabolism by two pathways, and the pharmacokinetics of the metabolites.

7.4 EVALUATION

The major pathway of PER metabolism in all species, including humans, is cytochrome P450 mediated oxidation to TCA. Significant species differences have been observed. In both humans and rats, the oxidative pathway appears to be saturated following exposure to atmospheric concentrations above approximately 100 ppm, since no increase in metabolite (TCA) excretion has been found at higher exposure concentrations. In contrast, the TCA level in the blood of mice continues to increase with the external dose of PER, indicating that the oxidative metabolism is not saturated following exposure to concentrations up to 400 ppm, the highest concentration tested. After oral administration, saturation of the cytochrome P450 pathway was observed in mice at doses above 200 mg/kgbw (roughly equivalent to 1,000 ppm/6 h; 6,890 mg/m^3/6 h).

A second minor pathway involving conjugation of PER with GSH has been identified in the rat. The resulting GSH-conjugate is metabolised to a mercapturic acid derivative, which is excreted in the urine. This metabolite could subsequently be activated by renal β-lyase to intermediates that react with proteins. *In vitro* studies have failed to provide evidence for GSH conjugation of PER in humans (ECETOC, 1990).

It is believed that the mercapturic acid derivative seen in humans exposed to PER (Birner *et al*, 1998) is the consequence of the metabolism of PER by GSH transferase, as has been seen in the rat. In comparison, therefore, the rates of metabolism of PER by the P450 pathway, as assessed by measuring urinary levels of TCA and trichloroethanol, were over 3 orders of magnitude higher than those for the GST pathway in humans. In rats, the ratio of utilisation of these two pathways is approximately 2 orders of magnitude, with the P450 pathway being dominant. The low levels of the mercapturic acid derivative excreted suggests that this pathway accounts for only a small proportion of the metabolism of PER in humans. Furthermore, humans metabolise PER less efficiently by GSH conjugation than rats, supporting previous findings (Green *et al*, 1990) that the risk of renal toxicity in humans from this pathway is significantly lower than that in rats.

The results of all published studies based on pharmacokinetic models are in good agreement. Following inhalation, PER is readily absorbed and distributed in the human body and approximately 70% of the inhaled dose is excreted via the lungs in the first 24 hours after exposure. A part of the inhaled dose is accumulated in the adipose tissue and is exhaled with a long half-life (> 10 d). Furthermore these studies show that, due to a lack of sensitivity of the method for measuring PER concentration in alveolar air, the amount of metabolised PER could not be quantified since no difference between the amount of inhaled and exhaled PER was detected.

Thus, measurement of the excretion of TCA in urine would seem to be the most appropriate method for determining the metabolised fraction of a given PER dose. This was shown in studies with

personal monitoring of exposure to atmospheric PER accompanied by analysis of urine for total trichlorinated compounds (trichloroethanol and TCA). At the end of an 8-h shift with exposure to 50 ppm PER, Ohtsuki *et al* (1983) calculated that approximately 38% of the inhaled dose would have been exhaled unchanged and less than 2% transformed to urinary metabolites; the remaining 60% would be eliminated later. The urinary metabolite levels increased linearly with external concentrations of PER up to 100 ppm (689 mg/m^3). Metabolite excretion was apparently reaching a plateau when the external exposure was higher, indicating that in humans metabolic saturation occurs at approximately 100 ppm (Ikeda *et al,* 1972; Ohtsuki *et al,* 1983).

A number of kinetic models have been developed for PER, several based on a PBPK approach. The models, in general, describe toxicological risk in terms of total metabolised dose and extrapolation between species using species specific physiology. None of the models yet provides a full description of the pharmacokinetic behaviour of PER and consequently are not entirely satisfactory for the prediction of the carcinogenic or other toxicological risks to man.

8. EFFECTS ON EXPERIMENTAL ANIMALS AND *IN VITRO* TEST SYSTEMS

8.1 ACUTE TOXICITY

8.1.1 Oral

Details of the findings of lethality in acute oral toxicity studies with PER are presented in Table 36.

Table 36: Acute Oral Toxicity

Species, sex	Effect / Parameter	Dose (mg/kgbw)	Remark	Reference
	Lethality			
Rat M F	LD_{50}	3,005 3,835	Ataxia and CNS depression preceding death	Hayes *et al*, 1986
Rat M F	LD_{50}	≥ 2,200 2,440	Tremors	Withey and Hall, 1975
Rat M	LD_{50}	4,460		Pozzani *et al*, 1959
Mouse M	LD_{50}	7,814		Wenzel and Gibson, 1951
Mouse	LD_{50}	8,100		Dybing and Dybing, 1946
Mouse	-	6,022-7,528 7,528	No deaths All animals died within 2 - 9 h	Lamson *et al*, 1929
Rabbit	-	4,517 7,528	No deaths All animals died within 7 - 20 h	Lamson *et al*, 1929
Dog	-	3,000, 6,000	No deaths during 7 d observation	Barsoum and Saad, 1934

Only in a few, limited studies have the acute toxic effects other than death following oral exposure of experimental animals to PER been described. Tremors, ataxia and depression of the CNS preceding the death of rats exposed to high levels of PER (≥ 2,200 mg/kgbw) have been reported (Hayes *et al*,1986).

There is some evidence of fatty changes in the liver (without changes in levels of relevant serum enzymes) and of decreases in cardiac and respiratory rates in dogs receiving ≥ 286 mg /kgbw PER (Christensen and Lynch, 1933).

8.1.2 Dermal

Results and details of acute dermal toxicity studies are presented in Table 37.

Table 37: Acute Dermal Toxicity

Species	Effect / Parameter	Dose (mg/kgbw)	Remark	Reference
	Lethality			
Mouse	LD_{50}	5,000		Plaa *et al*, 1958
Rabbit	LD_{50}	10,000		Wolf, 1956
Rabbit	-	2,200	Minimum lethal dose	Barsoum and Saad, 1934

Microscopic examination of livers of mice treated dermally under occluded patch with 2,800 - 6,000 mg PER/kgbw showed cytoplasmic vacuolation and alterations in staining of centrilobular cells, but no necrosis (Plaa *et al*, 1958; Osani, 1967).

8.1.3 Inhalation

Results and details of acute inhalation studies are presented in Table 38.

Table 38: Acute Inhalation Toxicity

Species, sex	Effect / Parameter	Duration (h)	Concentration (ppm)	(mg/m^3)[a]	Remark	Reference
	Lethality					
Rat	-	4	2,328 - 5,163	16,040 - 35,570	All animals died after exposure to 5,163 ppm; no deaths at 2,445 ppm	NTP, 1986
Rat M	LC_{50}	6	4,100	28,250		Bonnet *et al*, 1980
Rat F	LC_{50}	8	5,027	34,640		Pozzani *et al*, 1959
Rat M	LC_{50}	4	4,000	27,560		Carpenter *et al*, 1949
Mouse	-	4	2,328 - 3,786	16,040 - 26,090	All animals died after exposure to 2,971 or 3,786 ppm; no deaths at 2,445 ppm	NTP, 1986
Mouse	LC_{50}	6	2,978	20,520		Duprat and Bonnet, 1979
Mouse	LC_{50}	4	5,200	35,830		Friberg *et al*, 1953

[a] Converted values

Animals exposed to PER by inhalation died as a consequence of respiratory failure following CNS depression (narcotic or anaesthetic effects) (Section 8.9).

Effects on the Liver

Small increases in liver weight, slight cloudy swelling and elevated total lipids were seen in Wistar rats 24 hours after exposure to near lethal concentrations of PER (> 2,000 ppm (13,780 mg/m^3) for up to 14 hours (Rowe *et al*, 1952). Increased levels of acetone in expired air, a possible indicator for enhanced lipid peroxidation, occurred when Wistar rats were exposed to ≥ 110 ppm PER (≥ 758 mg/m^3) for up to 25 hours (Filser and Bolt, 1980; Filser *et al*, 1978, 1982).

Moderate fatty degeneration of the liver was observed in female mice at 24 hours and 72 hours following a single 4-h exposure to PER concentrations of > 400 ppm (> 2,756 mg/m^3) and at 24 hours following a single 4-h exposure to 200 ppm (1,378 mg/m^3) (Kylin *et al*, 1963). Increased triglyceride levels were also observed in female mice (Cb strain) in time-course studies following 3-h exposure to 800 ppm (5,512 mg/m^3); total lipids reached maximum levels at 8 hours, but were still elevated at 20 hours post-exposure. ATP levels in the liver decreased rapidly during exposure to 800 ppm, continued to decrease until 8-h post-exposure and returned to normal levels by 20 hours (Ogata *et al*, 1968).

A dose-related increase in the levels of marker enzymes for hepatic damage was found in the serum of male CD1 rats immediately following exposure to PER for 4 hours. Aspartate aminotransferase (AST) and ornithine carbamoyl transferase (OCT) levels were increased following exposure to 500 ppm PER (3,445 mg/m^3) (the lowest dose examined); alanine aminotransferase (ALT) and glucose-6-phosphatase were elevated at levels ≥ 1,000 ppm, (6,890 mg/m^3) for at least 48 hours after cessation of the exposure (Drew *et al*, 1978). Significantly elevated AST levels were found in approximately 50% of mice exposed to 3,700 ppm PER (25,490 mg/m^3) for 7 - 8 hours (Kylin *et al*, 1963; Gehring, 1968).

Cardiac Effects

Following exposure of conscious New Zealand White rabbits to 5,200 ppm PER (35,830 mg/m^3) for 1 hour, the heart became sensitised to arrhythmias induced by doses of noradrenaline (≤ 3 mg/kgbw) (Carlson, 1975). Exposure of dogs to concentrations of 5,000 or 10,000 ppm PER (34,450 or 68,900 mg/m^3) for 10 minutes did not result in cardiac sensitisation to adrenaline (Reinhardt *et al*, 1973).

8.1.4 Intraperitoneal

Results are presented in Table 39.

Table 39: Acute i.p. Toxicity

Species, sex	Effect / Parameter	Dose (mg/kgbw)	Reference
	Lethality		
Mouse	LD_{50}	4,600	Klaassen and Plaa, 1966
	LD_{50}	5,700	Gehring, 1968
Dog	LD_{50}	3,200	Klaassen and Plaa, 1967

Minor histopathological changes (enlarged hepatocytes with cellular infiltration and vacuolation) have been shown in the livers of Sprague-Dawley rats, guinea pigs and dogs following i.p. doses of 2 - 4 g PER/kgbw. Serum levels of liver enzymes were increased in the rat (≥ 400 mg/kgbw), mouse, guinea pig (≥ 200 mg/kgbw) and in the dog (Klaassen and Plaa, 1966, 1967; Gehring, 1968; DiVincenzo and Krasavage, 1974). Toxic effects on the kidney have been reported at high i.p. dose levels in the mouse and the dog (Plaa and Larson, 1965; Klaassen and Plaa, 1966, 1967). Histopathological examination of Swiss mice treated with 3,800 mg/kgbw (a near-lethal dose) showed swelling of the proximal convoluted tubules in all animals, with more than 50% of the tubules affected in 67% of the animals. Protein was seen in the urine of mice 24 hours after dosing with 3.8 or 7.5 g PER/kgbw (Plaa and Larson, 1965).

8.1.5 Intravenous

Results are presented in Table 40.

Table 40: Acute i.v. Toxicity

Species, sex	Effect / Parameter	Dose (mg/kgbw)	Remark	Reference
	Lethality			
Dog	-	85	Minimal lethal dose; death due to respiratory failure	Barsoum and Saad, 1934
Cat	-	81.4	Median lethal dose	Hobara *et al*, 1981

Superoxide dismutase (SOD) activity was markedly reduced in heart, lung and liver, spleen, kidney, brain, muscle, small intestine and pancreas of dogs anaesthetised by pentobarbitone following i.v. injection of 50 mg PER/kgbw. There were no significant changes in the blood levels of this enzyme (Hobara *et al*, 1981).

Studies in the dog, rabbit and cat showed that single i.v. doses of PER (10 - 24 mg/kgbw) caused a sensitising effect to noradrenaline-induced cardiac arrhythmias (Kobayashi *et al*, 1982).

8.1.6 Summary

PER exhibits low acute toxicity by all routes of administration, excepting the i.v. route. Death is due to respiratory failure following CNS depression.

Effects on the liver of various animal species occur at ≥ 200 ppm (1,378 mg/m^3) by inhalation and at ≥ 400 mg/kgbw i.p. Renal effects in mice are seen following high parenteral doses (> 3,000 mg/kgbw i.p.).

Cardiac sensitisation to catecholamine-induced arrhythmias is observed in rabbits, but not in dogs, following exposure by inhalation to 5,200 ppm PER (35,830 mg/m^3) and in the rabbit, dog and cat following i.v. administration of 10 - 24 mg/kgbw.

8.2 IRRITATION, SENSITISATION AND IMMUNOTOXICITY

8.2.1 Skin Irritation

PER was reported to be a severe irritant to the skin of rabbits following application of 0.5 ml under an occlusive dressing for 24 hours (Duprat *et al*, 1976). A study in New Zealand White rabbits, carried out according to the then current OECD and EEC guidelines and using a semi-occlusive dressing also showed severe skin irritation. The primary irritation index for PER in this latter study was 5.7 on a scale of 0 to 8 (Van Beek, 1990).

Application of 1 ml of PER to the guinea pig skin under an occlusive dressing for more than 15 minutes caused severe karyolysis, oedema, spongiosis and pseudo-eosinophilic infiltration at the site of application (Kronevi *et al*, 1981).

8.2.2 Respiratory Irritation

The respiratory irritation potential of PER was investigated in rats exposed to approximately 10,000 ppm (68,900 mg/m^3) for 25 minutes (Janssen, 1990). Respiratory frequencies were measured before, during and after exposure in a protocol similar to that proposed by Alarie (1981). No decrease in respiratory rate was found and it was concluded that under the test conditions PER was not irritating to the respiratory tract. On the contrary, an increase of the respiratory rate was found and interpreted as being due to a systemic effect on the nervous systems.

8.2.3 Eye Irritation

Liquid PER was irritant when instilled into the rabbit eye (Torkelsson and Rowe, 1981). Application of PER (0.1 ml) to the rabbit eye caused a mild to medium discharge with epithelial damage that was reversible (Duprat *et al*, 1976). The authors concluded that PER was a mild eye irritant.

8.2.4 Sensitisation

Skin Sensitisation

The skin sensitising potential of PER was investigated in a group of 9 male guinea-pigs using the split adjuvant technique. No skin sensitisation was observed in any of the test animals (Rao *et al*, 1981).

Respiratory Sensitisation

No data are available.

8.2.5 Effects on the Immune Function

Following an aerosol challenge of viable *Streptococcus zooepidemicus*, a group of 140 female CD1 mice that had been previously exposed to 50 ppm PER (344.5 mg/m^3) for 3 hours showed a significant increase in mortality when compared to controls. A corresponding decrease in pulmonary resistance to inhaled *Klebsiella pneumonia* was also observed. No effects were seen in mice exposed to 25 ppm PER (172 mg/m^3) for 3 hours, either as a single exposure or following 5 daily exposures (Aranyi *et al*, 1986). The significance of these findings for human health hazard assessment is unclear.

Rats exposed to 2.8 ppm PER (19 mg/m^3) continuously for 94 days gave a negative result in the haemagglutination test suggesting the absence of an immunological response to PER (Bonashevskaya *et al*, 1977; Tsulaya *et al*, 1977).

8.2.6 Evaluation

PER is a severe skin irritant when applied under occlusive or semi-occlusive dressings; it is a mild eye irritant. PER is not a skin sensitiser and no significant effects on the immune function have been described.

8.3 SUBCHRONIC TOXICITY

8.3.1 Oral

Details of subchronic oral toxicity studies are given in Table 41.

Table 41: Oral Toxicity following Repeated Exposure

Species, strain / Route	Number of animals, sex[a]	Dose (mg/kgbw/d)	Exposure regime, duration	Result	Reference
Gavage					
Rat, Sprague-Dawley	NS	0, 500	NS, 12 d	No effects on liver histopathology, liver to body weight ratio or DNA synthesis	Schumann *et al*, 1982
Rat, Wistar	NS	0, 16 - 405	5 d/wk, 4 wk	At 405 mg/kgbw increased liver weight and aniline hydroxylase activity; no histopathological changes; NOEL = 16 mg/kgbw	De Vries *et al*, 1982
Mouse, Swiss-Cox	12 - 15 M/group	0, 20, 100, 500, 1,000, 1,500 or 2,000	5 d/wk, 6 wk	Increased relative liver weights and triglyceride levels at ≥ 100 mg/kgbw/d; ALT activity increased at ≥ 200 mg/kgbw/d; histopathological changes in liver at 200 and 1,000 mg/kgbw/d. NOEL = 20 mg/kgbw/d	Buben and O'Flaherty, 1985
Mouse, $B6C3F_1$	NS	0, 500	1 x/d, 12 d	Histopathological changes in the liver; increased relative liver weights; 82% increase in liver DNA synthesis	Schumann *et al*, 1982
Drinking water					
Rat, Sprague-Dawley	5 M, 5 F/group	0, 14, 400 or 1,400	90 d	Relative kidney and liver weights significantly increased at 1,400 mg/kgbw; no histopathological examination	Hayes *et al*, 1986
Mouse, NMRI	30 F/group	0, 0.05 or 0.1	7 wk	Changes suggestive of minimal haemolysis in spleen and red blood cells	Marth *et al*, 1985a,b
Diet		(mg/kg food)			
Rat, NS	10 NS/group	0, 500 0, 25	7 d 14 d	Significant increase in cytochrome P450 Significant increase in hepatic P450	Kaemmerer *et al*, 1982

[a] NS, not stated; M, male; F, female

Gavage

No effects on liver histology, relative liver weights or hepatic DNA synthesis were reported in Sprague-Dawley rats following oral dosing with 500 mg/kgbw/d for 12 days (Schumann *et al*, 1982).

Increased relative liver weights and increased liver aniline hydroxylase activity (without histopathological changes) were observed in Wistar rats following oral dosing with 405 mg/kgbw/d for 4 weeks. No effects on the liver were observed in rats receiving 16 mg/kgbw/d (De Vries *et al*, 1982).

Buben and O'Flaherty (1985) administered PER in corn oil by gavage to groups of Swiss-Cox mice at several doses up to 2,000 mg/kgbw/d for 6 weeks. Statistically significant, dose-related increases occurred in relative liver weights and liver triglyceride levels at doses of 100 mg/kgbw/d or more. Alanine aminotransferase (ALT) activity was significantly increased at doses of 200 mg/kgbw/d and above. Maximal levels in triglyceride and ALT activity were reached following 1,000 mg/kgbw/d. Glucose-6-phosphatase activity in the liver was significantly decreased following 500 mg/kgbw/d. Histological examination of mice receiving 200 or 1,000 mg/kgbw/d groups showed severe degenerative changes in the liver with evidence of nuclear disintegration at both dose levels. Following 1,000 mg/kgbw/d, centrilobular necrosis was seen in some livers. The NOEL for all effects was 20 mg/kgbw/d.

Schumann *et al* (1982) reported (unspecified) histological changes in the liver of the $B6C3F_1$ mouse, as well as a significant (25%) increase in liver to body weight ratio and an 82% increase in DNA synthesis, suggesting cytotoxicity after 12 oral doses of 500 mg/kgbw/d PER.

Drinking Water

PER was administered via the drinking water to male and female Sprague-Dawley rats at estimated daily doses of 0, 14, 400 or 1,400 mg/kgbw/d for 90 consecutive days. The dosing solutions were made in de-inonised water with 4% polyoxylated emulsion. There were no treatment-related mortalities. Body weights were significantly lower in both sexes in the higher dose groups. Relative liver and kidney weights were significantly increased in males receiving 400 mg/kgbw/d, and in both sexes receiving 1,400 mg/kgbw/d. Gross examination of tissues revealed no abnormalities (Hayes *et al*, 1986). In view of the low solubility of PER in water, the exact dose received by each group is not clear. Because of the uncertainties in the study design, it was judged inappropriate to use this study to derive a NOEL.

Changes suggestive of slight haemolysis were apparent in spleen and red blood cells of NMRI mice (30 females/group) following administration of 0.05 or 0.1 mg/kgbw of PER in the drinking water (Marth *et al*, 1985a,b). The results are inconsistent with other findings.

Diet

Rats were administered PER in the diet at 25 mg/kg (14 d) and 500 mg/kg (7 d). The only effects noted were an increase in cytochrome P450 levels and an increase in thrombin and prothrombin time (Kaemmerer *et al*, 1982).

8.3.2 Dermal

No data are available.

8.3.3 Inhalation

Subchronic inhalation toxicity studies are detailed in Table 42.

Table 42: Inhalation Toxicity to Mammals following Repeated Exposure

Species, strain	Number of animals, sex[a]	Concentration (ppm)	(mg/m^3)	Exposure regime, duration	Result	Reference
Rat, NS	12 M, 12 F/group	0, 70, 230 or 470	0, 482, 1,585 or 3,238	8 h/d, 5 d/wk for 7 months	Effects on liver and kidney at 230 at 470 ppm; NOEL = 70 ppm	Carpenter, 1937
Rat, F344/N	5 M, 5 F/group	0, 100, 200, 425, 875 or 1,750	0, 689, 1,378, 2,928, 6,029 or 12,060	6 h/d, 5 d/wk for 2 wk	2/5 M and 3/5 F died at 1,750 ppm; dyspnoea, hypoactivity and ataxia in both sexes at 1,750 ppm; body weights reduced (72%) in M at 1,750 ppm	NTP, 1986
Rat, F344/N	10 M, 10 F/group	0, 100, 200, 400, 800 or 1,600	0, 689, 1,378, 2,756, 5,512 or 11,024	6 h/d, 5 d/wk for 13 wk	4/10 M and 7/10 F died at 1,600 ppm; body weights reduced (20% in M, 11% in F) at 1,600 ppm	NTP, 1986
Rat, Wistar	15 M, 15 F	0, 400	0, 2,756	7 h/d, 5 d/wk for 6 months	No adverse effects	Rowe *et al*, 1952
Rat, Wistar	F	0, 1,600	0, 11,024	18 x 7 h/d, 25 d	No deaths; decreased body weights; increased liver and kidney weights	Rowe *et al*, 1952
Guinea pig	7 M, 4 F 8 M, 8 F	0, 100 200 or 400	0, 689 1,378 or 2,756	7 h/d, 5 d/wk for 8 months	Effects on the liver at 200 and 400 ppm	Rowe *et al*, 1952
Guinea pig	NS	0, 2,500	0, 17,230	18 x 7 h/d, 24 d	Increased liver and kidney weights; fatty degeneration of the liver	Rowe *et al*, 1952

Table 42: Inhalation Toxicity to Mammals following Repeated Exposure (continued)

Species, strain	Number of animals, sex[a]	Concentration (ppm)	(mg/m^3)	Exposure regime, duration	Result	Reference
Mouse, $B6C3F_1$	5 M, 5 F/group	0, 100, 200, 425, 875 or 1,750	0, 689, 1,378, 2,928, 6,029 or 12,060	6 h/d, 5 d/wk for 2 wk	No deaths; dyspnoea, hypoactivity anaesthesia and ataxia, slightly decreased body weights at 1,750 ppm	NTP, 1986
Mouse, $B6C3F_1$	10 M, 10 F/group	0, 100, 200, 400, 800 or 1,600	0, 689, 1,378, 2,756, 5,512 or 11,024	6 h/d, 5 d/wk for 13 wk	2/10 M and 4/10 F died; slightly reduced body weights (M); effects on liver and kidney at $\geq$ 200 ppm	NTP, 1986
Mouse, NS	F	0, 200	0, 1,378	4 h/d, 5 d/wk for 1, 2, 4 or 8 wk	Fatty degenerative changes in the liver	Kylin *et al*, 1965
Mouse, NMRI	10 M, 10 F/group	0, 9, 37, 75 or 150	0, 62, 255, 517 or 1,034	Continuous, 30 d	Increased liver weights at all concentrations	Kjellstrand *et al*, 1984
		150	1,034	Continuous for 4, 8, 14, 30 or 120 d	Histopathological changes in liver $\geq$ 75 ppm	
		225	1,550	16 h/d for 30 d		
		450	3,101	8 h/d for 30 d		
		900	6,201	4 h/d for 30 d		
		1,800	12,400	2 h/d for 30 d		
		3,600	24,800	1 h/d for 30 d		
Rabbit	NS	2,280	15,710	45 d	Increased plasma and urinary levels of corticosterone and catechol amines	Mazza and Brancaccio, 1971

Table 42: Inhalation Toxicity to Mammals following Repeated Exposure (continued)

Species, strain	Number of animals, sex[a]	Concentration (ppm)	(mg/m^3)	Exposure regime, duration	Result	Reference
Rabbit	NS	2,790	19,220	45 d	Increased GDH, AST and ALT levels	Mazza 1972
Rabbit	2 M, 2 F	0, 400	0, 2,756	7 h/d, 5 d/wk for 7 months	No adverse effects	Rowe *et al*, 1952
Rabbit	NS	1.45 or 14.5	9.99 or 99.9	6 - 9 months	Non-dose related increases and decreases in urinary levels of 17-ketosteroids	Kashin, 1980 as quoted in HSE, 1987
Rhesus monkey	2 M	0, 400	0, 2,756	7 h/d, 5 d/wk for 8 months	No adverse effects	Rowe *et al*, 1952

[a] NS, not stated; M, male; F, female

Target organs for repeated inhalation exposure to PER are the liver, the kidney, the lungs and the CNS (Section 8.9).

Effects on the Liver

Carpenter (1937) exposed albino rats to PER vapour concentrations of 0, 70, 230 or 470 ppm (0, 482, 1,585, 3,238 mg/m^3) for 7 months. All animals survived, with growth being comparable to that of the controls. Following exposure to 470 ppm, rats showed cloudy and congested livers, but no necrosis or fatty degenerative changes. Reduced hepatic glycogen storage was observed in animals exposed to 230 ppm. A NOEL of 70 ppm (482 mg/m^3) was reported.

Rowe *et al* (1952) exposed guinea pigs to 100, 200 or 400 ppm PER (689, 1,378, 2,756 mg/m^3), and Wistar rats, rabbits and rhesus monkeys to 400 ppm PER (2,756 mg/m^3) for 6 - 8 months. No adverse effects were seen at any exposure level in albino rats, rabbits and monkeys. In guinea pigs exposed to 400 ppm, a significant growth reduction, increased liver weight, increased amounts of fat and esterified cholesterol, and moderate centrilobular fatty degeneration of the liver with slight cirrhosis were observed. Centrilobular fatty degeneration (without evidence of cirrhosis) and increased hepatic levels of total lipid and esterified cholesterol were also observed following exposure to 200 ppm. In addition, female guinea pigs exposed to 200 ppm showed a significant growth reduction and an increased liver weight. Liver effects in animals exposed to 100 ppm were minimal and of questionable biological significance.

No effects on kidney pathology or on serum indices of kidney function were observed in rats, guinea pigs, rabbits and monkeys after exposure to 400 ppm PER (2,756 mg/m^3) for 6 months.

Female albino mice (single strain) were exposed to 200 ppm PER (1,378 mg/m^3) for 1, 2, 4 or 8 weeks. Fatty degenerative changes in the liver were observed which increased in severity with increasing exposure (Kylin *et al*, 1965).

Kjellstrand *et al* (1984) exposed NMRI mice continuously to 0, 9, 37, 75 or 150 ppm PER (0, 62, 255, 517 or 1,034 mg/m^3) for 30 days. Further groups of males and females were continuously exposed to 150 ppm PER for either 4, 8, 14, 30 or 120 days, followed by a recovery period of either 5, 30 or 120 days, or received 30 intermittent daily exposures to PER from 225 ppm (1,550 mg/m^3) (16 h/d) to 3,600 ppm (24,800 mg/m^3) (1 h/d). Liver weights were significantly increased in all groups of exposed mice without a recovery period and in 6/10 groups of exposed mice with a recovery period. Kidney or spleen weights were not affected. The increase in liver weight is considered to be an adaptive change. Pathological changes in the liver (cell hypertrophy and cytoplasmic vacuolation) (enlargement, vacuolisation of hepatocytes) were reported following exposure to PER at concentrations as low as 9 ppm but were most pronounced following exposure to either 75 or 150 ppm

PER. These effects were not seen in mice that were exposed to 150 ppm PER and allowed to recover from the effects. Levels of plasma butyryl cholinesterase (BCE) were significantly elevated following exposure to 37, 75 and 150 ppm PER, activity returning to normal when measured 30 d after cessation of exposure. The significance of the increased serum BCE activity in this study is unclear.

NTP (1986) conducted inhalation toxicity studies in which $B6C3F_1$ mice and F344/N rats were exposed to various concentrations up to 1,750 ppm PER (12,060 mg/m^3) for 2 weeks. Dyspnoea, hypoactivity and ataxia were observed following exposure to the highest concentration in both species. In addition, hyperactivity and anaesthesia were observed in mice exposed to the highest concentration. Cytoplasm vacuolation of the hepatocytes was observed in male mice exposed to 875 ppm and in male and female mice exposed to 1,750 ppm.

In another study, NTP (1986) exposed $B6C3F_1$ mice and F344/N rats to concentrations up to 1,600 ppm of PER (11,024 mg/m^3) for 13 weeks. No adverse histopathological effects were observed in either species exposed to the lowest concentration. Liver enlargement occurred in mice exposed to concentrations above 200 ppm. Minimal to mild leukocytic infiltration, centrilobular necrosis and bile stasis were observed in mice following exposure to 400 - 1,600 ppm. Mild congestion of the liver was observed in rats exposed to 200 - 800 ppm (1,378 - 5,512 mg/m^3).

Effects of PER on serum levels of liver enzymes were investigated in the rat and rabbit. In the rabbit, increases in glutamate dehydrogenase (GDH), aspartate transaminase (AST) and alanine transaminase (ALT) were recorded following exposures of 2,790 ppm (19,220 mg/m^3) for 45 days (Mazza, 1972).

A dose-related increase in mixed function oxidase (MFO) activity was observed following 10 days of continuous exposure of rats to 50 - 200 ppm (344.5 - 1,378 mg/m^3). No change in MFO activity was observed following 240 hours continuous exposure of Wistar rats (6 males/group) to 50, 100 or 200 ppm (Koizumi *et al*, 1983). Cytochrome P450 levels in the liver of male Sprague-Dawley rats were unchanged after 4 daily 6-h exposures to 200 ppm PER (Henschler and Bonse, 1977).

Effects on the Kidney

Carpenter (1937) reported histological changes in the kidney of albino rats after exposure to 230 and 470 ppm PER (1,585 and 3,238 mg/m^3) for 7 months. Changes included light granular swelling following exposure to the lower concentration, which increased to cloudy swelling, desquamation and increased renal secretion following exposure to the higher concentration. There was no evidence of pathological changes in the kidneys of exposed rats. In addition, no change in urinary total nitrogen, total sulphatase, albumin or bilirubin was observed in either of the exposed groups.

Rowe *et al* (1952) reported increased kidney weights in female Wistar rats after 18 exposures over 25 days to 1,600 ppm PER (11,024 mg/m^3). In the guinea pig, an increase in kidney weight and slight to moderate cloudy swelling of the tubular epithelium was reported after 18 exposures over 24 days to 2,500 ppm (17,230 mg/m^3).

No changes occurred in the kidneys of mice exposed to 200 ppm PER (1,378 mg/m^3) for up to 8 weeks (Kylin *et al*, 1965).

Nuclear enlargement of the tubular epithelial cells was noted in B6C3F$_1$ mice exposed (6 h/d, 5 d/wk) to 200 ppm PER (1,378 mg/m^3) for 13 weeks, but not when exposed to lower concentrations (NTP, 1986).

Effects on the Lungs

Epithelial proliferation in the bronchi, bronchioles and alveoli and increased macrophage infiltration were observed in rats following continuous exposure to 0.6 and 2.8 ppm PER (4.1 and 19 mg/m^3) for 94 days or continuous exposure to 184 to 404 ppm PER (1,268 - 2,784 mg/m^3) for 7 days (Bonashevskaya *et al*, 1977; Tsulaya *et al*, 1977). A further evaluation of the results is not possible due to the lack of details provided, although it is possible that the exposed rats could have suffered from a chronic pulmonary infection.

Increased 3H-thymidine incorporation into lung DNA was observed in rats following exposure (6h/d, 5 d/wk to 120 ppm (827 mg/m^3) for 6 weeks (Duprat *et al*, 1979).

Other Effects

After subchronic exposure of rats to PER, there were no changes in red or white blood cell count in albino rats (strain not specified) at atmospheric concentrations up to 7,000 ppm (48,230 mg/m^3) (8 h/d) for up to 50 days or in male Wistar rats after 10 days of continuous exposure up to 200 ppm PER (1,378 mg/m^3) (Carpenter, 1937; Koizumi *et al*, 1983).

Slight, non-statistically significant increases in plasma and urinary levels of corticosterone and catechol amines were observed in rabbits exposed to 2,280 ppm PER (15,710 mg/m^3) for 45 days (Mazza and Brancaccio, 1971). Minor, non-dose related increases and decreases in urinary levels of 17-ketosteriods were observed in rabbits exposed to 1.45 or 14.5 ppm PER (9.99 - 99.9 mg/m^3) for 6 - 9 months (Kashin, 1980 as quoted in HSE, 1987). The significance of these findings for human health hazard assessment is unclear.

8.3.4 Intraperitoneal

Hepatic effects of intraperitoneal (i.p.) doses of PER included increased liver weight and histological changes (slight fatty accumulation, reduced glycogen levels) in Wistar rats after 3 i.p. injections (every other day) of 2,250 mg/kgbw. There were no changes in hepatic total lipids, cholesterol, phospholipid or triglyceride levels. Small increases were noted in serum AST. A reduction in alkaline phosphatase levels, which was probably related to the reported peritonitis, was seen in both sexes. There were no changes in serum alanine transaminase or cholinesterase activity and no effects on blood levels of total lipid, phospholipid, total cholesterol, free fatty acid, glycogen, and glucose or serum albumin/globulin ratio. No hepatic effects were observed after 37 i.p. injections at 750 mg/kgbw (Ikeda *et al*, 1969).

8.3.5 Summary

The NOEL and LOEL values for the subchronic toxicity studies are given in Table 43.

Inhalation

Target organs for toxicity after repeated inhalation exposure to PER are the liver, the kidney, the lungs and the CNS (Section 8.9).

Effects of PER on the liver were more pronounced in the mouse than in the rat, the guinea pig or the rabbit. These included increased liver weight, increased levels of lipids and cytochrome P450 and changes in serum levels of GDH, AST, ALT and BCE. In most studies, liver enlargement was not accompanied by histopathological changes.

The NOEL for liver effects on the basis of histological criteria in 6 - 8 month studies was 400 ppm (2,756 mg/m^3) in the rabbit and rhesus monkey using similar criteria. In the guinea pig and the rat with various exposure regimes, the LOEL was 200 ppm (1,378 mg/m^3), and the NOEL was 100 ppm (689 mg/m^3).

In a 90-d study in the mouse performed to current day standards, the LOEL for liver and kidney effects was 200 ppm (1,378 mg/m^3) and the NOEL was 100 ppm (689 mg/m^3). In a second study in the mouse exposed continuously for 30 days, minor histopathological changes in the liver were observed at concentrations ≥ 75 ppm (517 mg/m^3). These changes were likely to be a consequence of the high rate of metabolism of PER to TCA in the mouse (ECETOC, 1990).

Increased kidney weight and histological changes in the kidney were reported following repeated exposure to high concentrations PER in the rat (1,600 ppm; 11,024 mg/m^3) and in the guinea pig (2,500 ppm; 17,230 mg/m^3). There were no adverse effects in the kidneys of guinea pigs, rabbits or

rhesus monkeys following exposure to concentrations up to 400 ppm (2,756 mg/m^3), and no adverse effects in the kidneys of mice following exposure to concentrations up to 200 ppm (1,378 mg/m^3). The LOEL for kidney effects in rats was 230 ppm (1,585 mg/m^3).

Taking into account all of the information, a clear NOEL following repeated inhalation of 100 ppm PER (intermittent exposures) has been demonstrated in a wide range of species, on the basis of histological criteria for all critical organs in studies of up to 8 months duration. Changes in liver weight have been observed in mice following continuous exposure to lower concentrations (≥ 75 ppm) of PER. This effect is likely to be specific to the mouse. Furthermore, such adaptive responses in the mouse liver are well described and are not considered to be of significance to human health hazard assessment.

Oral

Liver effects (increased triglyceride levels, increased weight) were apparent in mice orally receiving 100 mg/kgbw/d. The NOEL in mice was 20 mg/kgbw/d. In rats to which PER (500 mg/kgbw/d for 12 d) was administered orally, no effects were observed on the liver in terms of histological changes, weight and DNA synthesis. In a further study, rats receiving 405 mg/kgbw/d PER for 4 weeks showed increases in liver weight and enzyme activity, but there were no histopathological changes.

Table 43: NOELs and LOELs after Repeated Exposure

Target organ	Species	Exposure regime and duration	NOEL		LOEL		Reference
Inhalation			ppm	mg/m^3	ppm	mg/m^3	
Liver	Rat	6 h/d, 5 d/wk, 13 wk	100	689	200	1,378	NTP, 1986
		8 h/d, 5 d/wk for 7 months	70	482	230	1,585	Carpenter, 1937
	Mouse	Continuously for 30 d	37	255	75	571	Kjellstrand *et al*, 1984; NTP,
		6 h/d, 5 d/wk for 13 wk	100	689	200	1,378	1986
	Rabbit	7 h/d, 5 d/wk for 6 months	400	2,756	-		Rowe *et al*, 1952
	Guinea pig	7 h/d, 5 d/wk for 6 months	100	689	200	1,378	Rowe *et al*, 1952
	Rhesus monkey	7 h/d, 5 d/wk for 6 months	400	2,756	-		Rowe *et al*, 1952
Kidney	Rat	8 h/d, 5 d/wk for 7 months	70	482	230	1,585	Carpenter, 1937
	Mouse	6 h/d, 5 d/wk for 13 wk	100	689	200	1,378	NTP, 1986
	Rabbit	7 h/d, 5 d/wk for 6 months	400	2,756	-		Rowe *et al*, 1952
	Guinea pig	7 h/d, 5 d/wk for 6 months	400	2,756	2,500	17,230	Rowe *et al*, 1952
	Rhesus monkey	7 h/d, 5 d/wk for 6 months	400	2,756	-		Rowe *et al*, 1952
Oral (gavage)			(mg/kgbw/d)		(mg/kgbw/d)		
Liver	Rat	NS, 12 d	500		-		Schumann *et al*, 1982
		5 d/wk for 28 d	16		405		De Vries *et al*, 1982
	Mouse	5 d/wk for 6 wk	20		100		Buben and O'Flaherty, 1985
I.p.			(mg/kgbw/d)		(mg/kgbw/d)		
NS	Rat	3 or 37 injections	750		2,250		Ikeda *et al*, 1969

NS Not stated

8.4 MUTAGENICITY

The mutagenic activity of PER has been investigated in a wide variety of tests; these are reviewed in Appendix D.

No mutagenic effects were observed in the following studies (the number performed indicated in brackets).

8.4.1 *In Vitro*

■ Gene mutation	Prokaryotes	*Salmonella typhimurium* (9)
		Escherichia coli (2)
	Fungi	*Saccharomyces cerevisiae* (1)
		Saccharomyces cerevisiae with mouse as host (1)
	Mammals	Mouse cell line (1)
■ Chromosome damage		
Chromosome aberration	Mammals	Hamster cell line (1)
Sister chromatid exchange	Mammals	Hamster ovary cells (1)
■ DNA damage (UDS)	Mammals	Rat / mouse (*in vitro*) (4)
	Humans	Fibroblasts (1)

8.4.2 *In Vivo*

■ Gene mutation	Insects	*Drosophila melanogaster* (2)
■ Chromosome damage		
■ Chromosome aberration	Mammals	Mouse (*in vivo*) (2)
		Rats (*in vivo*) (3)
■ Chromosome damage	Insects	*Drosophila melanogaster* (1)
■ Germ cell	Mammals	Rat (dominant-lethal) (1)
■ DNA damage (UDS)	Mammals	Rat (*in vitro/in vivo*) (1)
■ Sperm morphology	Mammals	Rat (1)

Weakly positive or equivocal results were obtained from a number of tests on technical and commercial grade material or in non-validated test systems. The presence of mutagenic stabilisers in the samples of PER tested is the most likely explanation for the weakly positive findings and therefore confounds the interpretation of these results. The significance of some of the studies could not be judged because of inadequate reporting, the lack of appropriate controls or the unconventional test-system used. Positive results were obtained only at concentrations of PER that were toxic to the organisms or cells and no dose dependence was established.

PER exposure did not produce significant DNA damage or binding. The conflicting results in different cell transformation systems and the different response between mouse and rat in a sperm morphology test are more likely to be due to the inherent properties of the test system than to an expression of the genotoxicity of PER. Negative results were obtained when pure PER was tested in a range of more reliable and better validated studies.

It is concluded from an overall assessment of the available data from a range of *in vivo* and *in vitro* assays, taking into account the quality of conduct and reporting of the studies, that PER is non-mutagenic.

8.5 CHRONIC TOXICITY

8.5.1 Oral

Groups of 50 male and 50 female B6C3F_1 mice received PER (administered 5 d/wk as a solution in corn oil) at TWA doses of 536 and 1,072 mg/kgbw/d (males) and 386 and 772 mg/kgbw/d (females) for 78 weeks, followed by an observation period without treatment of 12 weeks. Groups of 20 untreated and 20 corn oil treated mice of each sex served as controls. The mortality rate in treated mice was high early in the study and toxic nephropathy was observed in nearly all treated mice but not in the controls (NCI, 1977).

Groups of 50 male and 50 female Osborne-Mendel rats received PER (administered as a solution in corn oil) at TWA doses of approximately 475 and 950 mg/kgbw/d for 78 weeks followed by an observation period without treatment of 32 weeks. Groups of 20 untreated and 20 corn oil treated rats of each sex served as controls. Toxic nephropathy occurred in more than 85% of the treated male and in 50 - 82% of the treated female rats. Survival rate was low in the treated rats (NCI, 1977).

Groups of 40 male and 40 female Sprague-Dawley rats received (1x/d, 4-5 d/wk) by gavage 500 mg PER/kgbw (15% v/v in olive oil) for 104 weeks. The rats were observed for their lifetime. A group of 50 male and 50 female rats served as controls and were administered similar volumes of olive oil. Renal damage (cytomegaly and/or karyomegaly in renal tubular cells) was observed in 32.5% of the treated male rats, but not in the female rats (Maltoni and Cotti, 1986).

8.5.2 Inhalation

Groups of 50 male and 50 female B6C3F$_1$ mice were exposed (8 h/d, 5 d/wk) to PER by inhalation at either 100 or 200 ppm (689 or 1,378 mg/m^3) for 2 years. Further groups of 50 male and 50 female B6C3F$_1$ mice served as controls. Both groups of exposed male mice showed a small, but significant, increase in mortality compared to control groups as did the female mice exposed to 200 ppm PER. All groups of exposed mice showed evidence of toxic effects in both the kidney (tubular cell karyomegaly, casts and nephrosis) and the liver (necrosis). Lung congestion was also observed in the exposed male mice. No NOEL could be determined in the study (NTP, 1985).

Groups of 50 male and 50 female F344/N rats were exposed (8 h/d, 5 d/wk) to PER by inhalation at either 200 or 400 ppm (1,378 or 2,756 mg/m^3) for 2 years. Further groups of 50 male and 50 female F344/N rats served as controls. A small, but significant, increase in mortality was observed in male rats exposed to 400 ppm PER when compared with controls. All groups of exposed rats showed evidence of toxic effects in the kidney (tubular cell hyperplasia and nuclear enlargement). Vascular thromboses were observed in the nasal cavity of both male and female rats exposed to PER along with squamous metaplasia in the male. Other effects reported included hyperplasia of the adrenal medulla in exposed males, hyperplasia of the adrenal cortex in exposed females and forestomach ulceration in males exposed to 400 ppm PER. No NOEL could be determined from the study (NTP, 1985).

Groups of 96 male and 96 female Sprague-Dawley rats were exposed (6 h/d, 5 d/wk) to PER at either 300 or 600 ppm (2,067 or 4,134 mg/m^3) for 12 months, following which they were observed for a further 18 months. No significant effects were reported following an analysis of blood and urine parameters and a full pathological examination. A slight increase in mortality was observed in male rats exposed to 600 ppm PER when compared to controls. Mortality was slightly greater in high-dose males than in the controls. This was thought to be due to an earlier onset of spontaneous chronic renal disease (Rampy *et al*, 1978). This study suggested that the NOEL for PER in Sprague-Dawley rats is at least 600 ppm for 12 months exposure.

8.5.3 Evaluation

The principal target organ in both rats and mice following chronic exposure to PER by inhalation and by gavage is the kidney. Effects have been observed following exposure for 2 years at concentrations equal to or greater than 100 ppm (689 mg/m^3) (mouse) or 200 ppm (1,378 mg/m^3) (rat). Following administration by gavage, effects on the kidney were observed at doses of approximately 400 mg/kgbw/d and above when administered for at least 78 weeks. No NOEL has been determined for kidney toxicity following life-time exposure to PER either by gavage or by inhalation in the rat or the mouse.

Other target organs following inhalation of PER include the liver and lung in the mouse and the nasal epithelium, the adrenal gland and the forestomach in the rat.

8.6 CARCINOGENICITY

The chronic toxicity of PER in laboratory animals, in particular its carcinogenic activity, and the implications for human health have been extensively evaluated over the past decade (IPCS, 1984; RIVM, 1984; US-EPA, 1985; Gezondheidsraad, 1985; IARC, 1987; HSE, 1987; Werkgroep Deskundigen, 1987; DFG, 1988; ECETOC, 1990). Other draft regulatory documents exist.

8.6.1 Oral

The carcinogenicity of PER administered by gavage has been examined in two experiments in rats and one in mice.

Groups of 50 male and 50 female B6C3F_1 mice received during 5 d/wk TWA doses of 536 and 1,072 mg PER/kgbw/d (males) and 386 and 772 mg/kgbw/d (females) for 78 weeks, followed by an observation period without treatment of 12 weeks. PER was administered as a solution in corn oil. Groups of 20 untreated and 20 corn oil treated mice of each sex served as controls. The incidence of hepatocellular carcinoma was approximately 10% in both sexes in untreated and in vehicles control mice and 40% and 65% in low-dose and 40% and 56% in high-dose female and male mice respectively. The mortality rate was high early in the study and toxic nephropathy was observed in nearly all treated mice but not in the controls (NCI, 1977).

Osborne-Mendel rats (50 males and 50 females/group) received (5 d/wk) TWA doses of approximately 475 and 950 mg PER/kgbw/d for 78 weeks followed by an observation period of 32 weeks. PER was administered as a solution in corn oil. Groups of 20 untreated and 20 corn oil treated rats of each sex served as controls. Toxic nephropathy occurred in more than 85% of the treated male and in 50-80% of the treated female rats. It was not observed in control rats. PER did not increase the incidence of tumours in rats, although a low survival rate prevented the investigators from drawing definitive conclusions (NCI, 1977).

Sprague-Dawley rats (2 groups of 50 males and 50 females) received (1 x/d, 4-5 d/wk) by gavage 500 mg PER/kgbw (15% v/v in olive oil) for 104 weeks. The rats were observed for their lifetime. Control groups of 50 male and 50 female rats were administered similar volumes of olive oil. Renal damage (cytomegaly and/or karyomegaly in renal tubular cells) was observed in 32.5% of the treated male rats, but not in the female rats. The incidence of benign and malignant tumours in the treated groups was not increased when compared with the controls (Maltoni and Cotti, 1986).

8.6.2 Dermal

Two groups of 30 male and 30 female Ha:ICR Swiss mice received (3 x/wk) either 18 or 54 mg of PER in 0.2 ml acetone on the shaven dorsal skin for the duration of the experiment (imprecisely specified by authors, but at least 440 days). A third group received a single application of 163 mg of PER followed after 2 weeks by 5 mg of phorbol myristate acetate (PMA) in 0.2 ml acetone, (3 x/wk) for at least 428 days. There were 3 control groups: PMA alone, acetone alone, and no treatment. PER did not initiate nor induce dermal tumours or tumours at other sites (Van Duuren *et al*, 1979).

8.6.3 Inhalation

Two groups of 96 male and 96 female Sprague-Dawley rats were exposed (6 h/d, 5 d/wk) to 300 or 600 ppm PER (2,067, 4,134 mg/m^3) for 12 months. A control group consisted of 192 male and 192 female rats. The surviving rats were killed 31 months after the start of the study. Clinical signs of toxicity were not observed and mean body weights were similar in all groups. Mortality was slightly greater in high-dose males than in the controls. This was thought to be due to earlier onset of spontaneous chronic renal disease. PER did not increase the incidence of tumours in the rat under these exposure conditions (Rampy *et al*, 1978).

Groups of 50 male and 50 female F344/N rats or B6C3F$_1$ mice were exposed (6 h/d, 5 d/wk) to PER by inhalation for 103 weeks at atmospheric concentrations of 200 or 400 ppm (1,378 or 2,756 mg/m^3) (rats) or 100 or 200 ppm (689 or 1,378 mg/m^3) (mice) respectively. Groups of 50 male and 50 female rats or mice served as controls. A statistically significant increase in the incidence of heptacellular carcinoma was observed in treated mice for both sexes accompanied by non-significant increases in the incidence of renal tubular cell adenoma and adenocarcinoma (a tumour rarely found in control animals) in male rats. The authors reported a statistically significant increase in mononuclear cell leukaemia for both male and female F344/N rats. The statistical analysis was based on an evaluation of the stages of development of the leukaemia; a method that has not been fully evaluated. The incidence of mononuclear cell leukaemia in the concurrent F344/N control rats, in both males and females, was higher than the historical incidences reported by the NTP. In view of the high and spontaneous incidence of this tumour in the F344/N rat, it is concluded that the increased tumour incidence in the treated groups was not associated with exposure to PER. This conclusion has been reached by other competent reviewers of the study (HSE, 1987; NTP, 1986 see comments of the Peer Review Committee).

8.6.4 Intraperitoneal Studies

Groups of 20 male A/St mice (6-8 wk of age) received (3 x/wk) i.p. injections of PER in tricaprylin. The groups received 14 injections of 80 mg/kgbw or 24 injections of 200 mg/kgbw or 48 injections of 400 mg/kgbw (concentration and volume not given). The 50 control mice were injected with tricaprylin

only. A positive control group received 1 single i.p. injection of urethane (1,000 mg/kgbw). The mice were killed 24 weeks after the first injection. Special attention was given to the occurrence of lung adenomas. The number of lung tumours was not increased in the groups injected with PER, whereas an increased incidence was seen in the positive control group (Theiss *et al*, 1977).

8.6.5 Tumour Promotion

A rat liver foci bioassay was performed using *N,N*-diethyl-nitrosamine (DENA) as an initiator and PER as a promoter (protocol described by Pereira *et al*, 1982). DENA was injected i.p. into male Sprague-Dawley rats 24 hours after a partial hepatectomy. PER (1,100 mg/kgbw/d) administered (1 x/d, 5 d/wk) by gavage for 7 weeks, did not increase the number of foci/cm^2 nor the total foci area/cm^2 at 3 d (Lundberg *et al*, 1987) or 10 d (Lundberg *et al*, 1987; Holmberg *et al*, 1986) following the last dose of test compound. The studies thus provided no evidence for tumour promotion in the liver.

A liver foci bioassay was conducted in Osborne-Mendel rats using DENA as initiator. Glutamyl-transpeptidase (GGT) was used as an index of pre-neoplastic change. The incidence of GGT foci was significantly increased by PER and the extent of the increase was similar whether or not DENA was used (Milman *et al*, 1988). The significance of the liver foci bioassay and its predictive value for humans are uncertain.

In a pulmonary tumour promotion assay in strain A mice, PER was without promoting activity (Theiss *et al*, 1977).

Metabolite: Trichloroacetic Acid

In a study in mice in which the tumour promoting ability of PER was compared with that of its metabolite, a group of 22 male B6C3F_1 mice received TCA in their drinking water at a concentration of 5 g/l for 61 weeks. Seven out of the 22 treated animals developed hepatocellular carcinomas, and 8 developed hepatocellular adenomas. In a control group of 22 male mice receiving 2 g/l NaCl in their drinking water, 2 developed hepatocellular adenomas although no hepatocellular carcinomas were observed. This study provides some evidence for the hepatocarcinogenic effect of TCA, a metabolite of PER, in the mouse (Herren-Freund *et al*, 1987).

8.6.6 Evaluation

In summary, PER has been shown to be carcinogenic in male and female $B6C3F_1$ mice, causing hepatocellular carcinomas following oral and inhalation exposure. It is concluded that this response is due to metabolism of PER to TCA, which has been shown to cause hepatocellular carcinomas in male $B6C3F_1$ mice when administered in their drinking water. PER also caused an increase in the incidence of renal tubular cell tumours in male F344/N rats in one study. Increased incidences of mononuclear cell leukaemia were observed in treated male and female F344/N rats but not in Osborne-Mendel or Sprague-Dawley rats. Mononuclear cell leukaemia is known to have a high and variable incidence in F344/N rats, this being a strain specific effect.

There is no convincing evidence from a number of assay systems to suggest that PER acts as a tumour promoter.

8.7 MECHANISMS OF TUMOUR FORMATION

A considerable body of work has been conducted to examine the mechanisms by which PER causes liver tumours in the mouse and kidney tumours in the rat. These studies have been extensively reviewed in ECETOC (1990).

There is good evidence that mouse liver tumours are due to metabolism of PER to TCA which, itself, has been shown to be a rodent hepatocarcinogen. The mechanism of action of TCA as a liver carcinogen has been shown to involve peroxisome proliferation, a non-genotoxic mechanism of action common to a number of rodent liver carcinogens. Species differences in the metabolism of PER to TCA also explains why PER does not cause liver tumours in the rat.

Although PER causes the development of liver tumours in mice, the mechanism involved is unlikely to occur in humans because:

- the formation of TCA in humans is limited by the saturation of the oxidative pathway at atmospheric concentrations of PER above 100 ppm (689 mg/m^3); doses above this level are required to produce neoplasia in mice;
- TCA does not induce peroxisome proliferation in human hepatocytes *in vitro*, confirming a general observation that humans are not susceptible to the hepatotoxic and hepatocarcinogenic effects of peroxisome proliferators such as TCA.

The kidney tumours observed in male rats may arise from one or more of three potential mechanisms. They may be a consequence of the sex specific protein droplet nephropathy developed in male rats exposed to PER. In addition, (i) sustained chronic toxicity to the kidney and/or (ii) hepatic GSH-

conjugation and subsequent activation of cysteine conjugate by renal β-lyase, may have further contributed to the development of the renal tumours.

These mechanisms are probably specific to the rat or, at the very most, only operative following exposure to very high concentrations of PER for prolonged periods of time. Although mercapturic acid derivatives have been formed, at different rates, in the urine of both rats and humans, GSH-conjugation has not been detected in human liver samples. Protein droplet nephropathy is a species and sex specific event exclusively observed in the male rat. Sustained chronic toxicity will only occur following exposure to high concentrations of PER over a prolonged period of time.

Thus, interspecies comparisons of the mechanisms of toxicity and carcinogenicity indicate that the liver tumours in mice and kidney tumours in rats are unlikely to occur in humans. It may be concluded, therefore, that it is inappropriate to use these tumour incidences as the basis for risk assessment in humans. Some support for this view is obtained from the negative results obtained from a number of epidemiological studies.

8.8 REPRODUCTIVE TOXICITY, EMBRYOTOXICITY AND TERATOGENICITY

8.8.1 Reproductive Toxicity

Details of reproductive toxicity studies are explained in Table 44.

Table 44: Effects on Fertility Following Exposure by Inhalation

Species	Strain	Number of animals, sex	Exposure, duration	Concentrations tested (ppm)	(mg/m^3)[a]	Effects on fertility	References
Rat	NS	4 x 12	7 h/d for 7 months	0, 70, 230, 470	0, 482, 1,585, 3,238	70 ppm: reduced fertility 230, 470 ppm: increased fertility	Carpenter, 1937
Rat	Sprague-Dawley	NS	7 h/d for 5 d	0, 100, 500	0, 689, 3,445	No effect on fertility; no effect on sperm head morphology	Beliles *et al*, 1980
Rat	Alpk:APf50	4 x 24 M 4 x 24 F	6 h/d, 5 d/wk for 11 wk 11 wk F_0 and F_1A	0, 100, 300, 1,000	0, 689, 2,067, 6,890	No effect on fertility and mating performance. Testes weight reduction at 300 and 1,000 ppm in F_1A males	Tinston, 1995
Mouse	NS	NS	7 h/d for 5 d	0, 100, 500	0, 689, 3,445	Increase anomalies in sperm head morphology	Beliles *et al*, 1980

[a] Converted values
NS Not stated
M Male
F Female

No adverse effects on reproduction in albino rats were reported following exposure to PER at concentrations up to 470 ppm (3,238 mg/m^3) for 7 months. The design of the study was severely limited when compared to current standards and no statistical information was presented (Carpenter, 1937).

Beliles *et al* (1980) exposed rats and mice to 0 (controls), 100 or 500 ppm of technical grade (91.4% purity) PER (0, 689, 3,445 mg/m^3) for 5 consecutive days. An increased proportion of sperm with aberrant morphology was found in mice, but not in rats, exposed to 500 ppm during week 4 after exposure (19.7% versus 6% in controls). In a dominant lethal assay performed on the rats used in the study, no adverse effect was observed, including any effect on male fertility.

A multi-generation inhalation study has been conducted in the rat (Tinston, 1995). Groups of 24 male and 24 female (F_0 parents) weanling Alpk:APfSD rats were exposed by inhalation to 0 (control), 100, 300 or 1,000 ppm PER (0, 689, 2,067, 6,890 mg/m^3) for 11 weeks prior to being housed for mating for up to 21 days. Following mating, the males were exposed daily until termination and the females were exposed daily until day 20 of gestation. One litter (F_1A) was produced in the first generation when the dams, together with their litters, were exposed daily from day 6 to day 29 *post partum*. The second generation (F_1) parents were selected from the F_1A litters on day 29 *post partum* and were exposed to PER for at least 11 further weeks prior to mating. Two litters (F_2A and F_2B) were produced in the second generation.

There were no effects on fertility or reproductive performance of male or female rats in any of the exposed groups from either generation. Exposure to 1,000 ppm PER resulted in reduction of parental bodyweight gain during both the pre-pairing and lactation periods in both generations and during pregnancy in the second generation. A similar but less marked effect on parental bodyweight was seen in males and females exposed to 300 ppm PER. Histopathological changes were confined to kidneys of both sexes in both generations exposed to 1,000 ppm PER, but no significant changes were seen at 300 or 100 ppm. Exposure to either 300 or 1,000 ppm PER was also associated with poor growth of the F_1A and F_2A animals (confirmed in the F_2B offspring). Furthermore, the proportion of pups born alive and pup survival rate were reduced at 1,000 ppm. No treatment-related histopathological changes were seen in the testes of males of any generation although, in the F_1 parental generation, a statistically significant, dose-related weight reduction of the testes was observed in males exposed to 300 and 1,000 ppm PER. There was no effect on the weight of the testes of the males of the F_0 parental generation nor in the F_1 and F_2 males.

An F_2C generation was obtained after mating the PER-exposed F_1 male rats to stock (non exposed) female. No effects were seen in these pups.

The NOEL in this study was higher than 1,000 ppm (6,890 mg/m^3) for mating performance and fertility and was 100 ppm (689 mg/m^3) for other reproductive and for the non-reproductive parameters.

8.8.2 Developmental Toxicity

A number of teratology studies have been conducted in the rat, mouse, rabbit and chicken; details are given in Tables 45 and 46.

Schwetz *et al* (1975a,b) exposed groups of pregnant rats and mice to 0 or 300 ppm PER (0, 2,067 mg/m^3). Foetuses were examined on day 21 (rat) or 18 (mouse) of gestation. No teratogenic effects were observed in either species although some signs of maternal toxicity occurred, i.e. increased liver weight in mice and slight decrease in bodyweight in rats. In mice, increased incidences of subcutaneous oedema, delayed ossification of skull bones and sternebrae, but no major malformations, were observed. There was a decrease in foetal bodyweight in rats and mice and a slight increase in the incidence of foetal resorption in rats.

Beliles *et al* (1980) exposed groups of pregnant rats and rabbits to 0 or 500 ppm PER (0, 3,445 mg/m^3). One half were exposed 3 weeks prior to mating. All rats were exposed during gestation on days 0 - 18 or 6 - 18. All rabbits were exposed during gestation on days 0 - 21 or 7 - 21. No evidence of maternal toxicity was observed and no teratogenic effects were reported in rats or rabbits although foetal skeletal ossification anomalies were described in rats. In rats exposed to 500 ppm PER, a slight increase in the incidence of resorptions was observed when compared to the control group. However, although the difference was statistically significant, it has probably no biological significance because an unusually low incidence of resorptions occurred in the control group.

Hardin *et al* (1981) exposed pregnant rats and pregnant rabbits to 0 or 500 ppm PER (0, 3,445 mg/m^3) during the first 19 (rat) or 24 (rabbit) days of gestation. No effects were reported in the foetuses nor in the dams of either species. Due to many similarities, it would appear that the study reported by Hardin *et al* is part of the study reported by Beliles *et al* above.

In a behavioural teratology study (Table 44), Nelson *et al* (1979) exposed rats to 0, 100 or 900 ppm PER (0, 689, 6,201 mg/m^3) on days 7 - 13 or 14 - 20 of gestation. A number of behavioural tests were performed on one male and one female pup of each litter for each test on days 4 - 56 postnataly. In addition, histological examination of the pups' brains was performed and dopamine and acetylcholine levels in the brain were measured on days 0 and 21 of age. Frank maternal toxicity was observed following exposure to 900 ppm PER. Inconsistent results were obtained in the behavioural tests and decreases in the levels of both dopamine and acetylcholine were noted in the pups born from dams

exposed to 900 ppm PER. However, in those exposed to 100 ppm PER, no effects were observed in the dams or the pups.

Table 45: Prenatal Developmental Toxicity

Species	Strain	Number of animals	Exposure, duration	Concentration (ppm)	Concentration (mg/m^3)[a]	Results	Reference
Inhalation							
Rat	Sprague-Dawley	17/group	7 h/d, d 6 - 15 of gestation	0, 300	0, 2,067	No teratogenic effect; maternal toxicity (decreased bodyweight)	Schwetz *et al*, 1975a,b
Rat	Sprague-Dawley	19 - 24	7 h/d, d 0 to 18 of gestation or d 6 - 18 of gestation	0, 500[b]	0, 3,445	No teratogenic effect; maternal toxicity (decreased body weight, increased liver and kidney weight), delayed skeletal ossification	Beliles *et al*, 1980
Rat	Sprague-Dawley	30/group	6 - 7 h/d, d 1 - 19 of gestation	0, 500	0, 3,445	No teratogenic effect; no foetotoxic effect, no maternal effect	Hardin *et al*, 1981
Mouse	Swiss Webster	17/group	7 h/d, d 6 - 15 of gestation	0, 300	0, 2,067	No teratogenic effect; maternal toxicity (increased liver weight); foetotoxic effects	Schwetz *et al*, 1975a,b
Rabbit	NS	20/group	6 - 7 h/d, d 1 - 24 of gestation	0, 500	0, 3,445	No teratogenic effect; no foetotoxic effect; no maternal effect	Hardin *et al*, 1981
Injection							
Chicken (egg)	White Leghorn SK 12	6 eggs	d 2,3,6 d 1 - 19 of incubation	0, 5, 25, 50, 100 mmol/egg		Slight non dose-related excess of malformation	Elovaara *et al*, 1979

[a] Converted values
[b] Actual concentration fluctuating up to 568 ppm (3,914 mg/m^3)

Table 46: Postnatal Developmental Toxicity

Species	Strain	Number of animals	Exposure, duration	Concentration (ppm)	Concentration (mg/m^3)[a]	Results	Reference
Rat	Sprague-Dawley	15	7 h/d on d 14 - 20 of gestation	0, 100	0, 689	No behavioural effect on offspring (Observed on day 4 - 46 *post partem*)	Nelson *et al*, 1980
Rat	Sprague-Dawley	19	7 h/d on d 7 - 13 of gestation or d 14 - 20 of gestation	0, 900	0, 6,201	Contradictory results in behavioural tests. Brain acetylcholine and dopamine decreased: noradreanline normal (observed on day 4 - 46 *post partem*)	Nelson *et al*, 1980
Rat	Long Evans	NS	6 h/d, 5 d/wk, 2 weeks before mating to d 20 of gestation or d 0 - 20 of gestation	0, 1,000	0, 6,890	No remarkable effects on day 10 and 170 *post partem*	Tepe *et al*, 1982; Manson *et al*, 1982; both as quoted in US-EPA, 1985
Rat	Alpk:APfSD	NS	F_1A and F_2A: 6 h/d 26 - 29 d post-partum F_2B: not exposed during lactation	0, 100, 300, 1,000	0, 689, 2,067, 6,890	Reduction proportion of pups born live at 1,000 ppm. Reduced growth at 300 - 1,000 ppm. No effect at 100 ppm	Tinston, 1995

[a] Converted values

Another behavioural teratology study was cited by US-EPA (1985) (Tepe *et al*, 1982; Manson *et al*, 1982; both as quoted in US-EPA, 1985). Pregnant rats were exposed to 0 or 1,000 ppm PER (0, 6,890 mg/m^3) for 2 weeks before mating until day 20 of gestation or on days 0 - 20 of gestation. Both maternal and embryo-toxicity were observed (unspecified skeletal and soft tissue anomalies). Neurobehavioral testing of the pups on days 10 and 170 after birth did not reveal treatment-related effects.

Elovaara *et al* (1979) described effects of PER on developing chicken embryos. The test substance was injected three times into the air space of fertilised chicken eggs at doses lower than the LD_{50} (5 - 100 mmol/egg). After 19 days of incubation, the rate of macroscopic malformation (9;8%) was higher in the PER-treated group than in the controls treated with olive oil (3.5%), but it was lower than with other chlorinated solvents such as trichloroethylene and 1,1,1-trichloroethane.

The multi-generation study by Tinston (1995) is reported in Section 8.8.1.

8.8.3 Summary

PER had no effect on the fertility of rats and mice although there was evidence of aberrant sperm morphology in mice (but not in rats) and lower testicular weight in rats exposed to high levels of PER (500 ppm and above; ≥ 3,445 mg/m^3). Pre- and post-natal toxic effects to the pups were found in a 2-generation study in rats exposed by inhalation up to 1,000 ppm PER (6,890 mg/m^3). A NOEL of 100 ppm (689 mg/m^3) was established in that study and previous studies in rats and mice.

PER has been shown to induce foetotoxic effects but no teratogenic effects at high dose levels in several animal species, with the mouse being the most sensitive species. Because these foetal effects always appeared at dose levels which induced toxic effects in the dams during gestation, they are considered to be associated with maternal toxicity due either to PER or its metabolite, TCA.

8.9 NEUROBEHAVIOURAL EFFECTS AND NEUROTOXICITY

Anaesthetic Effects

Exposure to high atmospheric concentrations of PER causes CNS depression in all species studied. A single 8-h exposure of rats to 2,750 ppm PER (18,950 mg/m^3) initially caused anaesthesia, but after 6 exposures to this concentration, rats developed a tolerance to the effect (Carpenter, 1937). Anaesthesia has also been reported in the mouse, rabbit and dog (Lamson *et al*, 1929; Friberg *et al*, 1953; Truhaut *et al*, 1972).

Wistar rats exposed to ≥ 6,000 ppm PER (41,340 mg/m^3) for a few minutes or to 3,000 ppm (20,670 mg/m^3) for several hours showed unresponsiveness to external stimuli. Responsiveness was

retained during exposure to 2,000 ppm (13,780 mg/m^3) for 14 hours. Frequent loss of response to external stimuli was also observed in Wistar rats during repeated exposure (18 x 7 h) to 2,500 ppm PER (17,230 mg/m^3) for 25 days. Following exposure to 1,600 ppm (11,024 mg/m^3), drowsiness and signs of stimulation of the cholinergic system were observed. Rabbits and guinea pigs showed signs of CNS depression (anaesthetic effects) following exposure to 2,500 ppm PER. There were no effects in these species or in rhesus monkeys, following exposure to 400 ppm PER (2,756 mg/m^3) (Rowe *et al*, 1952).

Behaviour

Ataxia was reported after a single 4-h exposure of female CFE rats to 2,300 ppm PER (15,850 mg/m^3). In the same study, a lack of effect on conditioned avoidance escape response was observed in animals exposed (4 h/d, 5 d/wk) to 2,300 ppm for 2 weeks. No effects on the ability to perform a conditioned avoidance task were observed following exposure to 1,150 ppm PER (7,924 mg/m^3) (Goldberg *et al*, 1964).

Increased open field activity (ambulation) was observed in a group of 10 male Sprague-Dawley rats during the first 6 hours following 1 hour of exposure to 200 ppm PER (1,378 mg/m^3), but 17 hours later no effects were seen (Savolainen *et al*, 1977).

In a swimming immobilisation test conducted immediately following exposure to 596 - 820 ppm PER (4,106 - 5,650 mg/m^3) for 4 hours, mice showed significantly reduced duration of immobility within the test period (3 min). Assessments were not made at later time periods (De Ceaurritz *et al*, 1983).

Using a Doppler radar unit, the motor activity of mice was recorded 1 hour before, during and 2 hours after inhalation of 90 - 3,600 ppm PER (620 - 24,800 mg/m^3) for 1 hour. The motor activity was increased during exposure at all concentrations, although only slightly in mice exposed to 90 ppm PER. No increased motor activity was recorded 2 hours after exposure (Kjellstrand *et al*, 1985).

Male and female F344/N rats were exposed (6 h/d, 5 d/wk) by inhalation to 0, 50, 200 or 800 ppm PER (0, 344.5, 1,378, 5,512 mg/m^3) for 13 weeks and evaluated for neurotoxicity during the first week post-exposure by means of a functional observation battery (FOB). In addition, flash evoked potential (FEP) tests were made of the visual, auditory and somatosensory systems, the velocity of caudal nerves was evaluated and neuropathology examined. An FOB was also conducted monthly during the exposure period. No treatment-related alterations were observed (Mattsson *et al*, 1998).

Neurochemistry

Cholinesterase activity, protein, RNA and GSH levels in the brain did not show any significant changes after 5 daily exposures (6 h/d) of male Sprague-Dawley rats to 200 ppm PER (1,378 mg/m^3)

(Savolainen *et al*, 1977). However, due to the small number of animals used, the results of this study cannot be fully evaluated.

Biochemical analysis of mid-brain amino acid content in Sprague-Dawley rats (5 - 6 males/group) showed a dose-dependent increase in glutamine, threonine and serine (combined) following continuous exposure to 200, 400 or 800 ppm PER (1,378, 2,756, 5,512 mg/m^3) for 1 month. A small reduction in acetylcholine levels in the striatum was observed following exposure to 800 ppm PER. No effects were seen following exposure to 400 ppm or below (Honma *et al*, 1980a,b).

Mongolian gerbils (6 exposed and 7 control animals) continuously exposed to 120 ppm PER (827 mg/m^3) for 12 months had changes in fatty acid composition of ethanolamine phosphoglycerides in the cerebral cortex and hippocampus. According to the authors, these changes represented an increase in the fatty acids derived from linoleic acid with a corresponding decrease in those derived from linoleic acid and may be due to cell membrane effects. No changes were detected in the weight of whole brain, hippocampus or cerebral cortex, or levels of cholesterol, phospholipids or cerebrosides in these areas (Kyrklund *et al*, 1984).

Brain amino acid and GSH concentrations were also determined in this study. Treatment-related effects included decreases in taurine content in the hippocampus and posterior part of the cerebellar vermis and increased glutamine content in the hippocampus. The uptake of glutamate and γ-aminobutyric acid (GABA) into the cerebellum and hippocampus was unaffected by exposure to PER (Briving *et al*, 1986).

After continuous exposure of Mongolian gerbils to 320 ppm PER (2;205 mg/m^3) for 3 months, a slight but statistically significant decrease in brain weight was reported (Kyrklund *et al*, 1987). Body weights were similarly decreased and small changes in the pattern of fatty acids in the brain were observed. Some of these changes were inconsistent with the earlier findings (Kyrklund *et al*, 1984). Their toxicological significance is uncertain. Continuous exposure for 3 months to 60 ppm PER (413.4 - 2,205 mg/m^3) led to a slight decrease of DNA concentrations in the frontal cerebral cortex, but not to differences in DNA or protein content in other areas of the brain, or to differences in body or brain weight (Karlsson *et al*, 1987). No toxicological significance can be attributed to the decreased DNA levels.

In another study with groups of Mongolian gerbils (4/dose/sex), an increase in the levels of S-100, an astroglial protein, was observed in the brain after a 3-month continuous exposure to 60 or 320 ppm PER (413.4 mg/m^3) followed by a 4-month post-exposure period (Rosengren *et al*, 1986). There were no significant changes in body or brain weights. Decreased DNA concentration in the frontal cerebral cortex was the only effect associated with exposure to PER. The authors claimed that their results were consistent with astroglial hypertrophy and/or proliferation in the hippocampus, and atrophy of the

cerebral frontal cortex. However, the DNA levels reported appeared to be within the normal background levels. As no histopathological examination was conducted and given the non-validated status of the assays, no conclusions can be drawn from this study.

Kyrklund *et al* (1988, 1990) reported effects on the lipid and fatty acid composition of the brain of Sprague-Dawley rats (8 males/group) after continuous exposure to 320 ppm PER (2,205 mg/m^3) for 30 or 90 days. The 90-d exposure period was followed by a 30-d recovery period. A slight decrease in the contents of cholesterol and phospholipids of the cerebral cortex was reported. Changes in the pattern of long-chain unsaturated fatty acids were reported after 30 and 90 days of exposure, but most changes returned to normal values during the 30-d recovery period. No effects of exposure to PER on whole brain weights were observed.

In a study by Wang *et al* (1993), rats were continuously exposed to 300 ppm PER (2,067 mg/m^3) for 4 weeks or to 600 ppm (4,134 mg/m^3) for 4 or 12 weeks. Following exposure to 600 ppm, in particular after 12 weeks of exposure, statistically significant decreases in body weight gain, in total brain and some brain region weights were observed. DNA and protein contents of the frontal cerebral cortex and brain stem, but not of the hippocampus, were decreased following exposure to 600 ppm, statistically significant after 12 weeks of exposure. The levels of both glial and one of 2 neuronal cell marker proteins were lower in exposed animals than in controls. The toxicological significance of these findings not clear.

Neurophysiology

In an acute neurophysiological range-finding study, Albee *et al* (1991) exposed male F344/N rats to 800 ppm PER (5,512 mg/m^3). The animals showed significant pharmacological alterations in flash evoked potentials, electro-encephalograms and somatosensory evoked potentials that were recorded during the 4 hours of 4 daily exposures. The goal of this study was to identify a neurofunctional maximum tolerated dose for a subsequent 13-wk neurotoxicity study.

In the 13-wk study (Mattson *et al*, 1998), groups of 14 male and 14 female F344/N rats were exposed (6 h/d, 5 d/wk) by inhalation at to concentrations of 0, 50, 200 or 800 ppm PER (0, 344.5, 1,378, 5,512 mg/m^3) for 13 weeks and were evaluated for neurotoxicity during the first week post-exposure by FOB, by FEP testing of the visual, auditory and somatosensory systems, by conduction velocity evaluation of caudal nerves, and by neuropathology. The only effect possibly related to treatment was in the FEP recorded from the visual cortex, which had a somewhat greater amplitude in rats exposed to 800 ppm PER. No toxicological significance was attributed to this finding. No treatment-related alterations were observed in the flash evoked potentials recorded from the cerebellum, or in the auditory, somatosensory or caudal nerve evoked potentials at any of the exposure levels. No treatment-related lesions were noted during histopathological examination of tissues of the central and

peripheral nervous system. The No-Observed Adverse Effect Level NOAEL derived from this study is 800 ppm.

8.9.1 Summary

Investigations of effects on the nervous system have been conducted mainly in the rat, with additional studies in the rabbit, guinea pig, monkey and Mongolian gerbil. PER has a depressant effect on the CNS in the rat, rabbit and guinea pig following exposure to high atmospheric levels (2,500 ppm; 17,230 mg/m^3). Minimal depressant effects were observed in the rat following exposure to 1,600 ppm (11,024 mg/m^3). Based on behaviour, a NOEL for CNS depression of 400 ppm/d PER (2,756 mg/m^3/d) for 6 months was reported in all these species, as well as in the rhesus monkey. Slight excitatory effects (ambulation) are seen at lower concentrations (around 200 ppm). Studies in the rat demonstrate that the CNS effects of PER are rapidly reversible and that a tolerance develops on repeated exposures.

Behavioural and biochemical investigations have been conducted mostly in single dose level studies in the rat and show only minor effects. Changes observed are often small and within the normal range of the parameters in control groups. In most studies, their reversibility has not been examined and/or no pathological assessment has been performed. Furthermore, no consistent pattern of changes has been found and it is not certain to which degree recorded effects are toxic (adverse) or potentially adaptive. The extent to which these parameters are susceptible to change by altered diurnal variation due to sedative effects is unknown. The functional significance of such changes, therefore, remains obscure.

Neither histopathological nor functional observation of rats and mice exposed chronically to PER has provided any evidence of neurotoxicity in these species.

9. EFFECTS ON HUMANS

9.1 ACUTE TOXICITY

In this section, the toxic effects of single human exposures to PER will be discussed. Thus, this section also deals with what is usually considered subchronic toxicity. For CNS effects, see Section 9.4.

9.1.1 Oral

Data on oral exposure to PER derives mainly from its clinical use as a anthelmintic drug.

Kendrick (1929) compared the use of carbon tetrachloride and PER for the treatment of hookworm in humans, and reported vertigo, giddiness, nausea and sleepiness in approximately 50% of a study group of 200 patients receiving doses of 4.5 or 6.0 g PER. Kendrick (1929) and Sandground (1941) observed unconsciousness in 2 patients receiving similar doses; the effect occurred approximately 1 hour after dosing and lasted for 2 hours.

Two deaths following ingestion of PER have been reported. One occurred in a patient who was already suffering from jaundice and had received a dose of 4.5 g PER as an anthelmintic treatment (Goldbloom and Boyd, 1954). The second fatality was a child who died of ventricular fibrillation after accidental ingestion of PER. No further details on the patient and doses received were given (Lemburg *et al*, 1979).

Haerer and Udelman (1964) reported a state of psychosis that was induced in one man approximately 1 hour after ingestion of 7.5 g PER.

9.1.2 Dermal

Nausea, vertigo, fatigue and vomiting have been reported in a worker following dermal exposure to a PER-water mixture. The patient recovered when exposure ceased (Method, 1946).

9.1.3 Inhalation

Garnier *et al* (1996) reported a fatal case of accidental inhalation of PER (estimated concentration as high as 38,095 mg/m^3 (5,520 ppm) in a 2-year old child. The child was found dead 1.5 hours after being put to bed in a small room where curtains, freshly cleaned in a self-service coin-operated dry-cleaning machine, had been hung by a window to air. It was reported that the machine had been operated incorrectly and that the curtains were still wet with solvent (PER) when they were taken back home. PER concentrations found in the body were high, namely 79 mg/kg in brain and 31 mg/kg in

heart tissues, as well as 46 mg/kg in lungs and 68 mg/l in blood. The urine contained 0.4 mg PER/l, 1.7 mg trichloroethanol/l and 0.9 mg TCA/l.

Garnier *et al* (1996) further reported 28 non-fatal intoxication cases observed in the Paris Anti-poison Centre between 1989 and 1995 following inhalation of PER due to improper use of similar, self-service, coin-operated, dry-cleaning machines. (The author also refers to similar cases that occurred in Denmark during the 1970s.) In most cases, the dry-cleaning machine was overloaded with absorbent fabrics not recommended for dry-cleaning, such that clothes and fabrics were still wet with solvent when removed from the machine. Thus, PER could evaporate from the cleaned articles into vehicles during their transportation and into homes, producing unknown but presumably high indoor concentrations. Symptoms in exposed children and adults included headache, dizziness, drowsiness, vomiting and inebriety and loss of consciousness lasting from a few minutes up to 5 hours. All effects were reported to be reversible after either a few minutes or up to several hours. In the most severe case, BOCCRF (1995) measured TCA concentrations of 4.9 mg/l in blood and 13 mg/g creatinine in urine; trichloroethanol concentrations were 55.1 mg/l in blood and 26.4 mg/g creatinine in urine.

Effects on the Liver

Autopsy of several cases of fatal poisoning with PER revealed fatty degeneration of the liver was found (Trense and Zimmermann, 1969; Lukaszewski, 1979; Levine *et al*, 1981; McCarthy and Jones, 1983).

Hughes (1954) and Meckler and Phelps (1966) reported a case of acute hepatitis (jaundice, enlarged liver and abnormal tests of liver function) following exposure to PER.

Following non-fatal poisoning with PER, several authors observed palpable hepatomegaly and raised serum markers for liver damage (SGOT, SGPT), 10 times as high as the normal value. Recovery time appeared to be dose-dependent, with liver enlargement resolving completely 10 weeks after exposure to low concentrations, but persisting for over 6 months after higher exposures (Meckler and Phelps, 1966; Saland, 1967; Montalto and Mari, 1971; Einhorn, 1972; Hake and Stewart, 1977; Ferrau *et al*, 1980). Liver histology was normal after 7 months in one instance, but in a second case cirrhosis was diagnosed 14 months after the poisoning (Meckler and Phelps, 1966; Ferrau *et al*, 1980).

Other Systemic Effects

Pulmonary congestion was autopsied in several cases, following inhalation of high concentrations of PER (Trense and Zimmermann, 1969; Levine, 1981; McCarthy and Jones, 1983). In a further case, Lukaszewski (1979) also described fatty degeneration of the brain, together with degenerative changes in the kidneys.

Renal dysfunction and secondary pulmonary oedema following inhalation of PER (doses not stated) have been reported (Trense and Zimmermann, 1969; Einhorn, 1972; Montalto and Mari, 1971; Hake and Stewart, 1977; Patel *et al*, 1977; Levine *et al*, 1981; McCarthy and Jones, 1983).

9.1.4 Summary

The principle effects from inhalation of PER by humans are symptoms associated with CNS depression (Section 9.3). In addition, cases of acute hepatitis, reversible and dose dependent liver damage (palpable hepatomegaly and raised serum markers) are reported. Delayed effects include renal dysfunction and secondary pulmonary oedema.

One case of fatal ventricular fibrillation has been reported in a child exposed to high concentrations of PER.

9.2 HUMAN SKIN, RESPIRATORY AND EYE IRRITATION AND SENSITISATION

9.2.1 Skin Irritation

Stewart and Dodd (1964) reported that individuals experienced a mild burning sensation on their thumbs following their immersion in a solution of PER for 5-10 minutes. After the thumbs were withdrawn, the burning sensation persisted without a decrease in intensity for 10 minutes before gradually subsiding after 1 hour. A marked erythema was present in all cases and subsided between 1 and 2 hours post-exposure.

Hammerling Gold (1969) reported that prolonged or repeated skin contact with liquid PER causes defattening of the skin with dermatitis, dryness, roughness and cracking.

Morgan (1969) reported an accident where a container with liquid PER was spilled over a worker, soaking his clothes. The worker became anaesthetised by the vapour and remained unconscious for 0.5 hours. He suffered from skin erythema and blistering (30% of skin surface).

Ling and Lindsay (1971) reported severe skin burns when an individual, losing consciousness, fell into a pool of PER. The burns gradually healed within 3 weeks following exposure.

A case of exfoliative dermatitis due to PER has been reported, but no further details were given (Nicolis and Helwig, 1973).

Burns following prolonged PER contact have been reported in 3 other cases (Meyer, 1973; Hake and Stewart, 1977; Metz *et al*, 1982).

Redmond and Schappert (1987) reported irritant contact dermatitis associated with residual PER (0.83 to 32.01 mg/kg) in dry-cleaned garments that had been encased in sealed plastic bags.

9.2.2 Respiratory Irritation

Exposure of human volunteers to PER vapour at a concentration of 1,060 ppm (7,300 mg/m^3) caused marked irritation of the upper respiratory tract. The effect was mild in volunteers exposed to concentrations of 600 ppm PER (4,134 mg/m^3) and was confined to mild nasal irritation at 216 ppm (1,488 mg/m^3) for 2 hours (Rowe *et al*, 1952).

9.2.3 Eye Irritation

Human volunteers exposed to PER vapour concentrations of 280 ppm (1,929 mg/m^3) and above experienced substantial irritation of the eyes and mucous membranes. Following exposure to lower concentrations (> 100 ppm; 689 mg/m^3) only mild symptoms of irritation of the eyes and nose were reported (Rowe *et al*, 1952; Stewart *et al*, 1961, 1970). At 20 ppm (138 mg/m^3) for 90 minutes, no irritation was reported (Wayne and Orcutt, 1960).

9.2.4 Skin Sensitisation

Skin sensitisation was reported in a worker occupationally exposed to PER. A closed 48-h patch test with 1% PER in olive oil produced a positive response in this subject (Vail, 1974).

9.2.5 Respiratory System Sensitisation

Boulet (1988) reported one case of occupational asthma after regular exposure for short periods of time to PER originating from dry-cleaned linen. After complete recovery, the patient was challenged again with PER, and he presented cough and dyspnoea.

9.2.6 Summary and Evaluation

The effects of PER on the skin range from a mild to moderate burning sensation when direct contact occurs for 5 - 10 minutes. Marked erythema can occur after prolonged exposure and blistering might occur if, for example, PER was trapped against the skin under clothing or in shoes. Exposure to PER vapour at concentrations above 100 ppm (689 mg/m^3) causes irritation of the eyes and respiratory tract. Single reports of sensitisation of the skin or the respiratory system have been published. These reports are of such low frequency, that PER would not be considered to be a skin or respiratory sensitiser.

9.3 EFFECTS ON THE CENTRAL NERVOUS SYSTEM

9.3.1 Volunteer Studies

Details of the available studies in human volunteers are summarised in Table 47.

Rowe *et al* (1952) exposed human volunteers to PER at concentrations ranging from 106 to 1,060 ppm (730 - 7,300 mg/m^3) for periods from a few minutes up to 8 hours (no control group). Following exposure to 216 ppm (1,488 mg/m^3) and above, reversible signs of CNS depression were observed, which increased in severity with higher levels of exposure. The most frequently reported subjective complaints of CNS depression were, in order of increasing severity: light-headedness, dizziness, drowsiness, headache, nausea, fatigue and impaired co-ordination. Exposure to 280 ppm (1,929 mg/m^3) for up to 2 hours or 600 ppm (4,134 mg/m^3) for 10 minutes resulted in a loss of motor co-ordination in groups of 4 subjects. Exposure to 106 ppm (730 mg/m^3) for 1 hour showed no significant adverse CNS effects.

Stewart *et al* (1961) exposed groups of healthy male volunteers (6/group) to either 101 ppm PER (696 mg/m^3) for 183 minutes, or to 194 ppm (1,337 mg/m^3) for 83 or 187 minutes; there was no control group. The findings in this study were comparable to those reported by Rowe *et al* (1952). Exposure to 101 ppm (696 mg/m^3) resulted in slight eye irritation and slight light-headedness but not in significant adverse CNS effects.

In another study, Stewart *et al* (1970) exposed (7 h/d) 5 healthy males to a mean concentration of 101 ppm PER (696 mg/m^3) for 5 days. Symptoms such as mild eye and throat irritation, light-headedness and mild headache were reported. Five objective tests of CNS performance were conducted either every 60 minutes during the exposure or 5 hours post-exposure; none showed any abnormality except the Romberg test of balance (conducted hourly during the exposure), which was abnormal in 3 of the 5 subjects within the first 3 hours of exposure. No control subjects were included in this study.

Stewart *et al* (1977) exposed (5.5 h/d, 5 d/wk) 12 volunteers (6 males and 6 females) to 0.25 or 100 ppm PER (1.72 or 689 mg/m^3) for 11 weeks in which subjects were also given diazepam and/or alcohol in combination with an exercise regime. A battery of neurological and behavioural tests was conducted to evaluate the effects of exposure: Romberg balance test, Flanagan co-ordination test, eye saccade velocity measurement, the Lorr-McNair mood scale and a rotary pursuit test. In addition, EEGs were recorded during exposure. The only effect attributed to PER was a slight but significant change in Flanagan co-ordination scores when the values on control days were combined with those following receipt of placebo-diazepam, but not when scores following exposure to PER were compared with controls. The authors concluded that exposure to PER at concentrations up to 100 ppm (689 mg/m^3) had no consistent effects on test performance.

Table 47: Neurological Effects Observed in Volunteer Studies

N and sex	Exposure regime and duration	Exposure concentration (ppm)	Exposure concentration (mg/m^3)[a]	Effects	Remark	Reference
4, sex not specified	Few min to 8 h	106 - 1,060	730 - 7,300	At 216 ppm and above, marked eye irritation and reversible signs of CNS effects. At 280 ppm for 2 hours or 600 ppm for 10 minutes, loss of motor co-ordination was observed. Exposure to 106 ppm for 1 hours resulted in very slight eye irritation only.	No control group	Rowe *et al*, 1952
6 M/group	183 min 83 or 187 min	101 194	696 1,337	The findings in this study were comparable to those reported by Rowe *et al* (1952). Exposure to 101 ppm resulted in slight eye irritation and slight light-headedness but not in significant adverse CNS effects.	No control group	Stewart *et al*, 1961
5 M	7 h/d for 5 d	101	696	Mild eye and throat irritation, light-headedness and mild headache were reported. Five objective tests of CNS performance were conducted; none showed any abnormality except the Romberg test of balance, which was abnormal in 3 of the 5 subjects within the first 3 hours of exposure.	No control subjects	Stewart *et al*, 1970
6 M, 6 F	5.5 h/d, 5 d/wk for 11 wk	0.25 100	1.72 689	The only effect attributed to PER was a slight but significant change in Flanagan co-ordination scores when placebo-diazepam scores were combined with control day scores, but not when PER days were compared with control days alone. The authors concluded that PER at concentrations up to 100 ppm had no consistent effects on test performance.	Complicated study design. Subjects were also given diazepam and/or alcohol in combination with an exercise regime.	Stewart *et al*, 1977
M + F, exposed for 1 h/d (3+2 subjects), 3 h/d (3+2 subjects) or 7.5 h/d (4+4 subjects)	1, 3 or 7.5 h/d, 5 d/wk for 1 wk; females exposed to 0 or 100 ppm only	0 20 100 150	0 138 689 1,034	Subjective evaluation of EEG scores suggested cortical depression in both males and females during exposure to 100 ppm for 7.5 hours. Visual evoked responses and equilibrium tests were normal. In behavioural tests (M only), mathematical skills, time discrimination, inspection and reaction time remained normal. Flanagan co-ordination scores were significantly decreased on at least 1 day during the 1-wk exposures to 100 and 150 ppm.		Hake and Stewart, 1977

Table 47: Neurological Effects Observed in Volunteer Studies (continued)

N and sex	Exposure regime and duration	Exposure concentration (ppm)	Exposure concentration (mg/m^3)[a]	Effects	Remark	Reference
22 healthy M	4 h/d for 4 d	10 50	68.9 344.5	Pattern-reversal, visual evoked potentials were minimally affected by acute exposure to 50 ppm. No effects were observed on auditory brainstem potentials. The comparison (control) subjects were exposed to 10 ppm PER in an attempt to confuse them about the nature of their exposure; no data was presented about the success of this confusion tactic.	Lack of information of the success of hiding knowledge of the PER exposure level makes it impossible to differentiate psychological from pharmacological effects of PER on the pattern-reversed visual-evoked potential (VEP)	Altmann *et al,* 1990

[a] Converted values

Hake and Stewart (1977) reported the results of a study in which healthy volunteers were sequentially exposed (5 d/wk) to 0, 20, 100 or 150 ppm PER (0, 138, 689 or 1,034 mg/m^3). Males were exposed (5 d/wk) for 1 h/d (3 subjects), 3 h/d (3 subjects) or 7.5 h/d (4 subjects) for 1 week. Females were exposed for 1 h/d (2 subjects), 3 h/d (2 subjects) or 7.5 h/d (4 subjects) to 0 or 100 ppm for 5 consecutive days. Subjective evaluation of EEG scores suggested cortical depression in both males and females during exposure to 100 ppm PER for 7.5 hours. Visual evoked responses and equilibrium tests were normal. In behavioural tests (males only), mathematical skills, time discrimination, inspection and reaction time remained normal. Flanagan co-ordination scores were significantly decreased on at least one day during the 1-wk exposures to 100 and 150 ppm (689 and 1,034 mg/m^3).

Altmann *et al* (1990) conducted various neurophysiological tests on 22 healthy male volunteers exposed (4 h/d) by inhalation to 10 or 50 ppm PER (68.9 or 344.5 mg/m^3) for 4 days. The pattern-reversal, visual-evoked potentials were minimally affected by acute exposure to 50 ppm PER. No effects were observed on auditory brainstem potentials. For comparison, control subjects were exposed to 10 ppm PER in an attempt to confuse them about the nature of their exposure; no data were presented about the success of this confusion tactic. Pattern-reversal evoked potentials are generated in the cortex, and are affected by psychological factors as well as pharmacological and toxicological factors (Spielmann, 1985). The auditory brainstem response is not appreciably affected by psychological factors. Thus, lack of information of the success of hiding knowledge of the PER exposure level makes it impossible to differentiate psychological from pharmacological effects of PER in this study.

9.3.2 Occupational Studies

Details of occupational exposure studies are summarised in Table 48.

Table 48: Neurological Effects observed in Occupational Exposure Studies

N, job	Exposure duration	Exposure concentration[a] (ppm)	(mg/m^3)	Effects	Remarks	References
Not specified	Not specified	(98.3 - 393.2)	678 - 2,712	Moderate pre-narcotic effects, headache, drowsiness, vertigo, nervousness or fatigue have been reported during long-term exposure to PER in manufacture of semi-conductors and in dry-cleaning shops		Münzer and Heder, 1972; WHO, 1984
9 factory employees	2 months - 27 years	(< 30 ppm)	< 210	Fatigue, drowsiness, breathlessness and headache. No effect on serum aminotransferase activity.	No control group	Chmielewski *et al*, 1976
16 factory employees	2 months - 27 years	(58.0 – 435)	400 - 3,000	Above symptoms reported. Also, 6 workers diagnosed with “pseudoneurotic syndrome”, 4 with abnormal EEG recordings. Subjective complaints of irritation and neurological disorders not related to duration of exposure. 2 - 3 fold increase in serum aminotransferase activity.	No control group	Chmielewski *et al*, 1976
20 dry-cleaning workers	7.5 years	1.3 - 36.5, TWA	(9,0 - 252, TWA)	Neurotoxic effects, including differences in proximal motor latency of nerve cells and electrodiagnostic and neurological ratings. Correlation was found between years of exposure and certain behavioural variables.	No conclusions can be drawn from the data, because exposure to Stoddard's solvent was a confounding factor in this study	Tuttle *et al*, 1977
2 groups, not further specified	Not specified	< 45 > 45	(< 310) (> 310)	A cross-sectional study among dry-cleaners described symptoms of drunkenness, self-reports of irritability and a reduced ability to concentrate. Impairments of short-term memory and of psychomotoric dexterity were also reported.	A clear threshold for the risk of neuro-behavioural long-term effects was not found	Seeber, 1989
Not specified	Not specified	21, TWA	(145)	No indication of a harmful impact on the CNS was obtained, as measured in a series of psychomotor tests.		Lauwerys *et al*, 1983

Table 48: Neurological Effects observed in Occupational Exposure Studies (continued)

N, job	Exposure duration	Exposure concentration[a] (ppm)	(mg/m^3)	Effects	Remarks	References
A 68-year-old man, who had owned a dry-cleaning shop	> 30 years	Not specified	-	The man had suffered a complete loss of hair and finger nails in 1982 and had been sent to a clinic with a history of memory impairment that could have been due to progressive dementia (Alzheimer's Disease). Serum levels of PER appeared to be 15 times higher than that of the general population. Neuropsychological testing performed some months after the initial medical diagnosis of probable Alzheimer's Disease failed to confirm a significant cognitive impairment, thus questioning the initial diagnosis.	The authors concluded that the observed symptoms may have been occupationally related	Freed and Kandel, 1988
45 dry-cleaners, 103 people living close to dry-cleaning shops and 106 unexposed controls	Not specified	Not specified	-	Self-reports were made of drowsiness, nervousness, enhanced fatigue, decrease in the ability to concentrate, memory disturbances and increased perspiration among the exposed groups. Levels of PER in the blood were increased in the dry-cleaners (147 - 416 µg/l) and in the people living close to dry-cleaning shops (average value 13 µg/l) compared to the controls (average value 1 µg/l).	The authors concluded that following exposure to approximately 50 ppm PER (344.5 mg/m^3), reversible psychomotoric effects occur in humans.	Winneke *et al*, 1989
7 males, 50 females 5 males, 39 females (all 101 dry-cleaners)	141 d 127 d	(12.1) (52.8)	83.4 363.8	Statistically significant differences were observed between the exposure groups and the controls (20 males/64 females) in perceptual speed, digit reproduction, digit symbol, choice reaction and cancellation tests. No dose-related differences were found between the low and the high exposure group. In 5 of the 8 categories the high-exposure group performed better than the low-exposure group. Given that the high-exposure level was 4 times greater than the low exposure levels, this is strongly suggestive of differences from factors other than PER.	This study is an exploratory analysis (i.e. hypothesis generating), and it should be considered as such	Seeber, 1989

Table 48: Neurological Effects observed in Occupational Exposure Studies (continued)

N, job	Exposure duration	Exposure concentration[a] (ppm)	(mg/m^3)	Effects	Remarks	References
60 female dry-cleaners	Not specified	1 - 67, median: 15	(6.9 - 462, 103.4)	The exposed workers showed a slower response time on finger tapping, simple reaction time but no effects on tasks that were more cognitive (digit symbol, shape comparison tasks) were observed. Prolactin levels were increased in the exposed group. Neither duration of exposure nor air or blood levels of PER were significantly correlated to the performance or prolactin measurements.	Controls: 30 female workers from a cleaning plant that did not use solvents.	Ferroni *et al,* 1992
22 dry-cleaners	106 months	0.4 - 31.2, TWA 7.3 ± 8.3	(2.8 - 215, 50 ± 57)	The authors concluded that the exposed workers had a sub-clinical colour vision loss, mainly in the blue-yellow range, and claimed that this effect was related to PER exposure levels below current occupational exposure limits. However, no increase was observed for the group of ironers who had quite similar and comparatively low levels of exposure to PER.	Many possible confounders exist to account for the difference in colour performance.	Cavalleri *et al,* 1994
13 ironers (in 12 dry-cleaning shops)	106 months	0.5 - 11.3, TWA 4.8 ± 3.5	(3.4 - 78, 33 ± 24)			
30 male dry-cleaners	Not specified	TWA 15	(103.4)	Except for one male dry-cleaner and one male in the control group, no cases of colour vision loss were found.	Control group of 48 male and 72 female workers	Nakatsuka *et al,* 1992
34 female dry-cleaners		TWA 11	(76)			
3 groups of 65 dry-cleaners, incl. 4 cases	Not specified	Mean 11.2	(77)	All 4 cases were interviewed and underwent a battery of neuropsychological tests, which showed deficits in visospatial function and memory and disturbances in mood in these patients. The authors concluded that sub-clinical impairment on selected performance measures occurred in workers below 40 ppm.	This study had several deficiencies including a low participation rate (only 23 of the 125 shops approached actually participated in the study) and the lack of an unexposed control group. It is speculative to relate these effects to exposure to PER.	Echevarria *et al,* 1995
		Mean 22.3	(153.6)			
		Mean 40.8	(281.1)			

[a] Converted values in parentheses

Moderate pre-narcotic effects (headache, drowsiness, vertigo, nervousness or fatigue) have been reported during long-term exposure to concentrations ranging from 678 - 2,712 mg PER/m^3 (98.3 - 393.2 ppm) in the manufacture of semi-conductors and in dry-cleaning shops (Münzer and Heder, 1972; WHO, 1984).

Chmielewski *et al* (1976) reported fatigue, drowsiness, breathlessness and headache in a group of 9 factory workers exposed to low concentrations of PER (< 210 mg/m^3, < 30 ppm).

In another factory, Chmielewski *et al* (1976) identified 6 subjects diagnosed with “pseudoneurotic syndrome” and 4 subjects with abnormal EEG recordings among 16 workers exposed to 400-3,000 mg PER/m^3 (58.0 - 435 ppm) for periods ranging from 2 months to more than 20 years. Subjective complaints of neurological disorders such as irritability did not appear to be related to the duration of exposure.

Tuttle *et al* (1977) examined 18 dry-cleaners, with an average exposure of 7.5 years to a TWA level of 1.3 - 36.5 ppm PER (9.0 - 252 mg/m^3), and 9 controls in a behavioural/neurological test battery. Differences were reported between exposed and control workers in electrodiagnostic rating scores but limited correlation existed between years of exposure and some behavioural variables. However, no definite conclusions can be drawn from the data, because exposure to Stoddard's solvent (a mixture of hydrocarbons) was a confounding factor in this study.

A cross-sectional study among dry-cleaners described symptoms of drunkenness, self-reports of irritability and a reduced ability to concentrate. Impairments of short-term memory and of psychomotor dexterity were also reported. Subjects were divided into 2 groups: those who were exposed to PER at concentrations below 45 ppm and those exposed to concentrations above 45 ppm (310 mg/m^3). No clear threshold for the risk of neurobehavioral long-term effects was found (Seeber, 1989).

A group of dry-cleaners exposed to 21 ppm PER (145 mg/m^3) showed no indications of effects on the CNS when measured in a series of psychomotor tests, compared to a group of control subjects (Lauwerys *et al*, 1983).

Freed and Kandel (1988) described a case of a 68-year-old man who had owned a dry-cleaning shop for over 30 years. In 1981, he was forced to invest in new ventilation equipment (because his operation was found to have unacceptable vapour levels). He suffered a complete loss of hair and finger nails in 1982 and had a history of memory impairment that could have been due to progressive dementia (Alzheimer's Disease). His serum level of PER was 745 μg/l, i.e. 15 times higher than that of the general population (< 50 μg/l). Neuropsychological testing performed some months after the initial medical diagnosis of probable Alzheimer's Disease failed to confirm a significant cognitive

impairment, thus questioning the initial diagnosis. The authors concluded that the observed symptoms might have been occupationally related.

Winneke *et al* (1989) studied 45 dry-cleaners, 103 people living close to dry-cleaning shops and 106 unexposed controls. Self-reports were made of drowsiness, nervousness, enhanced fatigue, decrease in the ability to concentrate, memory disturbances and increased perspiration among the exposed groups. Levels of PER in the blood were increased in the dry-cleaners (147 - 416 µg/l) and in the people living close to dry-cleaning shops (average value 13 µg/l) compared to the controls (average value 1 µg/l). The authors concluded that following exposure to approximately 50 ppm PER (344,5 mg/m^3), reversible psychomotor effects occurred in humans.

Seeber (1989) studied 101 dry-cleaners, of which 57 workers (7 males, 50 females) were exposed to 83.4 mg PER/m^3 (12.1 ppm) for 141 days (average values) and 44 workers (5 males, 39 females) to 363.8 mg/m^3 (52.8 ppm) for 127 days (average values). The CNS effects of PER exposure were evaluated using a number of psychological tests. Age, gender, daily consumption of alcohol and intellectual level was taken into consideration in this study. Statistically significant differences were observed between the exposure groups and the controls (20 males/64 females) in perceptual speed, digit reproduction, digit symbol, choice reaction and cancellation tests. No dose-related differences were found between the low and the high exposure group. In 5 of the 8 categories the high exposure group performed better than the low exposure group. Since the high exposure level was 4 times greater than the low exposure levels, this is strongly suggestive of differences from factors other than PER. Alcohol consumption was not found to affect the exposure-related group differences. The statistical method (multiple t-tests) used by the author is an inappropriate method of analysis as it inflates the overall Type I error rate. The author himself cautions the reader against "over-interpretation" of the data. This study is an exploratory (hypothesis generating) analysis, and it should not be considered as definitive.

Ferroni *et al* (1992) conducted a cross-sectional study in 60 females working in dry-cleaning shops. The control group consisted of 30 female workers from a cleaning plant that did not use solvents. Prolactin blood levels were measured just prior to the performance of a battery of neurobehavioral tests (finger tapping, simple reaction times, digit symbol and shape comparison tests). Exposure levels to PER varied from 1 to 67 ppm (median 15 ppm) (6.9 - 462; 103.4 mg/m^3). The exposed workers showed a slower response time on finger tapping and simple reaction time but no effects on tasks that were more cognitive (digit symbol, shape comparison tasks) were observed. Prolactin blood levels were increased in the exposed group. However, neither duration of exposure nor air or blood levels of PER was significantly correlated to the performance or prolactin blood levels.

In a colour vision study by Cavalleri *et al* (1994), 22 dry-cleaners and 13 ironers from 12 dry-cleaning shops were compared to a paired number of controls. The mean 8-h TWA level of PER for the dry-

cleaners was 7.3 ± 8.3 ppm (range 0.4 - 31.2 ppm) (50 ± 57; 2.8 - 215 mg/m^3) and 4.8 ± 3.5 ppm (range 0.5 - 11.3 ppm) (33 ± 24; 3.4 - 78 mg/m^3) for the ironers; the mean exposure period was 106 months. The authors concluded that the exposed workers had a sub-clinical colour vision loss, mainly in the blue-yellow range, and claimed that this effect was related to exposure to PER. The "colour confusion index" for this group was significantly increased compared to the controls. However, no increase was observed for the group of ironers who had quite similar but low levels of exposure to PER. This study lacks sufficient information about how subjects were actually tested. If not tested in a random or counterbalanced order, then small but significant differences may be due to a group effect that is independent of exposure. Many possible confounders (e.g. non double-blind study, differential knowledge of controls and exposed subjects) could account for the difference in colour performance, and the data from Cavalleri *et al* do not support the authors' conclusion that exposure to low levels of PER causes loss of colour vision.

The results of Cavalleri *et al* are also in contrast to the findings of the study by Nakatsuka *et al* (1992) in which 30 men and 34 women working in the dry-cleaning industry were screened for colour vision loss using the same test. Mean (8-h TWA) exposure levels of PER were 15 ppm (103.4 mg/m^3) for males and 11 ppm (76 mg/m^3) for females. The control group consisted of 48 male and 72 female workers from the same factories. Except for one male dry-cleaner and one male in the control group, no colour vision loss was found.

Echevarria *et al* (1995) reported 4 case studies of neurobehavioral effects of PER. The 4 patients were referred by physicians for neuropsychological evaluation for possible solvent encephalopathy. All were interviewed and underwent a battery of neuropsychological tests, which showed deficits in visospatial function and memory and disturbances in mood in these patients. The diagnostic criterion used by the physicians was that PER was the major source of toxicant exposure, although no exposure levels were available for these patients. This form of logic is error prone as the "solvents syndrome" is non-specific and depends almost entirely on elimination of alternate causes. The association of these effects to exposure to PER is speculative.

The same authors (Echevarria *et al*, 1995) reported an epidemiological evaluation of neurobehaviour of 65 dry-cleaners. PER was analysed in breath and air in order to classify the subjects into low-, moderate- and high-exposure groups with mean air levels of 11.2, 22.3 and 40.8 ppm (77, 153.6 and 281.1 mg/m^3), respectively. The authors concluded that sub-clinical impairment on selected performance measures occurred in workers exposed to levels below 40 ppm (275.6 mg/m^3). This study had several deficiencies including a low participation rate (only 23 of the 125 shops approached actually participated in the study) and the lack of an unexposed control group. The methods did not specify how to avoid bias by the subject's knowledge of exposure, the intent of the study or the presumed level of exposure. It is likely that employees were aware of potential health issues as occupational exposure limits had been reduced from 50 to 25 ppm (344.5 - 172 mg/m^3) at the time the

study was conducted. Partitioning the subjects into 3 exposure groups also caused an unbalanced representation of jobs (e.g. counter clerks most often in the low-exposure group), suggesting that the test results were confounded by occupation. There were other major differences between subjects at different exposure levels (age, vocabulary, and years on job). The likelihood of uncorrected differences affecting the data are made more plausible since the performance decrements (in tests for visual reproduction, pattern recognition and pattern memory) are small and considered to be sub-clinical. Given that confounding factors were not controlled and that the effects reported were small, it cannot be concluded that PER was the source of group differences in performance.

Summary and Evaluation

In humans, acute and chronic exposure to PER have been shown to produce effects on the CNS that are reversible and of a neuro-pharmacological nature. After single exposures, the threshold for these effects is around 100 - 200 ppm (689 - 1,378 mg/m^3).

There are isolated reports that suggest that chronic exposure to low levels of PER can lead to significant effects on the CNS. However, these reports are limited and potentially confounded by other factors. They do not establish a clear causal relation between exposure to PER and chronic damage to the CNS.

9.3.3 Non-Occupational Studies

Moderate pre-narcotic to severe anaesthetic effects have been frequently reported in humans acutely exposed to presumed high concentrations of PER from evaporation from clothes and fabrics following generally improperly used self-service coin-operated dry-cleaning machines (Garnier *et al*, 1996) (Section 9.1.3).

Altmann *et al* (1995) studied the effects on the CNS of chronic low-level exposure to PER in subjects living (mean residential time of 10.6 years) in the neighbourhood of dry-cleaning shops. Neurobehavioral tests were performed using a German version of the NES battery. Additionally, pattern reversed visual-evoked potentials (VEPs) were recorded. The authors claim a statistically significant difference between the exposed subjects and the controls for the NES test for vigilance, simple reaction time and visual memory. The mean indoor air concentration measured in the residences was 1.36 mg PER/m^3 (0.197 ppm). There are no data are available to evaluate dose-response relationship and it is doubtful whether the control group was adequate. Job satisfaction, personality, hobbies, diet, unfavourable work conditions and other variables that can affect the results of such a study had not been taken into account.

9.4 MUTAGENICITY

Studies on lymphocytes from 10 factory workers occupationally exposed to PER for periods ranging from 3 months to 18 years showed no significant dose-related differences from controls in numerical or structural chromosomal aberrations, SCE rate, the proportion of M2 and M3 metaphases and mitotic index (Ikeda *et al*, 1980). The study is of limited value because the workers studied were not matched to the control group with regard to age, sex, race or social-economic status. No indication was available of the medical histories of the subjects.

The frequency of sister chromatid exchanges (SCE) was studied in 27 men and women (both smokers and non-smokers) exposed to PER in dry-cleaning shops and 19 men and women exposed to PER, and also to trichloroethylene, during their manufacture. Increases in SCE were reported in males from both groups who were smokers. No increases were reported in the non-smokers (Seiji *et al*, 1990). The Task Force concluded that the effect of smoking could not be ruled out as a causative agent for this effect

Böttger *et al* (1990) found a slight, but statistically significant, increase in chromosome aberrations in peripheral lymphocytes of 7 volunteers exposed (4 h/d) to 50 ppm PER (344.5 mg/m^3) for 4 days. The frequency of these chromosome aberrations was comparable to those found in 6 volunteers before and after exposure to 10 ppm PER (68.9 mg/m^3). This study is of limited value because of the small number of exposed people and the lack of a suitable control group. In addition, no information was provided about age, sex, smoking or health status of the volunteers (e.g. alcohol consumption).

9.5 CARCINOGENICITY

9.5.1 Epidemiology

Estimates of the number of individuals in the USA potentially exposed to PER vary from 0.5 million (NIOSH, 1978 as quoted in Santodonato *et al*, 1985) to 1.6 million (NIOSH, 1977 as quoted in Brown and Kaplan, 1987). There are no epidemiological studies of populations in the USA exposed exclusively to PER but studies of some relevance have been performed among workers in the dry-cleaning and laundry industries; a single study has been performed in which PER was used in metal cleaning. Additional studies are available from Scandinavia, in which exposure to PER (along with solvents) occurred in the dry-cleaning and metal cleaning industries.

Studies in the Laundry and Dry-Cleaning Industry

PER was introduced into the dry-cleaning industry in the late 1930s but did not replace other synthetic solvents, such as carbon tetrachloride, trichloroethylene and benzene (used for spot cleaning) until early in the 1950s. Prior to 1960, petroleum derivatives were still the dominant solvents used. By

1977, at least 73% of the dry-cleaning shops in the USA were using PER as the main solvent; a similar figure (75%) has been estimated for 1987 (HSIA, 1989). The use of multiple and mixed solvents for dry-cleaning makes it difficult to draw conclusions from epidemiological studies about possible associations between exposure to any single solvent, including PER, and the incidence of cancer. In addition, none of the studies reported have given good estimates of the extent of exposure to PER.

Many of the epidemiology studies involve both dry-cleaning and laundry workers. The assumption made is that laundry workers do not have regular occupational exposure to solvents. Dry-cleaning workers are exposed to solvents of many types, including PER. Typical levels of exposure to PER are described in Section 5.3.2 and Table 23.

Cohort Mortality Studies

Investigators at the US National Cancer Institute conducted a retrospective cohort mortality study of members of a union of dry-cleaning workers in Missouri, United States (Blair *et al*, 1986, 1990). The union had 11,062 members between 1945 and 1978, but the study was restricted to 5,790 persons who had held membership for one year or more. After exclusion of 425 members for whom information on race, sex, date of birth or date of entry was unavailable, analysis was restricted to 5,365 members (407 white males, 912 black males, 2,565 white females and 1,481 black females). The members were followed-up from entry to the unions or 1 January 1948 (whichever came later) until 1 January 1979. The vital status of 88% of the cohort was achieved. No measurements were made of the exposure of study members to PER. Instead, subjects were assigned a relative exposure score based on the job(s) they held within the industry. Based on published data, cleaners were estimated to have had the highest average exposures. Counter workers, pressers, sewers and maintenance workers were estimated to have had similar levels of average exposure, which were approximately one sixth of the average level of exposure of the cleaners. Cleaners and maintenance workers were estimated to have had the highest peak exposure levels, which were approximately an order of magnitude higher than those of other workers. The investigation considered that a member first employed as a dry cleaner after 1960 would be more likely to have been exposed to PER than those first employed before 1960. However, data were provided only for the entire cohort; SMRs were stated to have been similar for workers first employed before 1960 and those first employed after that date.

The SMR for all causes of death was 90 based on 1,129 deaths (compared to expected numbers based on general US mortality rates), significantly lower than expected. However, deaths due to all cancers were significantly elevated (SMR = 120; 95% CI 100 - 130; 294 deaths). Significant excesses were reported for oesophageal cancer (SMR = 210; 95% CI 110 - 360; 13 deaths) and cervical cancer (SMR = 170; 95% CI 100 - 200; 21 deaths). The excess of oesophageal cancer was

due to raised mortality in black men (11 of 13 deaths; SMR = 350). Non-significant excesses occurred for lung cancer (SMR = 130; 95% CI 90 - 170; 47 deaths), bladder cancer (SMR = 170; 95% CI 70 - 330; 8 deaths) and lymphosarcoma and reticulosarcoma (SMR = 170; 95% CI 70 - 340; 7 deaths). There was no excess of cancers of the liver or the kidney.

No association between the level of exposure and mortality from all cancers, cervical cancer, oesophageal and bladder cancer was observed. However, a significant exposure response trend for all lymphatic and haematopoietic cancer was reported which was entirely due to an excess of such cancers in cleaners, the highest exposed group of workers (5 observed and 1.3 expected deaths). Analyses by duration, peak and cumulative trend did not uncover any significant trends, although the sub-group with the highest level of cumulative exposure was reported to have an elevated death rate from oesophageal cancer (SMR = 280), but the number of deaths in this sub-group was not reported. SMRs of 90 and 30 were reported for the low and medium cumulative exposure categories, respectively. Proportional mortality among the same workers was reported in a previous study (Blair *et al*, 1979).

An updating of an earlier cohort mortality study in the USA (Kaplan, 1980; Brown and Kaplan, 1987) included 1,701 dry-cleaning workers in dry-cleaning unions in four cities in California, Illinois, Michigan and New York (Ruder *et al*, 1994). Employees who had worked for at least one year before 1960 at a shop using PER as the primary solvent, and who were not known to have been exposed to carbon tetrachloride, were eligible for inclusion. A survey in 1977-79 (Brown and Kaplan, 1987) reported geometric mean, TWA, concentrations of 22 ppm PER (151.6 mg/m^3) for operators and 3 ppm PER (21 mg/m^3) for other workers. Other solvents used for spot cleaning were not detected in the samples. The vital status of 95% of subjects was determined as at 31 December 1990. The period of observation started on 1 January 1940 or one year after employment in a PER shop, whichever was later. The investigators were able to determine a sub-cohort of 625 subjects who had only worked in dry-cleaning shops where PER was the primary solvent. The mean duration of employment in dry-cleaning up to 31 December 1990 was 6.4 years for subjects in the PER only group and 11.4 years for those also exposed to other solvents; the latter group had a mean duration of 6.0 years employment in shops where PER was the primary solvent. Expected deaths were calculated using general US mortality rates.

Deaths from all causes were slightly elevated (SMR = 101; 95% CI 94 - 109; 769 deaths) and cancer deaths overall were in excess (SMR = 123; 95% CI 107 - 141, 209 deaths). There were significant elevations of oesophageal cancer (SMR = 214; 95% CI 102 - 394, 10 deaths), cancers of the colon and small intestine (SMR = 156; 95% CI 102 - 229; 26 deaths) and bladder cancer (SMR = 254; 95% CI 116 - 482; 9 deaths). Excesses of pancreatic cancer (SMR = 166; 95% CI 93 - 275; 15 deaths), lung cancer (SMR = 118; 95% CI 85 - 159, 43 deaths) and cervical cancer (SMR = 180; 95% CI 86 - 331, 10 deaths) were also reported. There were also 3 cancers of the tongue

(SMR = 354; 95% CI 73 - 1040) and 4 kidney cancers (SMR = 146; 95% CI 116 - 482). Only one cancer of the liver and bilary tract was reported (4.8 expected). When the analysis was restricted to workers with a 20-year latency since first employment and a length of employment ≥ 5 years, the SMRs were increased for cancers at all sites (SMR = 150; 95% CI 120 - 190; 83 deaths) and in particular, for oesophageal cancer (SMR = 540; 95% CI 230 - 1100; 8 deaths) and bladder cancer (SMR = 650; 95% CI 280 - 1320; 8 deaths). However, there was no excess of lung cancer in this group (SMR = 91; 95% CI 50 - 160; 12 deaths). In the PER-only sub-cohort, there was only a slight excess of all cancers (SMR = 101; 95% CI 76 - 132; 54 deaths). A non-significant excess of oesophageal cancer (SMR = 264; 95% CI 72 - 676; 4 deaths) was reported in the PER-only sub-cohort and all of these workers had a 20-year latency and ≥ 5 years duration (SMR = 717; 95% CI 192 -1982). It was not stated whether cervical cancer was in excess in the PER-only sub-cohort, but an excess of cancer of the female genital organs was reported (SMR = 157; 95% CI 68 - 310; 8 deaths). There were no deaths from bladder cancer in the PER-only sub-cohort (1.0 expected deaths) and only 1 kidney cancer death (0.9 expected deaths).

Other Laundry and Dry-cleaning Studies

Several studies of proportional mortality amongst dry cleaners have also been reported. Katz and Jowett (1981) reported a proportional mortality study of 671 deaths of white females who had worked at laundries and dry-cleaning shops in Wisconsin (USA) between 1963 and 1977. Nakamura (1985) reported a proportional mortality study of 1,711 deaths between 1971 and 1980 of members of the All-Japan Laundry and Dry-cleaning Association. Duh and Asal (1984) reported on a proportional analysis of the causes of death of 440 laundry and dry-cleaning workers which occurred between 1975 and 1981 in Oklahoma (USA). None of these studies provides sufficient information to distinguish between laundry workers and dry-cleaning workers. In addition, Nakamura (1985) reported that in recent years only 30% of dry-cleaning was done using PER and Duh and Asal (1984) noted that petroleum solvents accounted for more than 50% of the dry-cleaning solvents used in Oklahoma.

Lynge (1994) updated an earlier study (Lynge and Thygesen, 1990) of cancer incidence among 10,600 persons enumerated in the 1970 Danish population census and who were stated to be employed in the “laundries, cleaning and dyeing” industries. Lynge (1994) reported a Standardised Incidence Ratio (SIR) of 270 for liver cancer in women (95% CI 150 - 450; 14 cases). Three cases were observed in men (2.5 expected). Lynge and Thygesen (1990) had earlier reported no increase in kidney cancer incidence in this cohort of laundry and dry-cleaning workers.

A nested case-control study of the 17 cases of primary liver cancer and 16 cases of renal cell carcinoma was later performed (Lynge *et al*, 1995). Five referents for each case were randomly selected from the cohort, the cases being matched on age, gender, occupation and location at the time of diagnosis. All 17 primary liver cancer patients and 13/16 renal cell carcinoma patients had

worked in laundries at the time of the census, whereas only 74% and 84% of the respective referents had worked in laundries. The relative risk of renal cell cancer was 0.7 (95% CI 0.2 - 2.6) and hence, there was no elevated risk of liver cancer or renal cell cancer associated with work in the dry-cleaning industry.

Laundry and dry-cleaning workers in the Swedish population at the time of the 1960 census have also been followed up for cancer incidence (Malker and Weiner, 1984; McLaughlin *et al*, 1987). The results provide little information about the possible effects of exposure to PER because it is not possible to separate dry cleaners from laundry workers and because the level of exposure of dry cleaners to PER is not known. However, the SIR for cancer of the liver and bilary passages cancer was reported as 120 (95% CI 70 - 180; 16 observed) by Malker and Weiner (1984) for the follow-up period 1961-73. McLaughlin *et al* (1987) reported results for renal cancer for the follow-up period 1961-1979. The SIR was 99 (95% CI 60 - 160; 18 cases) in men and 86 (95% CI 60 - 130; 25 cases) in women.

Other Cohort Studies

Anttila *et al* (1995) studied a cohort of 3,974 persons in Finland who were biologically monitored for occupational exposure to three halogenated hydrocarbons (3,089 for trichloroethylene, 849 for PER and 271 for 1,1,1-trichloroethane) during 1965-83. The cohort was followed-up for incident cancer cases through 1992, and the expected numbers were calculated on the basis of Finnish national rates. The median measured level of PER in blood during 1974-83 was 0.7 µmol/l in men and 0.4 µmol/l in women. On average, 3.2 measurements/ individual were made for PER in blood. A total of 31 cancer cases were observed in the sub-cohort exposed to PER (SIR = 90; 95% CI 61 - 130). Increased risks were seen for cancers at some sites, but none was significant. There were 2 cases of cervical cancer (SIR = 320; 95% CI 39 - 1160) and 3 cases of NHL (SIR = 380; 95% CI 22 - 656).

Spirtas *et al* (1991) analysed a cohort of 14,457 civilian employees who had worked for at least one year at an airforce base in Utah (USA) between 1 January 1952 and 31 December 1956. The cohort was followed until 31 December 1982 and vital status was ascertained for 97%. The study subjects maintained and overhauled aircraft and missiles, cleaning and repairing small parts. The study was conducted in response to concerns about adverse health symptoms reported by around 120 workers in one building at the base and preliminary evidence of a raised proportion of deaths from neoplasms of lymphatic and haematopoietic tissue, especially multiple myeloma. Of the 14,457 cohort members, 10,256 were classified as having been exposed to mixed solvents and 851 to PER. Mortality findings in the sub-cohort exposed to PER were only presented for two cancer sites; multiple myeloma and non-Hodgkin's lymphoma (NHL). These analyses showed 2 deaths from multiple myeloma in women (0.12 expected) and 4 deaths from NHL in men and women (SMR = 315, 95% CI 86 - 609).

Olsen *et al* (1989) studied a cohort of 2,610 white men employed for one or more years in a chemical company in Louisiana (USA). PER was one of many chemicals produced in the 16 production plants

at the site. The cohort was followed-up between 1.1.56 and 1.1.81 and vital status was ascertained for 98.9% of the cohort. All cause mortality was significantly reduced (SMR = 56; 95% CI 42 - 75; 48 deaths) and overall cancer mortality was also reduced (SMR = 76; 95% CI 38 - 140; 11 deaths), both in comparison with local rates. There was a significant increase in mortality from leukaemia and aleukaemia (3 observed, 0.61 expected), but these were all of different types and occurred in men with different employment histories. No information was provided about the proportion of employees that had been exposed to PER or their levels of exposure.

Case-Control Studies

Liver and Biliary Tract Cancer

Hardell *et al* (1984) conducted a study of 98 patients with liver cancer and 200 matched controls from the Umea region of Sweden. One patient reported exposure to PER. Bond *et al* (1990) conducted a case-control study nested in a cohort of 21,347 workers employed at chemical plants in Michigan (USA). The cases consisted of 44 men who had died between 1940 and 1982 and whose death certificates mentioned liver or bilary duct cancer. A total of 6,259 men in the cohort had died between 1940 and 1982. A random sample of 1,888 men was selected as controls and employment records searched for potential exposure to PER and 10 other chemicals. Six of the liver and bilary duct cancer cases were exposed to PER giving an odds ratio of 1.8 (95% CI 0.8 - 4.3).

Lymphoma

Hardell *et al* (1981) studied 169 patients with malignant lymphoma and 338 controls in the Umea region of Sweden. One patient reported exposure to PER.

Brain Cancer

Heineman *et al* (1994) reported findings from a case-control study of 300 white men who had died from astrocytic brain tumours and a matched group of 320 deceased controls. Heineman *et al* (1994) originally undertook to study 741 white men who had died from astrocytic brain tumours, but it was only possible to obtain interviews from the next of kin of these cases and a hospital diagnosis of astrocytic brain cancer could only be confirmed for 300 of these. Exposure to 6 solvents was assessed on the basis of a job exposure matrix. A total of 111 of the 300 astrocytic brain tumour cases had job titles that were compatible with exposure to PER (odds ratio = 1.2; 95% CI 0.8 - 16).

Multiple Sites

Siematycki (1991) studied men aged 33 - 70 years in Montreal (Canada) during 1979-85. A total of 3,730 men with cancer at 21 sites and 533 population controls were interviewed about their

occupations and their exposure to 293 agents and mixtures assessed. The estimated prevalence of exposure to PER was approximately 1%. Only the odds ratio for prostatic cancer was significantly elevated for substantial exposure to PER (odds ratio = 3.2; 95% CI 1.1 - 9.3; 8 cases).

Ill-Defined Exposure

A case-control study of renal cell carcinoma patients evaluated exposure to degreasing solvents, the most common of which were reported to be PER, 1,1,1-trichloroethane, trichloroethylene and methylene chloride. In addition, dry-cleaning has been evaluated for possible associations with several types of cancer in case-control studies. The studies addressed cancers of the colon (Frederiksson *et al*, 1989), liver (Suarez *et al*, 1989), lung (Brownson *et al*, 1993), kidney (Asal *et al*, 1988; McCredie and Stewart, 1993) and bladder (Schoenberg *et al*, 1984). However, these studies provide inadequate information about the exposure to PER and are not discussed further.

Studies of Drinking Water

Several studies have been conducted of cancer occurrence in populations exposed to drinking water contaminated by PER (Isacson *et al*, 1985; Lagakos *et al*, 1986; Vartainen *et al*, 1993; Cohn *et al*, 1994). These studies are difficult to interpret because of a number of methodological problems, in particular, co-exposure to trichloroethylene and other compounds (IARC, 1995). However, none of these studies reported any elevations of cancer incidence that could be related to PER exposure.

Aschengrau *et al* (1993) studied residents of 5 towns in Massachusetts where PER from the lining of distribution pipes had contaminated the drinking water. Results were presented for study groups consisting of 61 people with cancer of the urinary bladder and 852 controls, 35 people with kidney cancer and 777 controls and 34 people with leukaemia and 737 controls. Six other types of cancer were studied but not reported. Results were presented only for “high” exposure defined as exposure to PER at or above the 90th percentile. None of the kidney cancer cases had “high” exposure to PER but odds ratios of 4.0 (95% CI 0.65 - 25; 4 cases) and 8.3 (95% CI 1.5 - 45; 2 cases) were reported for urinary bladder cancer and leukaemia, respectively, in people with “high” exposure to PER.

9.5.2 Summary

Three cohort studies provide the most relevant data for assessing the relationship between exposure to PER and cancer risk (Blair *et al*, 1990; Ruder *et al*, 1994; Anttila *et al*, 1995). All three studies contain a sub-cohort whose exposure was principally to PER and all contain some information about exposure to PER. However, Blair *et al* provided no detailed findings for the post-1960 sub-cohort who would have been predominantly exposed to PER. The limitations of only these three studies will be discussed in detail.

Exposure assessment is the main weakness of the three cohort studies which provided the most relevant epidemiological data (Blair *et al*, 1990; Ruder *et al*, 1994; Anttila *et al*, 1995). In the study reported by Ruder *et al* (1994), the only information about the exposure of the cohort to PER is provided by a 1977-1979 survey of a random sample of facilities (still in business). No attempt was made to calculate measures of exposure for individual workers. Blair *et al* (1990) estimated qualitative indices of solvent exposure based on other published data. For the post 1960 sub-cohort, the solvent exposure indices provide a primary estimate of exposure to PER. The cohort studied by Anttila is the only group of workers for which individual measurements were available for all cohort members. However, only one blood-PER sample was analysed for 61% of the workers and fewer than 3 samples for 79% of the workers. In addition, it is not known when these workers were first exposed to PER, how long they were exposed and in what circumstances. Some of the sub-cohort of workers monitored for blood-PER will also have been exposed to other halogenated hydrocarbons as approximately 5.6% of the study population were monitored for at least two solvents. The authors noted that the biological monitoring data did not allow a reliable internal comparison within the cohort.

Other than factors such as gender, race and calendar year of follow-up, none of the investigators collected data on determinants of mortality for the various cancers of interest. Of greatest concern is the possibility that dry cleaners and the general US and Finnish populations differ with respect to risk factors for the incidence of one or more types of cancer (i.e. the possibility of confounding). Blair *et al* (1990) note that there is evidence that dry cleaners may smoke more than members of other occupations and may also consume more alcohol; alcohol use often parallels tobacco use.

A further limitation of these studies is their low power to detect changes in cancer incidence for specified cancer sites. It is not known how many dry-cleaning workers in the cohort studied by Blair *et al* (1990) started work after 1960, when PER was the predominant exposure. However, it is probable that less than 50% started work after 1960, since the mean entry date for the whole cohort was 1956. Thus, the 3 cohorts which contain sub-cohorts of workers who were predominantly exposed to PER (Anttila *et al*, 1995; Ruder *et al*, 1994; Blair *et al*, 1990) probably contain fewer than 4,000 workers. Less than 1,000 of these have been monitored for cancer incidence.

In two other cohort studies, exposure was to other chemicals as well as to PER (Olsen *et al*, 1989; Spirtas *et al*, 1991). One of these studies (Spirtas *et al*, 1991) was conducted because of concerns about a proportionate excess of deaths from cancer from the lymphatic and haematopoietic tissue, especially multiple myeloma. Spirtas *et al* (1991) only reported findings for multiple myeloma and NHL in the sub-cohort with exposure to PER; limited weight should be attached to the findings given the *a priori* concerns. Olsen *et al* (1989), provided no information about the proportion of workers exposed to PER and their level of exposure.

The incidence of cancer in two cohorts of dry-cleaning and laundry workers derived from census records has been studied (Malker and Weiner, 1984; Lynge, 1994; McLaughlin *et al*, 1997). These do not allow any evaluation of the carcinogenic risk because it is not possible to distinguish those who worked in dry-cleaning from those who worked in laundries. A nested case-control study of liver and renal cancer was conducted in one of these cohorts (Lynge *et al*, 1995), and this study provides some information about risks associated with dry-cleaning work. The proportional mortality studies of workers engaged in dry-cleaning work also provide little information about the carcinogenic risk of PER exposure because of a lack of information about PER exposure and the high proportion of workers exposed to other solvents.

A number of case-control studies have been conducted which have evaluated exposure to PER (as opposed to dry-cleaning work). The major limitation of the case-control studies is the lack of information provided about the exposure of cases. The limitations of the drinking water studies have been well described by IARC (1995).

9.5.3 Evaluation

Table 49 summarises the data from the three most relevant studies (Blair *et al*, 1990; Ruder *et al*, 1994; Anttila *et al*, 1995). In the case of the study by Ruder *et al* (1994), separate results are given for the sub-cohorts who either only been employed in dry cleaning shops where PER was the primary solvent (PER-only) or had worked in both PER and other solvent shops (PER-plus).

Table 49: Summary of Data from Three Cohort Studies

	Studies in which subjects were exposed predominantly to PER						Studies in which subjects had mixed exposures, including PER					
	Anttila *et al*, 1995 292 men and 557 women monitored for exposure (Finland, 1974-92)			Ruder *et al*, 1994 (PER-only) 621 men and women employed in dry-cleaning (USA, 1940-90)			Blair *et al*, 1990 5,365 men and women employed in dry-cleaning (USA, 1948-78)			Ruder *et al*, 1994 (PER-plus) 1,080 men and women employed in dry-cleaning (USA, 1940-60)		
Cancer site	SIR	95% CI	Obs	SMR	95% CI	Obs	SMR	95% CI	Obs	SMR	95% CI	Obs
All cancers	90	61 - 127	31	101	76 - 132	54	120	100 - 130	294	133	113 - 156	155
Oesophagus	NR			264	72 - 676	4	210	110 - 360	13	190	69 - 414	6
Stomach	NR			-		0	80	40 - 140	11	87	28 - 204	5
Colon	NR			100	32 - 233	5	100	60 - 140	25	181	112 - 276	21
Cervix	320	39 - 1,160	2	157[b]	68 - 310	8	170	100 - 200	21	117[b]	60 - 204	12
Kidney	182	22 - 656	2	116	3 - 645	1	50	10 - 180	2	160	33 - 468	3
Urinary bladder	NR			-	[1.0 expected]	0	170	70 - 330	8	352	161 - 668	9
Brain and nervous system	115	14 - 415	2	NR			20	0 - 120	1	NR		
Lympho-haematopoietic system	138	28 - 402	3	49	6 - 177	2	120	80 - 180	24	78	31 - 161	7
Non-Hodgkin's lymphoma	376	77 - 1,100	3	NR			170[c]	70 - 340	7	NR		
Leukaemias	NR			NR			90	40 - 180	7	NR		

SIR, standardised incidence ratio; CI, confidence interval; Obs, number of cases or deaths observed; SMR, standardised mortality ratio; NR, not reported

[a] In comparison with local mortality rates

[b] Female genital organs

[c] Lymphosarcoma and reticulosarcoma

In the two cohorts of dry cleaners (Blair *et al*, 1990; Ruder *et al*, 1994), mortality from oesophageal cancer was elevated by approximately a factor of two. In the former study, the excess of oesophageal cancer was restricted to black male workers (8 observed, 2.9 expected). Only 1 death (0.7 expected) was observed in a worker with high exposure; a further 3 oesophageal cancer deaths occurred in workers whose exposure was unknown. Ruder *et al* (1994) reported that the magnitude of the risk increased in workers in the PER-only sub-cohort who had more than 20 latency-years and at least 5 years of employment in PER shops (SMR = 717, 95% CI 192-1982; 4 deaths). Ruder *et al* (1994) did not report results for males in the PER-only sub-cohort. However, the excess of oesophageal cancer in males in the full cohort was smaller (5 observed, 3.1 expected) than the excess in females (5 observed,1.5 expected), although the authors noted that their exposures would have been expected to have been higher. Anttila *et al* (1995) did not report the incidence of oesophageal cancer in the sub-cohort monitored for PER, but in the whole cohort there was only one case of oesophageal cancer (2.4 expected) and this case occurred within 10 years of the first biomonitoring test result.

The potential for confounding is particularly great when studying oesophageal cancer given the very strong associations between this disease and the combination of cigarette smoking and alcohol consumption. There is evidence that in the USA, cigarette smoking is more common in dry cleaners than other occupational groups (Sterling and Weinkam, 1976; Walrath *et al*, 1985). The increased levels of lung cancer and emphysema reported by Blair *et al* (1990) support this view, but there was no increased risk of lung cancer in long term workers in the cohort studied by Ruder *et al* (1994). Furthermore, there was no evidence of an increased mortality risk from cirrhosis of the liver, although there is evidence that the level of alcohol consumption needed to increase the risk of oesophageal cancer, is well below that required for cirrhosis (Pottern *et al*, 1981; Yu *et al*, 1988). Nevertheless, the unusual pattern of findings in the three studies, the lack of biological plausibility and the potential for confounding, all suggest that there is insufficient evidence to establish a causative link between PER exposure and oesophageal cancer.

Excesses of cervical cancer were reported by all three of the most informative studies (Blair *et al*, 1990; Ruder *et al*, 1994; Anttila *et al*, 1995). However, the largest excess reported by Blair *et al* (1990) was found in the group of counter workers at pick-up stations who had little or no exposure (SMR = 210; 7 observed). The SMR for workers with medium and high exposure was 133 (11 observed) and was not statistically significant. Blair *et al* (1990) noted that these data suggest that socio-economic factors and non-occupational factors may be involved. In the cohort of dry cleaners studied by Ruder *et al* (1994), there was a non-significant excess of cervical cancer. However, there was no obvious relationship between the risk of cervical cancer and time since first employment in a PER shop and duration of work in a PER shop. There was insufficient exposure data to examine the dose-response relationship. Overall, there was little indication that the excess of cervical cancers reported by Ruder *et al* (1994) was related to PER exposure. A small excess of cervical cancers was

also seen in the small group of PER exposed workers studied by Anttila (1995) (2 observed, 0.63 expected). No other information is presented about these 2 cases of cervical cancer.

Anttila *et al* (1995) reported an excess of NHL in the sub-cohort of workers monitored for PER in blood (3 observed, 0.80 expected); these were the only cases of cancer of the lympho-haematopoietic tissues (2.2 expected). Blair *et al* (1990) did not provide results for NHL as a cause of death, but reported a non-significant excess of deaths due to lymphosarcoma and reticulosarcoma (7 observed, 4.2 expected). However, there was a deficit of deaths in the category of other lymphatic causes which includes other lymphomas categorised as NHL, as well as multiple myeloma (4 observed, 5.8 expected). There was no excess of deaths due to lymphosarcoma and reticulosarcoma in the cohort studied by Ruder *et al* (1994) and no excess of deaths due to other lymphatic/haematopoietic cancers. Thus, the two studies of cohorts of dry cleaners provide little support for the finding by Anttila *et al* (1995) of an increased risk of NHL. An excess of NHL was also reported in the cohort studied by Spirtas *et al* (1991) (4 observed, 1.3 expected) but this finding carries less weight because of the a priori reasons for studying this group of aircraft maintenance workers.

Bladder cancer deaths were elevated in the two cohorts of dry cleaners, but neither excess appeared to be related to PER exposure. As in the case of cervical cancer, Blair *et al* (1990) reported the largest excess in the group of workers with little or no exposure to PER (3 observed, 1.1 expected). In workers with medium or high exposure, there were 5 cases (3.4 expected). Overall, the excess was not statistically significant in this cohort. Ruder *et al* (1994) reported a significant excess of bladder cancer deaths (9 observed, 3.5 expected) but all 9 deaths were in workers in the PER-plus group, i.e. workers who had worked in dry-cleaning shops where the predominant solvent was not PER. In the PER-only group, there were no bladder cancer deaths (1.0 expected). No cases of bladder cancer were listed by Anttila *et al* (1995) in the workers monitored for blood-PER. There was no excess of bladder cancers in the full cohort of workers exposed to halogenated hydrocarbons studied by Anttila *et al* (1995) (5 observed, 6.9 expected).

Mortality from primary tumours of the liver, the tumour most clearly related to PER in mice, was lower than expected in both dry-cleaning cohorts (e.g. SMR 68, 95% CI 20 - 170, Blair *et al* 1990). Ruder *et al* (1994) reported only one death due to cancer of the liver and bile ducts (4.76 expected) and Blair *et al* (1990) reported 5 deaths versus 7.3 expected. No cases were reported by Anttila *et al* (1995) in workers monitored for PER in blood. As noted earlier, the excess of liver cancers in the group of laundry and dry-cleaning workers studied by Lynge (1994) has since been demonstrated to have no relationship with dry-cleaning work (Lynge *et al*, 1995). The suggestive findings for kidney tumours in some strains of rat are given little support by the epidemiology data. Anttila *et al* (1995) reported a small excess of kidney tumours in workers monitored for blood-PER (2 observed, 1.1 expected). There was a small excess of deaths due to kidney cancer in the cohort of dry cleaners studied by

Ruder *et al* (1994) (4 observed, 2.74 expected), but the excess was confined to the PER-plus group (with mixed exposure).

The excess of mononuclear cell leukaemia in the F344 rat is considered to be of no significance for humans (Section 8.6.6). Although there were some small excesses of some sub-types of lympho-haematopoietic cancer in particular studies, there was no consistency between studies.

Overall, the epidemiological studies of greatest relevance are insufficient in both their design and outcome to demonstrate a relationship between exposure to PER and the occurrence of cancer in humans.

9.6 REPRODUCTIVE TOXICITY

A review of possible mechanisms by which PER might influence reproduction has been published (Van der Gulden and Zielhuis, 1989).

9.6.1 Fertility

An overview of the data related to fertility is on Table 50.

Table 50: Exposure to PER and Fertility

Endpoint	Association[a] (95% CI) with exposure	Type of exposure	Study design	Subjects		Reference
				Cases	Controls	
Men		Dry cleaning chemicals[b]	Case-control	927	3,728	Rachootin and Olsen, 1983
Sperm abnormalities	OR 1.0 (0.5 - 2.0)					
Idiopathic infertility	OR 1.3 (0.5 - 3.3)					
Women						
Hormonal disturbances	OR 0.2 (0.0 - 1.4)					
Idiopathic infertility	OR 2.7 (1.0 - 7.1)					
Spontaneous abortion	OR 0.5 (0.2 - 1.5)	Paternal exposure to PER	Nested case-control	120	251	Taskinen *et al*, 1989
Sperm abnormalities	No association for standard clinical measures of semen quality	PER	Cross-sectional	34	48	Eskenazi *et al*, 1991a
Time to pregnancy	IDR 0.54 (0.23 - 1.27)	Paternal exposure to PER	Cross-sectional	17	32	Eskenazi *et al*, 1991b
Number of births	No difference					
Spontaneous abortion	No difference					
Time to pregnancy	IDR 0.63 (0.34 - 1.17), low PER IDR 0.69 (0.31 - 1.52), high PER	PER	Retrospective cohort	20 PER exposed 85 Other solvents	92	Sallmén *et al*, 1995
Menstrual pattern	Increased prevalence of some menstrual disorders	Dry-cleaning	Cross-sectional	68	76	Zielhuis *et al*, 1989a,b

[a] OR, odds ratio; IDR, incidence density ratio
[b] Dry-cleaning also studied, but results not presented in this table

Rachootin and Olsen (1983) conducted a case-control study in Denmark based on data collected from 927 infertile case couples and 3,728 fertile control couples using a self-administered questionnaire. The two main sub-groups of infertile couples included couples with a male diagnosis of sperm abnormalities or a female diagnosis of hormonal disturbances. These two groups were not mutually exclusive. In addition, the investigations focused on a further sub-group of couples with idiopathic infertility. The infertile couples were examined or treated for a problem of infertility at a hospital in Odense, Denmark between 1977 and 1980; the control group consisted of couples who had a healthy child born at the same hospital between 1977 and 1979. A further series of analyses were performed for control couples in order to investigate effects on delayed conception. The exposures of 436 of the control couples who gave birth to a healthy child after experiencing a delay in conception of over a year were compared with those of couples who had conceived a healthy child within a year. Exposure to dry-cleaning chemicals and work in a dry-cleaning shop were investigated, but not exposure to PER specifically.

Information was obtained from 927 case and 3,728 control couples; associations of sub-fecundity with chemical exposures were assessed in a sub-group of couples who were infertile for at least a year and who resided in the catchment area of the hospital. Females reporting exposure to dry-cleaning chemicals experienced a statistically significant increased risk of idiopathic infertility (after adjustment for confounding factors). There was no corresponding increased risk of idiopathic infertility in males exposed to dry-cleaning chemicals. Sperm abnormalities, hormonal disturbances and delayed conception were also not associated with exposure to dry-cleaning chemicals. Occupational analyses demonstrated associations in female workers between work in a dry-cleaning shop in the year prior to hospital admission and the prevalence of hormonal disturbances and delayed conception. In males, the prevalence of sperm abnormalities was raised in those whose longest held occupation was in a dry-cleaning shop.

These findings were based on small numbers of exposed cases and controls while the authors examined a large number of occupations and chemical exposures. No details were given about the dry-cleaning chemicals to which subjects were exposed or the type of work performed in dry-cleaning shops.

Taskinen *et al* (1989) conducted a case-control study nested in a cohort monitored biologically for exposure to 6 solvents (PER, trichloroethylene, 1,1,1-trichlorethane, styrene, toluene and xylene). The study was conducted in order to investigate the effect of paternal exposure on pregnancy outcome. Wives with a spontaneous abortion were defined as cases (120) and women who did not have a spontaneous abortion or congenitally malformed child during the study period, 1973-1983, were eligible as controls (251). The father's exposure was assessed during the period of spermatogenesis preceding the study pregnancy. No association was found between paternal exposure to PER and spontaneous abortion (OR 0.5; 95% CI 0.2 - 1.5). However, paternal exposure to PER was only

present in 4 cases and 17 controls and confounders were not controlled for in this analysis. Odds ratios adjusted for potential confounders (including maternal factors) were calculated for different levels of exposure to halogenated hydrocarbons but these showed no evidence of an exposure effect.

One small study has investigated the influence of PER on the menstrual cycle (Zielhuis *et al*, 1989a,b). A self-administered questionnaire was used to obtain information on the menstrual disorders in dry-cleaners and laundry workers. Only women who did not use contraceptive pills were eligible for inclusion and the authors compared 68 female dry-cleaning workers, with 76 female workers in laundries. Mean cycle lengths in the two groups were similar and the women were able to predict their menstrual cycle with equal accuracy. Significantly increased risks of dysmenorrhea, unusual cycle lengths, menorrhagia and pre-menstrual syndrome were reported in dry-cleaning workers. The authors concluded that these findings did not have any real practical consequences because of the small size of the study and the lack of exposure data. They also concluded that these findings support the hypothesis that PER may affect the hormone system, but no information was collected about the exposure to PER of dry-cleaning workers.

Eskenazi *et al* (1991a) examined the association of semen quality with expired air levels of PER as an index of exposure in 34 workers exposed to PER (dry-cleaners and laundry workers who performed dry-cleaning work) and 48 laundry workers who were unexposed to PER. On average the dry-cleaning workers as well as the laundry workers had semen which was within normal limits. The average number of spermatozoa did not differ, but in both groups 25% of the men were oligospermic (< 20 million sperm/cc). The average of motile sperm for both groups was barely within normal limits. A slightly larger proportion of dry-cleaners (44%) than of laundry workers (31%) had less than 60% motile sperm. The difference was not statistically significant. However, more laundry workers (63%) than dry cleaners (50%) had greater than 40% abnormally shaped sperm. This difference was also not statistically significant. No significant associations were found between any of the three measures of exposure and the standard clinical measures of semen quality, but PER exposed men were more likely to produce sperm with a tendency to swim with greater amplitude of lateral head displacement.

Eskenazi *et al* (1991b) reported on a study of the pregnancy outcomes of the female partners of the dry-cleaning workers and laundry workers who participated in the study of semen quality described above (Eskenazi *et al*, 1991a). Twenty of the dry-cleaning workers exposed to PER and 36 unexposed laundry workers had female partners with whom they currently lived. Telephone interviews were conducted with 17 partners of dry-cleaning workers and 32 partners of unexposed laundry workers. The investigation compared fertility ratios, rates of spontaneous abortion and time to pregnancy. An analysis of births showed that the wives of dry-cleaning workers and laundry workers had higher fertility rates when compared to expected numbers of births calculated using birth probabilities specific to race, birth cohort, parity and age. Dry-cleaning workers had slightly higher standardised fertility ratios than laundry workers. Rates of spontaneous abortion during the years that

their partners worked in the industry were not significantly different, although they were highest in the wives of laundry workers. The relative likelihood of women in different exposure categories achieving clinical pregnancy during a menstrual cycle was expressed as an incidence density ratio (IDR). Wives of dry-cleaning workers had a pregnancy rate per cycle that was approximately half that of wives of laundry workers, although this difference was not statistically significant. (IDR 0.54; 95% CI 0.23-1.27). However, analyses containing measures of the PER exposure of the male partner demonstrated little evidence of a PER exposure effect.

Sallmén *et al* (1995) performed a retrospective time to pregnancy study among women biologically monitored for exposure to 6 organic solvents (PER, trichloroethylene, 1,1,1-trichlorethane, styrene, toluene and xylene) at the Finnish Institute of Occupational Health during 1965-83. The study subjects were participants in case-control studies of spontaneous abortion and malformations reported by Lindbohm *et al* (1990). The same pregnancy for each woman as in the spontaneous abortion study described above (Taskinen *et al*, 1989) was selected for the fertility study; a registered spontaneous abortion for the cases and a birth for the controls. Additionally, 30 controls from the malformation study of Kyyrönen *et al* (1989) (Section 9.6.3) were included. Out of 335 eligible women, 235 replied and this number was reduced to 197 after application of exclusion criteria. The number of menstrual cycles that women required before becoming pregnant was used as a measure of fertility. Time to pregnancy data were collected 8-18 years after the pregnancies. The women were classified into exposure categories on the basis of work description and the use of solvents as reported in questionnaires and indicated by biological exposure measurements. Menstrual cycle-specific exposure assessments were used in analyses that were adjusted for a range of potential confounding factors.

More than half of the subjects (105) were exposed to organic solvents during their time to pregnancy and nearly a quarter (46) were highly exposed, which was defined as handling solvents daily or 1-4 d/wk, supported by evidence of clear occupational exposure. Exposure to organic solvents was significantly associated with decreased fecundity after adjustment for potential confounders (IDR 0.41; 95% CI 0.27 - 0.62 and IDR 0.69; 95% CI 0.48 - 0.99 for high and low exposure, respectively). Compared to subjects not exposed to solvents, decreased fecundity was also observed for the 7 women with high exposure to PER and the 13 women with low exposure to PER, although this was not statistically significant (IDR 0.69; 95% CI 0.31 - 1.52 and IDR 0.63; 95% CI 0.34 - 1.17 for high and low exposure to PER, respectively). Ten of the 20 women exposed to PER worked in dry-cleaning shops.

9.6.2 Pregnancy

The Finnish Hospital Discharge Register (FHDR) has been used in a series of studies to identify cases of spontaneous abortion and healthy births and to link these to other databases containing surrogate

information relating to exposure to PER (Hemminki *et al*, 1980, 1984; Lindbohm *et al*, 1984, 1990; Kyyrönen *et al*, 1989). The studies are difficult to interpret because there is considerable overlap between the cases in the different studies. An overview is presented in Table 51

Table 51: Exposure to PER and Pregnancy and Birth Defects

Endpoint	Association[a] (95% CI) with exposure	Type of exposure	Study design	Subjects		Reference
				Cases	Controls	
Spontaneous abortion	Approximately 2 x general population rate No difference from other UCW[c] members	Laundry and dry-cleaning	Cross-sectional	280,000 pregnancies 69 laundry/dry-cleaning		Hemminki *et al*, 1980
	No difference from other UCW[c] members	Laundry and dry-cleaning	Cross-sectional	Not stated		Hemminki *et al*, 1984
	OR 1.48; (1.09 - 2.02)	Laundry and dry-cleaning	Cross-sectional	294, 309 pregnancies 416 laundry/dry-cleaning		Lindbohm *et al*, 1984
	OR 0.7[d] (-) Low PER OR 3.4 (1.0 - 11.2) High PER	PER	Case-control	130	289	Kyyrönen *et al*, 1989
	OR 0.5 (0.1 - 2.9) Low PER OR 2.5 (0.6 - 10.5) High PER	PER	Case-control	73	167	Lindbohm *et al*, 1990
	OR 1.0 (0.4 - 2.2) Low PER OR 0.9 (0.4 - 2.1) High PER	PER	Case-control	116[e]	241	Ahlborg, 1990a
	OR 1.17 (0.74 - 1.85) Low PER OR 2.88 (0.98 - 8.44) High PER	PER	Meta-analysis of 3 studies	31 10 118	53 (Sweden) 119 (Denmark) 264 (Finland)	Olsen *et al*, 1990
	Non-significant increase in spontaneous abortion rate in pregnant dry-cleaners	PER	Retrospective cohort	67 dry-cleaning workers		Bosco *et al*, 1987
	Obs/Exp = 1.05 (36 obs)	Laundry and dry-cleaning	Cross-sectional	56,067 pregnancies 202 laundry/dry-cleaning		McDonald *et al*, 1987a
	OR 4.7[d] (1.1 - 21.1)	PER	Case-control	626	1300	Windham *et al*, 1991
	OR 1.51 (0.81 - 2.84) Operator vs. non-operator (based on first pregnancies of 56 subjects)	Dry-cleaning operator	Retrospective cohort	2,711 dry-cleaning workers 399 laundry workers		Doyle *et al*, 1997

Table 51: Exposure to PER and Pregnancy and Birth Defects (Continued)

Endpoint	Association[a] (95% CI) with exposure	Type of exposure	Study design	Subjects		Reference
Birth defects	Obs/Exp = 1.41 (9 obs) Obs/Exp = 1.31 (6 obs) when restricted to women employed for 15 h/week or more at conception	Laundry/dry-cleaning	Cross-sectional	56,067 pregnancies 202 laundry/dry-cleaning		McDonald *et al*, 1987a, 1988
	OR 0.8 (0.2 - 3.5)	PER	Case-control	24	93	Kyyrönen *et al*, 1989
Adverse outcomes among births	OR 1.4 (0.4 - 5.3) Low PER OR 1.6 (0.4 - 7.1) High PER	PER	Case-control	116	241	Ahlborg, 1990a
	OR 1.72 (0.40 - 7.12) Low PER OR 0.87 (0.20 - 3.69) High PER	PER	Meta-analysis of 3 studies	16 14 2	26 (Sweden) 28 (Norway) 131 (Denmark)	Olsen *et al*, 1990

[a] OR, odds ratio; IDR, incidence density ratio
[b] Dry-cleaning also studied, but results not presented in this table
[c] UCW = Union of Chemical Workers
[d] Unadjusted
[e] All cases of adverse pregnancy outcome

Hemminki *et al* (1980) reported an increased rate of spontaneous abortions between 1973 and 1976 in female laundry workers (including dry-cleaning workers) compared to the general population. The FHDR was linked to the files of the Union of Chemical Workers, which provided occupational information. However, there was no increase in the spontaneous abortion rate when compared with that of all female members of the Finnish Union of Chemical Workers. Hemminki *et al (*1984) extended the period of observation up to 1979 and reported a slightly lower rate of spontaneous abortion in laundry and dry cleaning workers than in other Union members.

Lindbohm *et al* (1984) also studied births and spontaneous abortions during the same time period (1973-6) using the FHDR. The final study material comprised 294,309 pregnancies. Information on the occupation of women and their husbands and a number of other details was collected from the 1975 national population and housing census. After occupations with less than 30 pregnancies were excluded, a total of 64 female and 80 male occupations were analysed. The relative risk of spontaneous abortion for laundry work (including dry cleaning work) was statistically significant (OR 1.48; 95% CI 1.09 - 2.02) based on 416 pregnancies in laundry workers. Adjustment was made for age, place of residence and number of children. No information was available on other confounding factors such as smoking, alcohol, prior abortions, medication or maternal illness. It is not clear what proportion of the workers described as laundry workers in this study and the two earlier studies (Hemminki *et al*, 1980, 1984) were dry-cleaning workers, and no conclusion can be drawn from these studies about pregnancy outcome and exposure to PER.

Kyyrönen *et al* (1989) identified a study population of 5,700 female workers in laundries and/or dry-cleaning shops from the registers of the Union of Chemical Workers and the Municipal Workers Union of Finland for the period 1973-1983. According to the FHDR, the cohort had 3279 pregnancies between 1973 and 1983, of which 306 had resulted in a spontaneous abortion. Women with a spontaneous abortion were defined as cases and 3 controls were age-matched with each case. If a woman had experienced 2 or more spontaneous abortions, only one was randomly selected. A questionnaire was used to obtain data on exposure during the first trimester of pregnancy. The response rate was 77.2%, but 23.9% of spontaneous abortion cases did not report exposure during the correct pregnancy. After excluding these cases, and controls with a missing case, the final study material consisted of 130 cases (53%) and 289 controls (43%). The proportion of cases exposed to PER during the first trimester of pregnancy (17 cases, 13.1%) was similar to that of controls (29 controls, 10.0%). However, a greater proportion of cases (9 cases, 6.9%) had high exposure to PER during pregnancy than controls (6 cases, 2.1%). The odds ratio (adjusted) for high exposure to PER was 3.4 (95% CI 1.0 - 11.2). High exposure was defined as dry-cleaning tasks > 1h/d or as handling PER more than once a week. The odds ratio for low exposure to PER was not elevated (OR 0.7). For 7 study subjects, biological monitoring results from the same work were available. For 6 subjects, the measurements were taken within 1 - 10 months from the first trimester of the study pregnancy and for one subject, the measurement was taken 5 years after the study pregnancy. The

data are of limited value for assessing the validity of self-reported exposure to PER but suggest that some workers engaged in dry cleaning work (and hence categorised as high exposure) may have had similar levels of exposure as pressers and packers in dry cleaning shops.

Lindbohm *et al* (1990) identified a cohort of women who were biologically monitored for exposure to organic solvents between 1965 and 1983. Pregnancies between 1973 and 1983 in this group of women were identified from the FHDR. The design of the study was similar to that of Kyyrönen *et al* (1989), with each spontaneous abortion age-matched to 3 controls and exposure ascertained during the first trimester of pregnancy. The response rate was 85.5%, but 21.6% of spontaneous abortion cases did not report the correct pregnancy. The final study material included 73 cases of spontaneous abortion and 167 controls. The proportion of cases exposed to organic solvents during the first trimester of pregnancy was significantly higher than in controls (42/73 cases, 70/167 controls, OR 2.2, 95% CI 1.2 - 4.1). Eight cases and 15 controls mentioned exposure to PER (OR 1.4; 95% CI 0.5 - 4.2). The odds ratio for the low PER exposure group was 0.5 (95% CI 0.1 - 2.9) and 2.5 (95% CI 0.6 - 10.5) for the high PER exposure group. For dry-cleaning work involving exposure to PER, the OR was 2.7 (95% CI 0.7 - 11.2, 4 cases and 5 controls), but for other work in a dry-cleaning shop, the OR was 0.6 (95% CI 0.1 - 5.5, 1 case and 6 controls).

Ahlborg (1990a) used similar methodology to perform two case-control studies among Swedish female laundry and dry-cleaning workers, employed for at least one month in 1973-1983. Adverse outcomes of interest included spontaneous abortion, perinatal death, congenital malformations and birth weight less than 1,500 g. The first study (described as the primary study) included 7,299 women from 475 workplaces who had 955 pregnancies in this period. In all, 66 cases of adverse outcome were registered (44 spontaneous abortions). Two controls were individually matched to each case by using the mother's age, year of pregnancy and parity. The final study material was 48 cases and 110 controls, but the author did not state what proportion of the cases were spontaneous abortion. In the second study, 5176 female workers in laundry or dry-cleaning shops were found through the national census of occupations. A further 755 pregnancies were identified and among these, 55 spontaneous abortions and 28 other cases of adverse outcome were found. The final study material in this second study was 68 cases and 131 controls. The OR for spontaneous abortion in the combined study material, for low PER exposure and high PER exposure mothers respectively, were 1.0 (95% CI 0.4 - 2.2) and 0.9 (95% CI 0.4 - 2.1).

The study by Kyyrönen *et al* (1989) and the primary study by Ahlborg (1990a) were part of a multi-centre case-control study performed in Denmark, Norway, Sweden, Finland to study reproductive hazards of women doing dry-cleaning work (Olsen *et al*, 1990). In addition, Kolstad *et al* (1990) provided limited information about the Danish arm of the study. A common study protocol was used, but not all of the centres could follow the same procedures in data collection. For this reason, the data were not pooled and Olsen et al (1990) combined summary measures from each study. The most

significant finding was an increased risk of spontaneous abortion among the most exposed women in the Finnish data. This finding had been earlier reported by Kyyrönen *et al* (1989), although it should be noted that there are differences between Olsen *et al* (1990) and Kyyrönen *et al* (1989) in respect of the number of cases studied and especially in the exposure status of cases and controls. Olsen *et al* (1990) noted that the Finnish finding was only supported by the results of other studies to a minor degree and the combined odds ratio had confidence limits which included unity (OR 1.17, 95% CI 0.74 - 1.85 low PER and OR 2.88, 95% CI 0.98 - 8.44 high PER). There were no cases of spontaneous abortion in the Norwegian arm of the study and the combined report of Olsen *et al* (1990) adds little new information to the reports of Kyyrönen *et al* (1989) and Ahlborg (1990a).

Ahlborg (1990b) studied the validity of exposure data obtained by questionnaire in occupational reproductive studies. Exposure data from self-administered questionnaires in the Swedish study described earlier (Ahlborg, 1990a), were compared with information obtained from the employer. A higher percentage of cases than controls did not know whether they had been exposed to PER (47% versus 37%). However, the exposure status of cases that did not know whether they had been exposed was similar to that of cases who stated that they did know and the same was true for controls. Reclassification of the exposure status using data obtained from the employers raised the OR of spontaneous abortion in high exposure workers from 0.92 to 1.24, although neither was statistically significant.

McDonald *et al* (1987a) described the overall results of a large cross-sectional study of 56,067 Canadian women delivered or treated for a spontaneous abortion in 11 Montreal hospitals over the period 1982-1984. All women were interviewed in detail regarding their occupational, social and personnel characteristics and the results analysed in relation to spontaneous abortion, stillbirth, congenital defect and low birth weight. Expected numbers for these 4 adverse pregnancy outcomes were calculated adjusting for up to 8 confounding variables, such as smoking, age, alcohol, ethnic origin, education and previous reproductive history. In this cohort, 202 pregnancies occurred in women who were employed in laundry and/or dry-cleaning shops. For spontaneous abortions, the observed to expected ratio was 1.05 (36 spontaneous abortions) which was not significantly increased.

Some limited information is obtained from a study by Bosco *et al* (1987), which collected details on pregnancies of 67 women working in dry-cleaning shops in Rome, Italy. In all, 102 pregnancies were reported, of which 56 had occurred during the period of their employment in dry-cleaning establishments and 46 during the periods that they were not employed. Of the 56 pregnancies that had occurred during employment, 5 had resulted in a spontaneous abortion, whereas only 1 of the 46 pregnancies occurring during non-employment had this outcome. This difference is not statistically significant and the proportion of exposed pregnancies ending in spontaneous abortion is similar to that reported in general population studies.

In a US case-control study of spontaneous abortions, exposure to solvents was ascertained by a computer-assisted telephone interview (Windham *et al*, 1991). Cases were defined as women, at least 18 years of age, who had a spontaneous abortion by the 20th week of gestation. Two controls per case were randomly selected among residents who had a live birth. A response rate of 80% was achieved and 1926 subjects participated in the study (626 cases, 1,300 controls). Of the 1,361 working women that were included in analyses of occupational solvent exposure, 249 had been exposed to solvents (20% of employed cases and 17.5% of employed controls). The adjusted OR for any solvent exposure was 1.1 (95% CI 0.77, 1.5). Among the cases, 5 (1.1%) were exposed to PER compared with 2 (0.2%) in the control group. The crude OR for these cases was 4.7 (95% CI ; 1.1 - 21.1). The adjusted OR for repeated exposure to PER ranged from 4.2 (95% CI 0.86 - 20.2) to 6.0 (95% CI 1.4 - 25.8). However, only one subject worked in the dry-cleaning or laundering industry and it is unclear how the exposures to PER of the other subjects compare with those of workers in the dry cleaning industry studied by other investigators.

Doyle *et al* (1997) performed a retrospective occupational cohort study of the pregnancies of women who were currently employed or used to work in 696 dry-cleaning shops and 13 laundry units in the UK. A total of 7,305 employees was sent a postal questionnaire of which 1,593 (21.8%) could not be delivered. Of those delivered, 3,110 (54.5%) were returned completed by 2,711 dry-cleaning shop workers and 399 laundry workers. The questionnaire was used to collect information about the outcome of each pregnancy of subjects and workplace exposure. Maternal age, pregnancy order and year of event were adjusted for in the analyses, but no information was collected on smoking habits, alcohol consumption and whether a woman worked during pregnancy. In all, 172 workers reported a spontaneous abortion, but only 71 of these gave permission to consult their GP to confirm the spontaneous abortion. A total of 3,517 pregnancies were reported, of which 392 were spontaneous abortions (foetal losses within 28 weeks of gestation). For pregnancies ending between 1980 and 1995, the risk of spontaneous abortion was 17.9% in dry-cleaning operators, 12.3% in non-operators, 15.5% in laundry workers and 13.5% in workers who were not employed in a dry-cleaning shop or laundry during the pregnancy or 3 months before conception. The spontaneous abortion rate in dry-cleaning operators was compared to that in non-operators. A small, but statistically significant increase was reported in an analysis of all pregnancies completed 1980-95, but this increase was not statistically significant when the analysis was restricted to first pregnancies to account for a possible lack of independence among women who experienced more than one pregnancy (OR 1.51; 95% CI 0.81 - 2.84). There was no difference between dry-cleaning work and laundry work in the analysis of first pregnancies (OR 1.03; 95% CI 0.48 - 2.21). In another analysis, the investigators reported a significantly increased risk of spontaneous abortion in pregnancies of women who were employed as dry-cleaning operators during pregnancy compared to unexposed pregnancies. No corresponding increase was seen for dry-cleaning non-operators, but an elevated non-significant increase was reported for laundry workers. However, the authors did not know the place or type of work of women

reporting unexposed pregnancies or even whether they worked at all during the pregnancy. For this reason, the validity of such a comparison is not clear.

9.6.3 Birth Defects

In a study described above (Section 9.6.2), McDonald (1987a) did not report any statistically significant associations between stillbirth, congenital defects and low birth weight, and occupation in a laundry and/or dry-cleaners. The observed to expected ratio for congenital defects was 1.41 (9 observed). McDonald *et* al (1988) reported a more detailed analysis of congenital defects in a sub-set of women studied by McDonald *et al* (1987a). These were women employed for 15 hours a week or more at the time of conception. A total of 180 pregnancies occurred in women whose occupation was categorised as laundry and dry-cleaners. The observed to expected ratio for congenital defects was 1.31 (6 observed) and this was not statistically significant. McDonald (1987b) also conducted a case-control study in which the cases were 301 women giving birth to a child with a congenital defect in the Montreal study described previously. The study was limited to women employed 30 or more hours a week until at least the 13th week of gestation. The cases were individually matched with 301 women whose children were normal. None of the cases or controls were exposed to PER.

Kyyrönen *et al* (1989) also studied congenital malformations in a case-control study employing similar methodology to the spontaneous abortions study described above (Section 9.6.2). The subjects included 24 cases of malformations and 93 controls. The odds ratio for PER exposure was 0.8 (95% CI 0.2 - 3.5).

In the study of Ahlborg (1990a), the cases also included cases of perinatal death, congenital malformations and low birth weight. The OR for all adverse outcomes among births for low exposed or high exposed mothers respectively, were 1.4 (95% CI 0.4 - 5.3) and 1.6 (95% CI 0.4 - 7.1).

Olsen *et al* (1990) summarised data from the studies of Ahlborg (1990a), Kyyrönen *et al* (1989) and other study material from Norway and Denmark. They present the relative risk for congenital malformation, stillbirth and low birth weight, according to exposure to PER in various trimesters of pregnancy. The authors concluded that most of the results were in line with the null hypothesis. The summary OR for all adverse outcomes among births for low and high exposed mothers (exposure throughout pregnancy) respectively, were 1.72 (0.40, 7.12) and 0.87 (0.20 - 3.69).

Windham *et al* (1991) presented some information about the foetal growth of live-born controls in relation to solvent exposure. A high odds ratio for intrauterine growth retardation was reported, but this was based on one case exposed to PER and trichloroethylene.

9.6.4 Evaluation

Fertility

Only one study provides information concerning the fertility of women exposed specifically to PER in the workplace (Sallmén *et al*, 1995). An increased time to pregnancy was reported for women exposed to PER, but the finding was not statistically significant and there was no difference between low and high exposed women. Another study reported a small, but statistically-significant increased risk of idiopathic infertility in women exposed to dry-cleaning chemicals (Rachootin and Olsen *et al*, 1983), but this finding has limited relevance to an assessment of effects of exposure to PER. Other reports provide information on menstrual disorders and the effects on the sperm quality of male dry-cleaners and the reproductive performance of their partners. However, no clinically significant effects were reported.

Pregnancy Outcome

A series of Finnish studies have been conducted which have identified cases of spontaneous abortions from a national hospital discharge register (Hemminki *et al*, 1980, 1984; Lindbohm *et al*, 1984, 1990; Kyyrönen *et al*, 1989). Only the two most recent studies assessed exposure specifically to PER and there is considerable overlap between the cases in these two studies and the earlier studies. Kyyrönen *et al* (1989) reported a significantly increased risk of spontaneous abortion in women whose exposure to PER was assessed as high, but no increase in women with low exposure. Lindbohm *et al* (1990) also reported an increased risk in women whose exposure was defined as high, but this was not statistically significant. The study by Kyyrönen *et al* (1989) was part of a Scandinavian study (Olsen *et al*, 1990) which also included spontaneous abortion data from Denmark and Sweden. There was no support for the Finnish finding in the Swedish arm of the study or in an enlarged Swedish study reported by Ahlborg (1990a), which added further cases and controls to those reported by Olsen *et al* (1990). There were too few cases in the Danish arm to draw meaningful conclusions.

A recent UK study by Doyle *et al* (1997) employing different methodology appears to lend support to the Kyyrönen finding. However, the investigators had no data on individual exposures to PER and machine operator versus non-operator was used as a surrogate measure of exposure. There was no difference in the risk of spontaneous abortion between all dry-cleaning workers and a comparison group consisting of laundry workers but an increased risk of spontaneous abortion was reported for dry-cleaning operators relative to non-operators. However, when the analysis was properly restricted to the first births of subjects, the increased risk of spontaneous abortion in dry-cleaning operators relative to non-operators was not statistically significant. The poor response rate with resultant potential for bias and inability to adjust for confounding further reduces the weight that can be attached to this finding.

The study by Windham *et al* (1991) also reported an increased risk of spontaneous abortion in women exposed to PER. However, it is difficult to relate these findings to the studies of Kyyrönen *et al* (1989) and Doyle *et al* (1997) conducted in the dry-cleaning and laundry industry. Only one of the 7 subjects exposed to PER in the study of Windham *et al* (1991) was employed in the dry-cleaning industry. The other subjects were drawn from a broad industry base and some would have been exposed to other chemicals in addition to PER. In addition, it is not possible to compare the exposure levels of subjects in this study with those of workers in the dry-cleaning industry.

Taken together, the studies by Kyyrönen *et al* (1989) and Doyle *et al* (1997) provide suggestive evidence of an elevated risk of spontaneous abortion in women with the highest exposures to PER in dry-cleaning establishments. However, the study by Kyyrönen *et al* (1989) was conducted in an industry where concern might have been high because of the findings of earlier studies and this may have led to reporting bias. Similarly, there may have been heightened awareness in the population studied by Doyle *et al* (1997) which, taken together with the low response rate, may have led to reporting bias. Neither study reported an increased risk of spontaneous abortion associated with working in a dry cleaning shop, and neither study has satisfactorily demonstrated an exposure gradient for PER. The Windham *et al* (1991) study does not support the finding because only one subject (a control) was a dry-cleaning worker and exposures are not comparable between this study and those by Kyyrönen *et al* (1989) and Doyle *et al* (1997). Hence, it is not possible to link the increased incidence of spontaneous abortion in the three studies to PER exposure, and the findings are capable of explanation by bias or confounding. Thus, the evidence is insufficient to support a causative association between PER exposure and spontaneous abortion.

Birth defects

There is no evidence from several studies of an association between exposure to PER and an increase in the incidence of birth defects.

9.7 OTHER CHRONIC TOXIC EFFECTS

In this section, human data on chronic toxicity will be described in terms of morbidity and mortality.

9.7.1 Morbidity

Case Studies

Abedin *et al* (1980) reported the case of a 24-year old man with complaints of headache, dizziness and irregular heartbeats, starting within one month of beginning to work in a dry-cleaning operation. After 7 months of employment the ECG revealed sinus rhythm and premature beats. During a 6-d stay in a hospital the symptoms gradually disappeared. Two weeks after returning to work the

symptoms and complaints recurred. The level of PER in his plasma was reported to be 3,800 mg/l. When he changed his job, his health problems resolved permanently.

Aoki *et al* (1989) described a 42-year old man with anosmia, who had been intermittently exposed for 16 years to PER soaked into clothes. X-ray and endoscopy of the nose showed obstruction by oedematous swelling of the nasal mucosa of the bilateral olfactory clefts and a severe bilateral ethmoidal sinusitis. There was no clear evidence of a causal relationship between exposure to PER and the occurrence of this effect.

Epidemiological Studies (Table 52)

Franke and Eggeling (1969) performed a cross-sectional study of 113 workers in dry-cleaning shops, together with environmental monitoring in 46 workplaces. Although not statistically significant, the exposed group had more complaints of headache, irritability and insomnia than 43 control subjects. Of the liver function tests performed, the thymol and bilirubin tests were statistically significantly different from the controls. SGOT and SGPT levels were not statistically different from controls.

Table 52: Other Chronic Effects of Occupational Exposure

Workplace (number of shops)	Number and (%) of measurements	Concentration[a] (ppm)	(mg/m^3)	N	Effect	Remarks	Reference
Dry-cleaning, small shops	222 (90) 222 (48)	(< 100) (< 20.3)	< 690 < 140	113 (out of 550), 43 controls	Only thymol-test and bilirubin were different from controls; no difference in GOT, GPT, thymol, bilirubin, Fe in blood, Fujiware and electrophoresis. 29, 30, 31 and 34% of the persons reported dizziness, fatigue, headache and irritability. 40 and 30% reported autonomic nervous dysfunction and dry skin. No data on controls	No mention of alcohol drinking habits	Franke and Eggeling, 1969
Dry-cleaning, large shops	104 (60) 104 (28)	(< 100) (< 20.3)	< 690 < 140				
All shops (46)	326 (10)	(> 406)	> 2,800[b]				
Dry-cleaning (55)	NS	(98.3 - 393.2)	678 - 2,712	200	71 workers had TCA level > 10 mg/l, of which 16/22 had subjective complaints and 21/40 abnormal blood parameters. No signs of liver malfunction	Similar to controls	Münzer and Heder, 1972
Railway (8)	NS (75) NS (11) NS (10) NS (3)	(2 - 50.8) (50.8 - 101.5) (101.5 - 152.3) (152.3 - 188.5)	14 - 350 350 - 700 700 - 1,050 1,050 - 1,300	113, 101 controls	No difference in liver and kidney function between both groups. Exposed complained of sleepiness (45%), skin rash (31%), nausea (18%) and loss of appetite (15%) against controls: 3, 12, 5 and 5%	During 11.5 y, approximately 80% of both groups drank alcohol up to 80 g/d	Essing *et al*, 1974
Dry-cleaning (NS)	NS	NS	-	55	No complaints, no symptoms in the electrocardiography. Significant increased ventricular wall thickness-to-radius ratio in the echocardiography	Japanese workers	Hara *et al*, 1985
Dry-cleaning (NS)	NS	NS	-	50	Increased urinary excretion of albumin and transferrin and other renal markers. No relationship between effect and duration or intensity of exposure to PER	During 10 y (average), 0.3 - 35 y	Mutti *et al*, 1992

[a] Converted values in parentheses
[b] Maximum concentration measured

Münzer and Heder (1972) measured the urinary TCA levels of 200 employees (71 males and 129 females) from 55 dry-cleaning shops exposed to PER at concentrations ranging from 678 - 2,712 mg/m^3 (98.3 - 393.2 ppm). From these 200 workers 71 workers (35 males and 36 females) had plasma TCA levels above 10 mg/l. Forty workers (23 males and 17 females) from the cohort with plasma TCA levels higher than 10 mg/l were studied and 16 out of 22 from this group reported a number of subjective complaints such as headache, vertigo, weariness, nervousness and irritability. In 21 out of 40 subjects, abnormal blood parameters were found including increases in blood sedimentation rate and in serum transaminases. However, in the non-exposed group of 23 males and 17 females, the same prevalence of abnormal blood parameters was found.

Essing *et al* (1974) investigated 113 workers with long-term exposure to solvents who were exposed to a mean concentration of 35 to 51 ppm of PER (241 or 351.4 mg/m^3), with a peak exposure of 245 ppm (1,688 mg/m^3). Of these, 101 workers were known to consume alcohol on a regular basis. Only 8 of the exposed workers had no subjective complaints. The most frequently occurring subjective complaints among the other 105 workers were: dullness (n = 50), dermatitis (n = 40), nausea (n = 25), loss of appetite (n = 20), undue perspiration (n $\geq$ 35) and decrease of libido (n = 30); 97 of the workers had abnormal liver function tests for SGOT, SGPT and bromophthalein. These abnormal test results were not related to the intensity and duration of PER exposure, but there was an association with the consumption of alcohol.

Takeuchi *et al* (1981) performed a survey of 187 workers exposed to PER from 57 companies. The main complaints found were: olfactory disturbances, eye irritation and unsteady feeling in the head. According to the results of some liver function tests, the liver function was slightly impaired. No details were given of exposure or confounding factors.

Hara *et al* (1985) evaluated the cardiovascular status of 55 Japanese dry-cleaning workers without any complaints. The cohort was selected with respect to the absence of a history of hypertension, the absence of diabetes mellitus and the absence of a heavy alcohol intake. No effects were seen on the electrocardiographic examination. However, echo-cardiography revealed a thickening of the ventricular wall, decreased fractional shortening of the internal dimension of the left ventricle and decreased mean velocity of circumferential fibre shortening at systole. The intensity was positively related with the intensity of exposure. Due to a number of limitations, such as mixed exposure to organic solvents and absence of data about the intensity of exposure, no causal relationship with exposure to PER could be determined.

Mutti *et al* (1992) performed a cross sectional study of 50 workers exposed to PER in dry-cleaning shops for an average of 10 years (0.3 - 35 years). Small, but statistically significant increases in the urinary excretion of albumin and transferrin and other potential markers of bilary damage were detected in exposed subjects when compared to a group of 50 controls (blood donors matched for age

and sex). Tubular Brushborder antigen and Uromucoid were also increased, whereas the serum α-2μ-globulin showed only slight changes. Urinary retinol binding protein and immunoglobulin levels were not significantly increased. In 20-50% of the cohort, signs of glomerular dysfunction or tubular damage were detected. There was no relationship between renal markers and either duration or intensity of exposure to PER.

9.7.2 Mortality

Case History Studies

Trense and Zimmerman (1969) described a fatal case of PER intoxication after an exposure intensity of 50 ppm to > 250 ppm (344.5 to > 1,723 mg/m^3) for more than 2.5 years. The actual peak values are likely to have been much higher due to pre-cleaning spraying of clothing with a mixture containing 39% PER and 10% isopropanol. After 2 days of influenza-like symptoms, the man was admitted to hospital with haemoptysis, dyspnoea and perspiration; he died 4 days later. In the post-mortem, toxic hepatosis, fatty change of heart muscle and lung oedema was diagnosed.

Epidemiological Studies

All of the studies described below have been discussed with respect to the incidence of malignant neoplasms (Section 9.5.1).

Blair *et al* (1990) reported significantly reduced mortality from all causes in a cohort of dry-cleaning workers (SMR = 90; 95% CI 90 - 100; 1,129 deaths). No results were provided for the cohort of workers who were first employed after 1960 when PER was the predominant solvent. In the full cohort, significantly elevated mortality was reported for emphysema (SMR = 200; 95% CI 110 - 340; 14 deaths).

Ruder *et al* (1994) studied another cohort of dry-cleaning workers but only reported deaths from all causes and deaths due to selected cancers. Deaths from all causes were slightly elevated (SMR = 101; 95% CI 94 - 109; 769 deaths). All cause mortality was lower than expected in a sub-cohort of workers who had only worked in shops in which PER was the primary solvent (SMR = 97; 95% CI 84 - 110; 222 deaths).

Antilla *et al* (1995) presented limited mortality information for the cohort of workers monitored for blood-PER. All cause mortality was significantly reduced in women (SMR = 51; 95% CI 30 - 90; 12 deaths) and lower than expected in men (SMR = 67; 95% CI 30 - 120; 10 deaths).

All cause mortality was reduced in the cohort of chemical workers studied by Olsen *et al* (1989) (SMR = 56; 95% CI 42 - 75; 48 deaths). Significant deficits of deaths due to arteriosclerotic heart

disease (10 observed and 21.9 expected) and deaths due to external causes (14 observed and 29.8 expected) were reported.

None of the other studies described in Section 9.5.1 provides information that permits an assessment of the effect of PER exposure on mortality from causes other than cancer.

9.7.3 Evaluation

Information on morbidity from specific causes in relation to PER exposure is limited. However, all relevant studies report mortality from all causes which was either significantly reduced or close to expected. No causal or dose-response relations could be determined.

10. HAZARD ASSESSMENT

10.1 ASSESSMENT OF HAZARD TO HUMAN HEALTH

10.1.1 Acute Health Effects

Although PER is of low acute toxicity, single exposure by inhalation to high vapour concentrations can induce CNS depression, potentially leading to pre-anaesthetic effects, loss of consciousness, coma and death if the exposed people are not removed from the contaminated area. High exposure of consumers may occur especially after use of self-service coin-operated dry-cleaning machines.

The inhalation threshold for acute effects on the CNS was established in human volunteers at 100 - 200 ppm PER (689 - 1,378 mg/m^3) for 1 hour. Evidence of loss of motor co-ordination in humans has been obtained with exposure to 600 ppm PER (4,134 mg/m^3) for 10 minutes (Rowe *et al*, 1952). These effects are clearly reversible on cessation of exposure. Several cases of fatal poisoning after accidental gross over-exposure by inhalation of PER have been reported. However, concentrations and precise exposure durations were unknown (Levine *et al*, 1981; McCarthy and Jones, 1983; Lukaszewski, 1979). Lethal inhalation concentrations following 4-h exposure of rats and mice were in the range of 2,300 - 5,200 ppm PER (15,850 - 35,830 mg/m^3) (Table 14). Inhalation of an estimated concentration of 38,095 mg/m^3 PER (5,520 ppm) for less than 90 minutes reportedly caused the death of a 2-year old child (Garnier *et al*, 1996).

10.1.2 Irritation Effects

PER may cause dermal irritation if the liquid is in close contact with the skin. Dermatitis can occur on repeated contact with liquid PER due to the skin defattening effect of the solvent.

PER vapours were reported to cause mild irritation of the eyes of human volunteers exposed to 100 ppm (689 mg/m^3) for 2 hours. At 280 ppm (1,929 mg/m^3), irritation became substantial (Rowe *et al*, 1952).

PER vapours were reported to cause marked irritation of the upper respiratory tract of human volunteers at a concentration of 1,060 ppm (7,300 mg/m^3). Lower concentrations (216 ppm (1,488 mg/m^3) for 2 hours) induced mild irritation, which was confined to the nose (Rowe *et al*, 1952).

10.1.3 Chronic Toxicity

Target organs following repeated exposure in animals are the liver, kidney, lungs and CNS. In humans, adverse effects on the CNS have been reported following repeated exposure to levels exceeding 100 ppm PER (689 mg/m^3).

A LOAEL following repeated inhalation (up to 8 h/d, 5 d/wk) of 100 ppm PER (689 mg/m^3) has been demonstrated in a wide variety of animal species, on the basis of histological examination of all critical organs in studies of up to 2 years duration (Section 8.3 and 8.5).

Based on the assumptions that all the inhaled PER is absorbed and an average laboratory rat weighs 0.25 kg and has a ventilation rate of 5 l/h, the total body burden for rats exposed to 100 ppm (689 mg/m^3) for 8 hours would be 0.689 mg/l x 5 l/h x 8 h/d $\approx$ 28 mg/d/rat, i.e. 112 mg/kgbw/d.

10.1.4 Reproductive Toxicity

PER has been shown to be foetotoxic, but not teratogenic, at maternally toxic dose levels in several animal species. No effect on fertility was demonstrated in a 2-generation inhalation study in rats up to 1,000 ppm (6,890 mg/m^3). A clear NOAEL of 100 ppm (689 mg/m^3) was established for parental and subsequent generations (Section 8.8). In humans, no persuasive evidence of an effect on reproduction (either development or fertility) has been found (Section 9.6).

10.1.5 Genotoxicity

The overall evidence from studies conducted to assess the genotoxicity of PER, including gene mutations, DNA damage, mutation in germ cells and chromosomal aberrations *in vitro* and *in vivo*, indicates that it is not genotoxic (Section 8.6). Limited information in humans provides no evidence of genotoxicity (Section 9.4).

10.1.6 Carcinogenicity

PER has been reported to increase the incidence of liver tumours in male and female mice and kidney tumours in male rats.

Studies of the mechanism of tumour formation in rodents lead to the conclusion that the increased incidence of liver tumours in mice is due to the metabolism of PER to TCA. TCA is known to be a peroxisome proliferator, inducing liver enlargement and liver tumours in rodents. PER is metabolised to TCA via the cytochrome P450 pathway, a route that is not saturated at the highest dose tested in mice. The absence of an increased incidence of liver tumours in the rats is explained by the fact that the oxidative pathway is saturable in rats, as it is in humans. It is predicted that liver tumours would not occur in humans at current occupational exposure levels because of (i) saturation of the oxidative pathway at atmospheric concentrations above 100 ppm leading to much lower blood levels of TCA than in mice, and (ii) the absence of peroxisome proliferation and associated events in human hepatocytes exposed to PER or TCA.

Mechanistic studies of the tumour development in male rat kidneys have led to the conclusion that these are due to a protein droplet nephropathy, a phenomenon specific to male rats, coupled with sustained chronic toxicity consequent on hepatic GSH conjugation of PER (leading to the activation of the resulting cysteine conjugate via renal β-lyase to a genetically active metabolite). Although mercapturic acid derivatives have been formed in the urine of both rats and humans, the GSH-conjugation pathway has not been detected in human liver samples. Thus, the kidney tumours are considered to be caused by a mechanism that occurs in male rats only.

The observation of increased incidence of mononuclear cell leukaemia in the F344/N rat, but not in the Osborne-Mendel nor the Sprague-Dawley rat, is considered to be of no significance for human hazard assessment because this neoplasia is known to be of a high and variable incidence, especially in the F344/N rat.

It is concluded that the tumour findings in rats and mice are not relevant for humans under reasonably foreseeable circumstances of chronic exposure (Section 9.5).

Available epidemiological studies were either negative or were not sufficient to provide evidence of a relationship between exposure to PER and cancer in humans (Section 9.7).

10.2 ASSESSMENT OF HAZARD TO ORGANISMS IN THE ENVIRONMENT

10.2.1 Aquatic Compartment

The acute toxicity of PER on aquatic organisms such as fish, crustaceans or algae has been studied extensively. Validated studies have shown the lowest acute LC_{50} for freshwater fish to be 5 mg/l. Similar values are found for salt-water fish. For *Daphnia,* EC_{50} values from 8.5 mg/l are reported. Acute EC_{50} values for fresh and salt-water algae are found at higher levels (> 500 mg/l). The lowest acute LC_{50} of 5 mg/l PER is considered to be representative of all aquatic trophic levels (Section 6.2.1).

In chronic toxicity studies, the lowest NOEC for *Daphnia* is 0.5 mg/l (28 days), whereas fish embryo-larval stages were resistant up to a concentration of 1.4 mg/l PER (Section 6.2.2).

Studies in ecosystems have demonstrated effects at concentrations of 0.1 mg/l and above in microfauna. In natural ecosystems, *Daphnia* appear to be more sensitive than in laboratory studies, acute lethal concentrations occurring at around 0.3 mg/l (Section 6.2.3).

10.2.2 Terrestrial Compartment

Several soil organisms have been used for testing PER toxicity including micro-organisms, invertebrates and plants after acute or prolonged exposure. Most of these studies have been conducted under non-standard conditions but on the whole, NECs are of the order of 1 mg/kg soil. Effects have been reported following exposure to PER at concentrations starting from 10 mg/kg for one plant species or 18 mg/kg for terrestrial worms. PER and its atmospheric degradation product, TCA, may have adverse effects on the photosynthetic apparatus of conifers and other higher plants (Section 6.3.1-2).

10.2.3 Secondary Poisoning ("Non-Compartment Specific Exposure Relevant to the Food Chain")

Based on its octanol-water partition coefficient, no significant bioaccumulation of PER is expected. Measured bioconcentration factors for PER in freshwater fish were found to be < 100 (range 26 - 77, see Section 4.2.5). Bioconcentration factors in sea-water have been estimated to be < 100 in fish liver, bird's eggs and seal blubber. PER concentration in marine algae and plankton have been shown to be < 180 times higher than in sea-water. Thus there is no evidence of biomagnification of PER along the food chain.

10.3 SUMMARY OF HAZARD DATA TO BE USED FOR RISK ASSESSMENT

10.3.1 Health Effects

Following acute inhalation exposure, adverse effects on the CNS can be found in humans at concentrations above 100 ppm PER (689 mg/m^3) after 1hour exposure and at higher concentrations over shorter time periods. At this level, reversibility will occur after removal from exposure. Mortality has been reported following exposure to high atmospheric concentrations or accidental ingestion of large doses of PER.

Repeated occupational exposure to levels lower than 100 ppm PER would be unlikely to cause any adverse effects. Repeated exposure to higher concentrations may cause adverse effects on the CNS, liver and kidney.

10.3.2 Environmental Effects

Aquatic Organisms

Results from laboratory studies of different aquatic trophic levels following of acute or chronic exposure to PER have demonstrated a NEC of 0.5 mg/l. Under field conditions, aquatic phytoplankton

appeared to be more sensitive to the effects of PER, a decrease in species diversity and productivity being seen at 0.1 mg PER/l

The PNEC for the aquatic environment can be estimated to be 0.05 mg PER/l.

Terrestrial Organisms

Effects on soil micro-organisms, invertebrates and plants have demonstrated a NEC of 1 mg PER/kg soil (dry weight). PER and its atmospheric degradation product, TCA, may have adverse effects on the photosynthetic apparatus of conifers and other higher plants.

Secondary Poisoning

PER is neither expected to bioaccumulate nor to be subject to biomagnification along the food chain. Secondary poisoning due to PER is, therefore, not expected to occur.

11. FIRST AID, MEDICAL TREATMENT AND SAFE HANDLING ADVICE

11.1 FIRST AID

Inhalation

Remove subject to fresh air; sit the subject down with the body upright. Do not induce vomiting. If breathing is difficult, give oxygen. If not breathing (narcosis or unconscious), give mouth-to-mouth resuscitation. Call a physician and/or transport to emergency facilities immediately.

Ingestion

Remove subject to fresh air; make subject sit down or lie down with body upright. Do not induce vomiting. If not breathing (narcosis or unconscious), give mouth-to-mouth resuscitation. If breathing is difficult, apply oxygen or artificial respiration. Call a physician and/or transport to emergency facilities immediately.

Eye Contact

Irrigate immediately with plenty of water for at least 10 min with the eyelids held wide-open.

Skin Contact

Remove contaminated shoes and clothes. Wash off in flowing water or shower with soap. Provide clean clothing.

11.2 SPECIAL FEATURES FOR MEDICAL TREATMENT

Inhalation

If aspirated, PER may be rapidly absorbed through the lungs and cause systemic effects. Immediate medical surveillance is recommended. Never administer sympathomimetic drugs such as adrenaline unless this is absolutely necessary, because of the risk of cardiac fibrillation. Give supportive care. Further treatment should be based on the judgement of a physician, in response to reactions of patient.

There is no specific antidote.

Ingestion

Since rapid absorption of aspirated PER may occur through the lungs and cause systemic effects, the decision of whether or not to perform gastric lavage should be made by a physician. If lavage is performed, endotracheal intubation is suggested. The danger from lung aspiration must be weighed against toxicity when considering emptying the stomach. Induction of vomiting is not recommended because of the risk of aspiration into the lungs, but the final decision has to be made by the physician.

11.3 SAFE HANDLING

11.3.1 Storage

PER should be stored in a dry, freshly aerated place in closed metal containers, away from direct sunlight and away from reactive or inflammable materials. Small quantities may be stored in brown glass bottles.

Always protect against fire: no smoking, no naked flames or sparks.

Containers for spills should be installed in places where large quantities are stored (ECSA, 1989).

11.3.2 Handling Precautions and Personal Protection

PER should be used only with adequate ventilation to ensure that workplace concentrations are below the appropriate occupational exposure limit. Local exhaust ventilation may be necessary for some operations. When respiratory protection is required for certain operations, an approved air-purifying respirator (organic vapour type) must be used. In confined or poorly ventilated areas, personnel should use an approved positive-pressure supplied-air respirator. Similar requirements should be adopted under emergency and other exceptional conditions where the exposure guideline may be greatly exceeded.

Use impermeable gloves when contact with the solvent could occur. Neoprene gloves are recommended for intermittent use, polyvinyl alcohol gloves are recommended for frequent or repeated handling. Chemical goggles, a face-mask and apron should be worn if there is danger of splashing.

Avoid breathing PER vapours. They are heavier than air and will collect in low areas such as pits, degreasers, storage tanks and other confined areas. Do not enter these areas if vapours of PER are suspected unless special breathing apparatus is used and an observer is present for assistance.

11.3.3 Health Surveillance and Biological Monitoring

Early detection of effects on target organs may involve: symptoms such as headache, sleepiness, dizziness; neurological examination including tests of co-ordination; biochemical blood tests for liver and kidney function. The results should be compared with the findings in a non-exposed control group.

To estimate the total exposure to PER over a whole working week, measurement of the following parameters has been proposed (Biological Exposure Indices, BEI; Biologische Arbeitsstoff-Toleranz-Werte, BAT-Werte).

- Concentration of PER in "end-exhaled" (alveolar) air (15-16 hours after last exposure, prior to last shift of working week) should be < 10 ppm (< 69 mg/m^3) (ACGIH, 1996; DFG, 1997);
- Concentration of PER in blood (15-16 hours after last exposure, prior to last shift of working week) should be < 1 mg/l (Henschler, 1989; ACGIH, 1996);
- Concentration of TCA in urine (at end of working week) should be < 7 mg/l; this parameter has been considered less appropriate as a specific parameter because TCA can arise as a metabolite of other chlorinated solvents (Lauwerijs *et al*, 1983; Henschler, 1989).

11.4 MANAGEMENT OF SPILLAGE AND WASTE

11.4.1 Spillage

Try to contain any spillage to as small an area as possible.

Small leaks: cover immediately with sand, sand dust, paper or other absorbent material and transfer PER-soaked absorbent into sealable metal containers for disposal. Supply fresh air. Clean the contaminated place with water and soap.

Large spills: evacuate the area. Contain the liquid and pump or transfer to closed metal containers. Keep out of drains and water courses.

PER vapours are heavier than air and will be slow to disperse in pits etc. below ground level, or in enclosed vessels. If spilled, they should be removed by local or natural ventilation.

11.4.2 Waste

The preferred options are to send PER containing waste in closed metal containers to a licensed reclaimer or to a permitted incinerator in compliance with local, state and national regulations. Dumping into sewers, on the ground or into any body of water is strongly discouraged and may be illegal.

Distillation of waste PER may be feasible. Small quantities may be evaporated in a fume-cupboard or in the open air.

APPENDIX A. ATMOSPHERIC FATE OF TETRACHLOROETHYLENE

A.1 CHEMICAL AND PHYSICAL REMOVAL PROCESSES

The atmospheric degradation of PER occurs mainly in the troposphere and is initiated principally by reaction with hydroxyl radicals and possibly to some extent by reaction with chlorine atoms. Reaction with other trace species and direct photolysis are believed to make only a minor contribution to the degradation of PER. Physical removal from the troposphere by "rainout" or uptake by the oceans is negligible compared to chemical destruction.

The mechanism and products of the degradation are discussed in Section A.3.

A.1.1 Reaction with the Hydroxyl Radical

Atkinson (1994) reviewed determinations of the rate constant for reaction of PER with the hydroxyl radical:

$$CCl_2{=}CCl_2 + {}^{\cdot}OH \longrightarrow HOCCl_2CCl_2{}^{\cdot} \qquad \text{(Eq. A.1)}$$

and recommended the value $k_{OH} = 9.64 \times 10^{-12} \exp(-1209/T)$ cm^3 molecule^{-1} s^{-1}, where T is the absolute temperature in K.

The tropospheric lifetime of PER (i.e. the time required for the concentration to fall to 1/e of its initial value, if all sources of PER are abruptly stopped) with respect to removal by reaction with hydroxyl radicals (τ_{OH}) can be estimated using the method recommended by Prather and Spivakovsky (1990), i.e. by scaling the lifetime to that of the reference compound 1,1,1-trichloroethane, by means of the equation:

$$\tau_{OH} = \tau_{OH,r} \times (k_{OH,r} \text{ at } 277 \text{ K}) / (k_{OH} \text{ at } 277 \text{ K}) \qquad \text{(Eq. A.2)}$$

where $\tau_{OH,r}$ is the lifetime of 1,1,1-trichloroethane (5.9 y, according to IPCC, 1996) and $k_{OH,r}$ is the rate constant for the reaction of 1,1,1-trichloroethane with the OH radical (6.7×10^{-15} cm^3 molecule^{-1} s^{-1} at 277 K, according to DeMore *et al*, 1994). This equation leads to a calculated lifetime τ_{OH} for PER equal to 0.32 years, i.e. 3.9 months.

A.1.2 Reaction with the Chlorine Atom

A detailed study of the reaction of PER with the chlorine atom:

$$CCl_2{=}CCl_2 + Cl^{\cdot} \longrightarrow CCl_3CCl_2{}^{\cdot} \qquad \text{(Eq. A.3)}$$

has been published, together with a review of previous determinations (Nicovich *et al*, 1996). The rate constant is found to be $k_{Cl} = 4 \times 10^{-11}$ cm^3 molecule^{-1} s^{-1} at 277 K and 1 bar (1,000 hPa). This is roughly

300 times greater than the rate constant k_{OH} for reaction of PER with the hydroxyl radical under the same conditions.

It is important to determine the relative contributions of reactions (A.1) and (A.3) to the atmospheric degradation of PER, since they lead to different breakdown products, as will be discussed in Section A.3. The relative rates of reactions (A.1) and (A.3) will depend not only on the ratio of their rate constants, but also on the relative atmospheric concentrations of chlorine atoms and hydroxyl radicals. While the levels of the latter have been fairly well established by modelling and measurement, no direct tropospheric measurements of chlorine-atom concentrations have been performed and only indirect evidence is available.

A number of recent studies have indicated that chlorine atoms are much more abundant in the marine boundary layer (up to roughly 1.5 km altitude over the oceans) than in the rest of the troposphere (see, for example: Graedel and Keene, 1995; Maben *et al*, 1995; Wingenter *et al*, 1996; and Singh *et al*, 1996a,b). From the available evidence it would appear likely that levels of chlorine atoms are high enough relative to hydroxyl radicals for reaction (A.3) to be faster than reaction (A.1) in this boundary layer. For example, Wingenter *et al*, 1996 report a $[Cl^{\cdot}]/[^{\cdot}OH]$ molar ratio of 0.1, so that, taking into account the rate constant ratio of reaction (A.3) to reaction (A.1) of 300, the addition of the chlorine atom would be <u>locally</u> 30 times faster than that of the hydroxyl radical.

On the scale of the whole atmosphere, however, the situation is very different. Rudolph *et al* (1996) calculated the rate of removal of PER by reaction with the hydroxyl radical, using as input observed mean tropospheric distributions and seasonal cycles of PER together with model-derived hydroxyl fields. The “budget” of PER (removal by chemical destruction compared to anthropogenic input) was then balanced by assuming an additional sink due to reaction with chlorine atoms. It was concluded that the latter sink is small or nil. Thus, for the troposphere of the northern hemisphere, where most of the PER is emitted and degraded, and for which the budget calculation can therefore be performed with greater certainty than for the southern hemisphere, it was concluded that the mean chlorine atom concentration may be close to zero and is at most 500 molecules cm^{-3}.

Aucott (1997) presented a similar budget analysis, taking into account also the possibility of natural production of PER in the oceans (see Abrahamsson *et al*, 1995a,b). Aucott assumed anthropogenic emissions of 438 kt/y, mainly in the northern hemisphere, and obtained a best fit between calculated and observed concentrations for an oceanic source-strength of approximately 100 kt/y and a global-mean tropospheric chlorine-atom concentration of close to 500 molecules cm^{-3}.

From the conclusions presented by Rudolph *et al* (1996) and Aucott (1997), and taking the average hydroxyl radical concentration as 10^6 molecules cm^{-3} (Prinn *et al*, 1995), one can conclude that reaction of PER with the chlorine atom is likely to be approximately $(500/10^6) \times 300 = 0.15$ times as

fast as reaction with the hydroxyl radical, leading to a yield of 13% for the Cl-atom initiated degradation pathway.

Finally, Singh *et al* (1996b) carried out similar calculations. They adopted an estimate of anthropogenic emissions taken from McCulloch and Midgley (1996), namely 395 kt/y (1989-1990 average), together with an additional ocean source of 35 kt/y, derived from measurements of over-saturation of PER in sea-water and assumed to be distributed as 40% in the northern hemisphere and 60% in the southern hemisphere. Singh *et al* (1996b) concluded that in a "mean case" calculation scenario, the Cl-atom concentration would be lower than 100 molecules cm^{-3} and that "on average 98% of measured C_2Cl_4 is accounted for by OH and at best 2% loss can be attributed to Cl." Singh *et al* (1996b) also derived an "upper limit" estimate of 30% removal of PER by reaction with chlorine atoms, resulting from an unlikely combination of extreme values of various parameters used as input to the model calculations. This latter scenario corresponded to a Cl-atom abundance of 1,000 molecules cm^{-3}. Singh *et al* (1996b) recognised that any errors were likely to be random rather than additive in nature and that a more reasonable upper limit to the Cl-atom concentration would be 500 molecules cm^{-3}, in agreement with the conclusions of Rudolph *et al* (1996) and Aucott (1997), so it is assumed henceforth in this assessment that the fraction of PER reacting with Cl is approximately 13%.

A.1.3 Other Processes

Other reactive species (NO_3, O_3, O^1D, O^3P, HO_2) present in the troposphere are unlikely to react with PER at rates approaching those of hydroxyl radicals or chlorine atoms, based on their known abundances and rate constants for reaction with PER (Franklin, 1994; Wiedmann *et al*, 1994).

Gas-phase photolysis may make a significant contribution, in addition to reaction with the hydroxyl radical, to the degradation of the small fraction of PER which reaches the stratosphere (Kindler *et al*, 1995). The lifetime of PER with respect to photolysis was calculated by Krüger *et al* (1987) to be approximately 3 years at an altitude of 20 km (stratosphere), but would be very much longer at tropospheric altitudes, so photolysis would be negligible in the troposphere.

On account of its high vapour pressure, PER will not partition to any appreciable extent onto particulate matter present in the atmosphere. Heterogeneous (photo)catalytic degradation is therefore not envisioned here as a possible sink.

Besemer *et al* (1984) concluded, on the basis of a methodology developed by Cupitt (1980), that "rainout" of PER is a negligible tropospheric removal process compared to chemical degradation. This conclusion has also been stated by Wiedmann *et al*, 1994. Furthermore, the latter authors presented data suggesting that uptake by the oceans is either small or completely negligible.

A.2 OVERALL LIFETIME, BUDGET CALCULATIONS, LONG-RANGE TRANSPORT

As stated above, the calculated lifetime of PER with respect to reaction with the hydroxyl radical in the troposphere is 0.32 years. Allowing for a possible small contribution to degradation by reaction with the chlorine atom (assumed yield 13%; see Section A.1.2), the calculated overall lifetime could be somewhat lower, approximately 0.28 years.

The atmospheric lifetime of PER can also be deduced, in an independent manner, from observed atmospheric concentrations and assumed or estimated atmospheric emission fluxes. The following overall lifetimes were obtained in this manner: 0.38 years (Class and Ballschmiter, 1987), 0.38 years (Kindler *et al*, 1995) and 0.45 years (Wang *et al*, 1995).

Other authors have performed similar “budget” calculations, but proceeded somewhat differently: they predicted the atmospheric concentrations of PER from assumed or estimated emission fluxes and degradation rates and then compared the calculated concentrations with the observed ones (Derwent and Eggleton, 1978; Altshuller, 1980; Koppmann *et al*, 1993; Wiedmann *et al*, 1994; Kindler *et al*, 1995; McCulloch and Midgley, 1996).

Broadly speaking, all these budget analyses demonstrate that the observed atmospheric background concentrations and their geographical distribution are consistent with the assumption that reaction with the hydroxyl radical in the troposphere is the dominant atmospheric sink for PER. As discussed in Section A.1.2, the modelling studies of Rudolph *et al* (1996), Aucott (1997) and Singh *et al* (1996b) demonstrate that the reaction with Cl is likely to be a minor sink and that there may be a rather significant natural input of PER into the atmosphere from the oceans.

The above-mentioned calculations were performed with atmospheric models of varying degrees of sophistication (one-, two-, multi-compartment, or global 2-dimensional models) and with input parameters (emission fluxes, atmospheric concentrations, inter-compartment exchange times, etc.) which have become increasingly better defined in recent years. Thus, for example, the global anthropogenic emission fluxes of PER and their geographical distribution have recently been deduced from audited production and sales data provided by members of trade associations in the USA, Europe and Japan, together with estimates for other countries (McCulloch and Midgley, 1996).

The overall lifetime of PER (0.3 - 0.4 y) is relatively long compared to the intra-hemispheric mixing time of approximately 1 month, so transport can occur to regions far removed from the emission source. It is, however, fairly short relative to the inter-hemispheric transport time of 1 - 1.5 years, resulting in higher concentrations in the northern hemisphere, where > 98% of the emissions occur (McCulloch and Midgley, 1996).

The existence of higher background concentrations in the northern hemisphere (average approximately 10 - 20 pptv; 68.9 - 138 ng/m^3) than in the southern hemisphere (average approximately 2 - 3 pptv; 14 - 21 ng/m^3) is well documented (Singh *et al*, 1983; Class and Ballschmiter, 1987; Koppmann *et al*, 1993; Wiedmann *et al*, 1994; Wang *et al*, 1995; Rudolph *et al*, 1996).

The lifetimes given above are average ones. The spatially and temporally varying "oxidising power" of the atmosphere (change in the OH concentration as the intensity of sunlight and water content vary) leads to a geographical and seasonal variation of the lifetime of PER and its concentration, particularly marked in the northern hemisphere (Singh *et al*, 1977; Makide *et al*, 1987; Koppmann *et al*, 1993; Wang *et al*, 1995; Rudolph *et al*, 1996; Yokouchi *et al*, 1996). This can lead to a longer lifetime - and hence a greater potential for long-range transport - when the oxidising power of the atmosphere is low, e.g. in the winter months.

A.3 DEGRADATION MECHANISM AND NATURE OF PRODUCTS FORMED

A.3.1 Simulated Atmospheric Studies

A number of studies have been carried out with PER under "simulated atmospheric conditions" in order to attempt to determine the nature of the products formed and elucidate the degradation mechanism. The products observed by different authors are summarised in Table A.1.

It must be emphasised that great caution is required in interpreting the data provided by simulated atmospheric experiments. An analysis of the validity of such experiments, for predicting both the atmospheric lifetime and the nature of the breakdown products, is given by Dilling (1982). Deviations from actual tropospheric conditions must be taken into account in order to propose likely breakdown pathways in the real environment, as discussed below.

Table A.1: Products Observed in Simulated Atmospheric Degradation of PER

Product \ Reference:	A	B	C	D	E	F	G	H	I	J
CCl_3COCl		x	x	x	x			x	x	x
$CHCl_2COCl$			?			x				
CCl_2CCl_2 epoxide										x
$COCl_2$	x	x	x	x	x	x	x	x	x	x
CO_2		x		?					x	
CO				x	x				x	
HCO_2H				x						
HCl				x	x					
Cl_2					x					
CCl_4			x						x	x
$CHCl_3$			?			x				x

A Lillian *et al* ,1975a,b
B Pearson and McConnell, 1975
C Lobban, 1975; Singh *et al*, 1975; Appleby, 1976; see also comments in Appleby *et al*, 1976
D Gay *et al*, 1976a,b
E Müller and Korte, 1977
F Crosby, 1980 as quoted in Pruden and Ollis, 1983; Crosby, 1982 as quoted in Ollis *et al*, 1984
G Goodman *et al*, 1986
H Winer *et al*, 1987; Tuazon *et al*, 1988
I Ibusuki *et al*, 1990; Itoh *et al*, 1994
J Behnke and Zetzsch, 1991
? Uncertain

A.3.2 Reaction Mechanisms

Phosgene and trichloroacetyl chloride (CCl_3COCl, abbreviation TCAC) are the main molecular products identified in the laboratory studies. A key contribution to understanding the mechanism of the formation of these products was made in a study carried out by Atkinson and co-workers (Winer *et al*, 1987; Tuazon *et al*, 1988). In experiments in which the oxidation was initiated by hydroxyl radicals, both phosgene and TCAC were formed. When ethane was added to scavenge chlorine atoms present in the system, the formation of TCAC was practically suppressed, with only phosgene remaining as an observed product (but the carbon balance was very poor, since the phosgene yield was only 23.5%). This confirms that TCAC is a product arising - most probably solely - from a reaction involving Cl atoms.

TCAC was indeed known previously in the literature to be the main product, along with phosgene, in the chlorine-atom sensitised oxidation of PER (i.e. in the absence of hydroxyl radicals) studied by Huybrechts *et al* (1967), Mathias *et al* (1974) and others. The proposed mechanism in this case is basically as follows:

$$CCl_2=CCl_2 + Cl^{\cdot} \longrightarrow CCl_3CCl_2^{\cdot} \quad \text{(Eq. A.3)}$$

$$CCl_3CCl_2^{\cdot} + O_2 \longrightarrow CCl_3CCl_2O_2^{\cdot} \quad \text{(Eq. A.4)}$$

$$2\ CCl_3CCl_2O_2^{\cdot} \longrightarrow 2\ CCl_3CCl_2O^{\cdot} + O_2 \quad \text{(Eq. A.5)}$$

$$CCl_3CCl_2O^{\cdot} \xrightarrow{85\%} CCl_3COCl + Cl^{\cdot} \quad \text{(Eq. A.6a)}$$

$$CCl_3CCl_2O^{\cdot} \xrightarrow{15\%} COCl_2 + CCl_3^{\cdot} \quad \text{(Eq. A.6b)}$$

$$CCl_3^{\cdot} + O_2 \longrightarrow CCl_3O_2^{\cdot} \quad \text{(Eq. A.7)}$$

$$2\ CCl_3O_2^{\cdot} \longrightarrow 2\ CCl_3O + O_2^{\cdot} \quad \text{(Eq. A.8)}$$

$$CCl_3O^{\cdot} \longrightarrow COCl_2 + Cl^{\cdot} \quad \text{(Eq. A.9)}$$

It is generally accepted that under atmospheric conditions (low concentrations of the chlorinated organic species and presence of NO), reactions A.5 and A.8 of the perchloroalkyl-peroxy radicals would be replaced by:

$$CCl_3CCl_2O_2^{\cdot} + NO \longrightarrow CCl_3CCl_2O^{\cdot} + NO_2 \quad \text{(Eq. A.10)}$$

$$CCl_3O_2^{\cdot} + NO \longrightarrow CCl_3O^{\cdot} + NO_2 \quad \text{(Eq. A.11)}$$

leading to the same perchloroalkoxy radicals.

The above reaction scheme shows that even when chlorine-atom addition to PER is the dominant primary step, some phosgene is formed along with TCAC. According to the data reviewed by Sanhueza *et al* (1976), the fraction of CCl_3CCl_2O radicals which break down to give ultimately 2 molecules of $COCl_2$ is approximately 15%, with little temperature dependence. The yield of 15% has been confirmed by Møgelberg *et al*, 1995.

As pointed out by Dilling (1982), any chlorine atoms which may be formed in the tropospheric degradation of PER will react much faster with other species (such as ozone and methane) than with PER itself, on account of the low concentration of the latter in the real background atmosphere (< 50 pptv; 344.5 ng/m^3). This is in contrast to the laboratory studies, in which the higher levels of PER may make the Cl + C_2Cl_4 reaction a predominant sink for the chlorine atom.

When conditions are such that addition of hydroxyl radicals to PER:

$$CCl_2 = CCl_2 + {}^{\cdot}OH \longrightarrow HOCCl_2CCl_2{}^{\cdot} \qquad \text{(Eq. A.1)}$$

is the predominant primary step, the precise nature of the ensuing steps has not been clearly established. Initial products formed subsequent to the addition of OH to PER, in the absence of oxygen, have been investigated by mass spectrometry (Kirchner, 1983; Kirchner *et al*, 1990; Helf, 1990). According to the proposed mechanism, the chemically activated adduct initially formed in reaction (A.1) can be stabilised by collision with other molecules, or can lose a chlorine atom to give either the unstable trichloroethenol (A.12a) or dichloroacetyl chloride (A.12b), or undergo C-C cleavage to yield phosgene (A.12c):

$$HOCCl_2CCl_2{}^{\cdot} \longrightarrow C(OH)Cl = CCl_2 + Cl{}^{\cdot} \qquad \text{(Eq. A.12a)}$$

$$HOCCl_2CCl_2{}^{\cdot} \longrightarrow CHCl_2COCl + Cl{}^{\cdot} \qquad \text{(Eq. A.12b)}$$

$$HOCCl_2CCl_2{}^{\cdot} \longrightarrow COCl_2 + CHCl_2{}^{\cdot} \qquad \text{(Eq. A.12c)}$$

The extent to which such reactions may occur under atmospheric conditions depends on their rates relative to that of the competing reaction:

$$HOCCl_2CCl_2{}^{\cdot} + O_2 \longrightarrow HOCCl_2CCl_2O_2{}^{\cdot} \qquad \text{(Eq. A.13)}$$

However, while the rate constant for reaction (A.13) may be estimated to lie between 10^{-12} and 10^{-11} cm^3 $molecule^{-1}$ s^{-1}, under atmospheric conditions, no kinetic data on reactions (A.12a), (A.12b) and (A.12c) are available. Atkinson (1986, p. 131) has nevertheless pointed out that reaction (A.1) is exothermic by approximately 35 kcal mol^{-1}, while reaction (A.12a) is endothermic by only approximately 11 kcal mol^{-1}, so the combination of the two processes is thermodynamically favourable.

Howard (1976) also postulated the occurrence of reactions (A.1), (A.12a) and (A.13) in the atmospheric breakdown mechanism, reaction (A.13) being followed by reactions (A.14 + A.15) and (A.16 + A.17):

$$HOCCl_2CCl_2O_2{}^{\cdot} + NO \longrightarrow HOCCl_2CCl_2O{}^{\cdot} + NO_2 \qquad \text{(Eq. A.14)}$$

$$HOCCl_2CCl_2O{}^{\cdot} \longrightarrow HOCCl_2COCl + Cl{}^{\cdot} \qquad \text{(Eq. A.15)}$$

$$HOCCl_2COCl + {}^{\cdot}OH \longrightarrow {}^{\cdot}OCCl_2COCl + H_2O \qquad \text{(Eq. A.16)}$$

$$OCCl_2COCl \longrightarrow COClCOCl + Cl{}^{\cdot} \qquad \text{(Eq. A.17)}$$

This speculative mechanism would lead to the formation of oxalyl chloride, which however has never been reported in product studies.

Graedel (1978, personal communication as quoted in Chen *et al*, 1983), suggested a more plausible sequence, consisting of reactions (A.1), (A.13) and (A.14), followed by:

$$HOCCl_2CCl_2O^{\cdot} \longrightarrow HOCCl_2^{\cdot} + COCl_2^{\cdot} \qquad \text{(Eq. A.18)}$$

$$HOCCl_2^{\cdot} + O_2 \longrightarrow COCl_2 + HO_2^{\cdot} \qquad \text{(Eq. A.19)}$$

Reactions (A.18) and (A.19) would explain the formation of phosgene reported by Tuazon *et al* (1988) as the major observed product in the presence of chlorine-atom scavengers.

It has recently been confirmed that in systems free from chlorine atoms, the yield of C_2 products in the OH-initiated oxidation of PER is negligible (Manning *et al*, 1996).

A.3.3 Formation of Carbon Tetrachloride and Chloroform

The mechanisms presented so far do not explain the formation of carbon tetrachloride and chloroform.

Carbon tetrachloride, an ozone-depleting substance, was observed in three series of studies, all of which were carried out in smog chambers, at ppm levels of PER and in the presence of simulated sunlight (Singh *et al*, 1975; Lobban, 1975; Appleby, 1976; Behnke and Zetzsch, 1991; Ibusuki *et al*, 1990; Itoh *et al*, 1994).

The first such report was by Singh and co-workers (Singh *et al*, 1975; Lobban, 1975; Appleby, 1976), who observed the formation of phosgene, TCAC and possibly dichloroacetyl chloride (DCAC) and chloroform (although the latter two compounds were later stated by Appleby *et al*, 1976, not to be present in significant amounts), together with carbon tetrachloride (CCl_4). These investigators noted that CCl_4 concentrations continued to increase well after all the PER had been consumed. At the same time, the initially formed TCAC continued to react, suggesting its role as the precursor of CCl_4. While phosgene was the main product, the formation of CCl_4 represented approximately 8% by weight relative to the initial PER, after 1 week of reaction.

In order to investigate CCl_4 formation further, two additional smog-chamber studies were initiated in 1990.

Behnke and Zetzsch (1991) performed experiments both in the absence and in the presence of added ethane as a scavenger for chlorine atoms, and monitored chlorine-atom and hydroxyl-radical concentrations using a hydrocarbon tracer technique. This work led to the following results:

- CCl_4 was indeed observed, albeit in considerably lower yields than those reported by Singh and co-workers (maximum approximately 2%, instead of 8%);

- a good correlation was established between the amount of CCl_4 formed and the calculated amount of PER having reacted with chlorine atoms, suggesting that CCl_4 is a product of the chlorine-atom initiated degradation pathway;
- the rate of CCl_4 formation increased with time, from an initial value of zero, showing that it is not a primary product of PER oxidation.

In order to check the hypothesis (Singh *et al*, 1975; Appleby, 1976) that TCAC is the precursor of CCl_4, Behnke and Zetzsch (1991) performed experiments on the photolysis of ppm levels of TCAC in air and found that:

- CCl_4 was indeed formed as a minor product, the major one being phosgene;
- the rate of formation of CCl_4 increased with rising relative humidity;
- photolysis of TCA, the hydrolysis product of TCAC, also led to CCl_4 and in this case the yield was further enhanced by the addition of gaseous HCl or NaCl aerosol.

These observations suggested that CCl_4 was formed by a heterogeneous photochemical process, occurring on the reactor walls or on the surface of the aerosols, in which TCA and chloride ion were probably the precursors of CCl_4.

From experiments on the photolysis of TCAC, carried out in the presence of the lowest amount of humidity possible, to prevent hydrolysis to TCA, Behnke and Zetzsch (1991) estimated an upper limit of 0.003 for the quantum yield of the hypothetical homogeneous gas-phase formation of CCl_4 from TCAC itself:

$$CCl_3COCl + h\nu \longrightarrow CCl_4 + CO \qquad \text{(Eq. A.20)}$$

analogous to the postulated (Yung *et al*, 1975; Chang and Kaufman, 1977) but not demonstrated photolysis of DCAC to chloroform:

$$CHCl_2COCl + h\nu \longrightarrow CHCl_3 + CO \qquad \text{(Eq. A.21)}$$

DCAC does indeed seem to have been formed in certain laboratory studies on the oxidation of PER (Singh *et al*, 1975; Appleby, 1976; Crosby, 1980 as quoted in Pruden and Ollis, 1983; Crosby, 1982 as quoted in Ollis *et al*, 1984), albeit in low yields (Appleby *et al*, 1976). Thus reaction (A.21), occurring either homogeneously or heterogeneously, might explain the formation of chloroform reported by some of the groups of investigators (Singh *et al*, 1975; Appleby, 1976; Crosby, 1980 and 1982; Behnke and Zetzsch, 1991) as a minor product (Appleby *et al*, 1976).

Behnke and Zetzsch (1991) estimated that the overall yield of CCl_4 from PER in the homogeneous gas-phase atmosphere would be less than 0.1%.

Ibusuki and co-workers (Ibusuki *et al*, 1990; Itoh *et al*, 1994), who conducted a smog-chamber study of the OH-initiated oxidation of PER in the absence of chlorine-atom scavengers, observed that the main oxidation products were TCAC, $COCl_2$, CO and CO_2. The yield of CCl_4 was typically only 0.07% and the formation of chloroform was not reported. Ibusuki and co-workers confirmed the conclusions of Behnke and Zetzsch (1991) that CCl_4 is not a primary product, but arises from the photochemical degradation of TCAC and thus is a low-yield product of the chlorine-atom initiated degradation pathway.

Based on the understanding of the degradation mechanism provided by the studies discussed above, it is concluded that the amount of CCl_4 formed by degradation of PER in the real atmosphere, if it is formed at all, will depend on the relative rates of various processes in competition with each other (Franklin, 1994):

- Attack on PER by chlorine atoms, rather than by hydroxyl radicals (as only the former can ultimately give appreciable yields of TCAC, according to Tuazon *et al*, 1988 and Manning *et al*, 1996). The yield of this process is assumed to be 13% (Section A.1.2).

- Dissociation of the intermediate pentachloroethoxy radical to TCAC rather than to phosgene. The TCAC yield is 85% (Section A.3.2).

- Photolysis of TCAC, rather than destruction of TCAC by hydrolysis subsequent to uptake by cloud droplets or deposition to the ocean or land surface. TCAC is hydrolysed only very slowly in the homogeneous gas phase (Butler and Snelson, 1979) but its lifetime with respect to uptake from the atmosphere to liquid water (clouds, oceans) is estimated to be of the order of 20 days (Kindler *et al*, 1995). Its lifetime with respect to photolysis, assuming a quantum yield of unity, has been variously estimated to be 6 days (WMO, 1994, p. 12.12) or approximately 50 days (Behnke and Zetzsch, 1991). Conservatively adopting the faster rate, photolysis could represent up to 77% of the overall removal of TCAC.

- Photolysis of TCAC to CCl_4 (quantum yield < 0.003, see above), rather than to phosgene (major product in air).

Thus the overall yield of CCl_4 from PER in the atmosphere is likely to be less than 0.13 x 0.85 x 0.77 x 0.003 x 100%, i.e. < 0.03%.

A.4 EFFECT ON STRATOSPHERIC OZONE DEPLETION

A rough estimate of the contribution of PER to stratospheric ozone depletion may be obtained by assessing its share of total atmospheric chlorine loading. As stated above (Section A.2), the atmospheric concentrations of PER are much higher in the northern hemisphere than in the southern hemisphere.

However, recent measurements by three groups give similar values for the global weighted-mean ground-level concentration: 8.5 pptv (58.6 ng/m^3) (Wiedmann *et al*, 1994), 7.3 pptv (50 ng/m^3) (Wang *et al*, 1995) and 8.4 pptv (58 ng/m^3) (Rudolph *et al*, 1996). Thus PER contributes approximately 8 x 4 = 32 pptv (220.5 ng/m^3) to tropospheric Cl loading.

In early 1996, the total chlorine loading of the troposphere was roughly 3,000 pptv (20,670 ng/m^3) (Montzka *et al*, 1996), so PER represented only approximately 1% of this total and hence it may be concluded that, roughly speaking, PER contributes approximately 1% to current ozone depletion. This calculation could be refined by :

- expressing the contribution of PER and other substances (including bromine compounds) in terms of "equivalent effective stratospheric chlorine loading" (Montzka *et al*, 1996);
- taking into account the fact that approximately a quarter of the contribution to reactive halogen loading is due to naturally occurring substances (CH_3Cl and CH_3Br).

These refinements would not have a very great impact on the estimate of the contribution of PER to the total amount of ozone-depleting species of anthropogenic origin.

WMO (1994, p. 13.8) concluded, on a similar basis to the one developed above, that PER probably contributes little to contemporary stratospheric chlorine loading, but hinted that future growth in emissions might pose a problem. However, as shown by McCulloch and Midgley (1996), emissions actually decreased by 35% between 1988 and 1992. They are expected to decline further in the future as a result of improved working practices.

Wang *et al* (1995) expressed the contribution of PER to stratospheric chlorine loading as follows: "... the transport of [organochlorine] molecules from the troposphere to the stratosphere takes place almost entirely through the tropical tropopause. Because the typical mixing ratios in the tropics in all seasons are around 5 pptv of CCl_2=CCl_2 or 20 pptv of Cl, the fraction of the current 4,000 pptv of tropospheric organochlorine attributable to CCl_2=CCl_2 as a source is approximately 0.5%. The delivery of only 20 pptv Cl to the stratosphere from yearly atmospheric emissions of approximately 400 kilotons contrasts strikingly with the delivery of more than 1,000 pptv Cl from CCl_2F_2 (2 Cl atoms x 500 pptv mixing ratio) from the accumulation from yearly emissions over the 1970's and the 1980's of approximately 400 kilotons/year."

It would not seem meaningful to attempt to calculate an Ozone Depleting Potential (ODP) for PER using a 2-dimensional modelling approach, as has been done for chlorofluorocarbons, hydrochloro-fluorocarbons and other compounds. Indeed, PER has such a short atmospheric lifetime (0.3 - 0.4 y) that its concentration varies considerably from one point of the Earth's surface to another; it also falls off significantly between ground level and the tropopause (Blake *et al*, 1996). Thus calculation of an ODP

would require 3-dimensional (altitude, latitude, longitude) modelling and the result obtained would depend to some extent on the point and time of emission to the atmosphere.

The ODPs reported by Kindler *et al* (1995) are in fact not model-calculated ODPs, but corrected Chlorine Loading Potentials (CLPs). The CLP is a quantity that can easily be calculated from the atmospheric lifetime and chlorine content of a compound. In some cases, it is a good approximation to the ODP. Assuming an atmospheric lifetime of 0.32 years, the (uncorrected) CLP of PER would be 0.007. An important conclusion of the Kindler *et al* (1995) paper is that any phosgene formed during the stratospheric degradation of PER is sufficiently stable in the lower stratosphere to be partially removed by transport to the troposphere, where it is destroyed by hydrolysis. Thus, not all the chlorine contained in the already small fraction of PER reaching the stratosphere (1.6% of ground-level emissions, according to Kindler *et al*, 1995, which confirms the value reported by Derwent and Eggleton, 1978) is actually converted into ozone-depleting inorganic chlorine species. This led to a downward correction of the CLP to 0.006 in the study by Kindler *et al* (1995), who assumed a 23.5% yield for the production of phosgene from PER on reaction with OH, based on the laboratory study by Tuazon *et al* (1988). If the actual phosgene yield were higher, the downward correction to the CLP would be even greater. However, it should be emphasised that the concept of CLPs (like ODPs) was developed for longer-lived substances than PER and it is not appropriate for compounds that do not become more or less uniformly distributed in the troposphere.

Kindler *et al* (1995) also concluded that :

- only approximately 0.4% of the phosgene produced in the troposphere by the breakdown of PER avoids removal by wet or dry deposition and subsequent hydrolysis and is transported to the stratosphere;
- stratospheric chlorine loading from any TCAC which might be formed as a product of the degradation of PER would be insignificant.

The possible formation of CCl_4, an ozone-depleting substance, in the atmospheric oxidation of PER, has been discussed in Section A.3.3. It would appear likely that only a very small proportion of PER (< 0.03%) is converted into CCl_4.

A.5 EFFECT ON TROPOSPHERIC OZONE FORMATION (PHOTOCHEMICAL SMOG)

Certain organic air pollutants known as VOCs (Volatile Organic Compounds) lead to the production of excess tropospheric ozone and other oxidants ("O_3/O_x") in the presence of sunlight and nitrogen oxides (NO_x). This phenomenon occurs particularly in or near urban areas, on account of high precursor concentrations and it leads to episodes of "photochemical smog". The degree to which individual pollutants contribute to such smog depends essentially on how fast the pollutants react in the

troposphere to give organic free radicals. Only the more reactive compounds make a significant contribution.

PER, while being reactive enough to be almost completely degraded in the troposphere, is sufficiently long-lived to be transported away from the polluted urban boundary layer and dispersed before being oxidised. For this reason it makes only a negligible contribution to local tropospheric O_3/O_x production.

Dimitriades *et al* (1983) reviewed and analysed existing evidence on photochemical O_3/O_x production by PER and concluded that PER is less "photochemically reactive" than ethane. Since ethane was itself considered by EPA to have a negligible reactivity and was one of the compounds exempted from regulation under State Implementation Plans to attain national ambient air quality standards for ozone, EPA proposed in 1983 to add PER to the list of substances exempted from being considered, as VOCs (US-EPA, 1996). A final rule exempting PER was published recently (US-EPA, 1996).

Derwent and Jenkin (1991) defined a Photochemical Ozone Creating Potential (POCP) for ranking various organic pollutants, assigning a value of 100 for the POCP of ethylene. By means of modelling studies, these authors concluded that "as a class the chlorocarbons show exceedingly low POCPs, illustrating their value as solvents with low ozone forming potentials". The POCP of PER was found to be roughly 0.5 (compared to 8.2 for ethane). Derwent and Jenkin (1990) showed that for a typical polluted air mass traversing southern England, the individual calculated contribution of PER was less than 0.06% of total ozone formation due to various classes of hydrocarbons, ketones, alcohols and esters.

POCP values derived by Andersson-Sköld *et al* (1992) are somewhat higher (0.7 - 1.4 relative to 100 for ethylene), but still point to the very low photochemical reactivity of PER.

A.6 OTHER EFFECTS OF REACTION PRODUCTS

A.6.1 Chloride

The atmospheric oxidation of PER leads, via the formation of intermediates such as phosgene and possibly small amounts of TCAC, to the presence of hydrochloric acid in clouds, rain and the oceans. Assuming that all the chlorine in the estimated global emissions of 295 kt/y (1992 figure from McCulloch and Midgley, 1996) is converted into HCl (260 kt/y), the amount of chloride deposited in this manner is negligible (< 0.003%) compared to the natural atmospheric chloride flux of around 10 Gt/y, primarily from sea-salt aerosols (Graedel and Keene, 1995).

A.6.2 Acidity

The main precursors of acid rain are sulphur dioxide (SO_2) and nitrogen oxides (NO_x). The current global natural and anthropogenic emissions of SO_2 and NO_x correspond to an amount of sulphuric and nitric

acids of the order of 10^{13} mol H^+/y (Galloway, 1995). This is 1400 times greater than the acidity due to the HCl formed by the degradation of PER, on a global scale. Furthermore, since PER has a lifetime of a few months and is therefore dispersed before being oxidised, it will not contribute to high local acidity in rainwater, near the emission sources.

A.6.3 Phosgene

PER is one of several anthropogenic and natural sources of phosgene in the atmosphere (Wilson *et al*, 1988; Kindler *et al*, 1995). It appears unlikely that the very low tropospheric concentrations of this compound, i.e. less than 30 pptv (207 ng/m^3), will cause any direct effects on animal or plant life. Phosgene hydrolyses in the environment to CO_2 and HCl.

A.6.4 Trichloroacetic Acid

Chloroacetic acids, including TCA, are found to be widespread in rainwater, surface waters, vegetation and soil. It has been postulated by a number of groups of researchers that these compounds arise from the atmospheric degradation of chlorinated solvents, including PER (see, for example: Frank, 1988, 1989, 1990, 1991; Frank and Frank, 1990; Frank and Scholl, 1990; Frank *et al*, 1989a,b, 1990, 1993, 1995; Reimann *et al*, 1996; Bauer, 1991; Plümacher and Schröder, 1994; Fillibeck *et al*, 1995; Juuti *et al*, 1996; and references cited therein). Furthermore, in a number of these papers, it is suggested that there is a causal link between forest decline and uptake of TCA by foliage.

Available evidence leads to the conclusion that TCA is likely to be only a rather minor product of the atmospheric degradation of PER.

As has been discussed above (Section A.3.2), TCAC - the possible precursor of TCA in the atmosphere - is almost certainly a product of the chlorine-atom initiated degradation of PER alone, and not of the predominant hydroxyl-radical initiated breakdown mechanism. The Cl-atom pathway is calculated to represent approximately 13% of the overall free-radical attack of PER (Section A.1.2). An estimated 85% of any pentachloroethyl radicals formed by Cl-atom addition will be converted ultimately to TCAC (Section A.3.2). The fraction of TCAC which is taken up by cloud droplets and hydrolysed to TCA can be estimated by assuming that the lifetime of TCA with respect to aqueous uptake is 20 days and its lifetime with respect to photolysis is approximately 17 days (the geometric mean of 6 and 50 days, see Section A.3.3), so that 46% of the TCAC is hydrolysed to TCA (and 54% photolysed to phosgene). Thus the best estimate of the overall conversion of PER to TCA is 0.13 x 0.85 x 0.46 = 5%; the uncertainty on this figure is very great. If one combines individual uncertainties on rate constants for reaction of PER with Cl and OH, atmospheric abundances of Cl and OH, yield of TCAC from the CCl_3CCl_2O radical, and lifetimes of TCAC with respect to aqueous uptake and photolysis, then the overall yield of TCA from PER could range between 0.1% and 33%. It should also be noted that these figures represent global average values, while there may be considerable local and temporal variations.

A rough "order-of-magnitude" check on whether the atmospheric degradation of PER might account for a significant part of the levels of TCA observed in precipitation can be performed by making the following assumptions :

- the background concentrations of PER in the middle and high latitudes of the northern and southern hemispheres are 15 and 2.5 pptv (103.4 and 17 ng/m^3), respectively (see references in Section A.2);
- the rate constants for reaction of PER with OH and Cl are 1.23×10^{-13} and 4×10^{11} cm^3 $molecule^{1}$ s^{-1} respectively, at an effective mean atmospheric temperature of 277 K;
- the global-mean atmospheric concentrations of OH and Cl are respectively 10^6 and 500 molecules cm^{-3};
- the overall yield of TCA from PER is 5%;
- degradation of PER occurs in the troposphere, between the earth's surface and 10 km altitude at a mean pressure of 0.6 atm and an effective temperature of 277 K;
- any TCAC formed is scavenged by precipitation and hydrolysed to TCA;
- the total world-wide precipitation (5×10^{14} t/y) is assumed to be distributed uniformly over the earth's surface, corresponding to an annual depth of 1 m of rainfall or the equivalent of snow.

These assumptions lead to the following results :

- the rate of degradation of PER is 2.3 x [P] molecule cm^{-3} s^{-1}, where [P] (pptv) is the local concentration of PER
- the amount of PER degraded in a column having a cross-section of 1 m^2 and extending up to 10 km altitude, is 1.2×10^{-6} x [P] mol/y
- the amount of TCA formed in such a column is 1.0×10^{-11} x [P] t/y (5% yield). Its concentration in the corresponding precipitation (1 t/y) is 10 x [P] ng/l.

The TCA concentrations anticipated in precipitation are therefore 150 and 25 ng/l, in the middle to high latitudes of the northern and southern hemisphere, respectively. These calculated values are based on the hemispheric background concentrations of PER, while local tropospheric concentrations of PER may be considerably higher, even in rural air (Table 8).

For comparison, TCA concentrations observed in precipitation are as follows:

- 115 "open-field" values ranging from < 30 to 840 ng/l, with a median of 120 ng/l, in southern Germany (Schleyer *et al*, 1996);
- mean "open-field" concentrations for 9 rural observation stations in southern Germany varying between 170 and 280 ng/l (maximum concentrations from 330 to 540 ng/l), with an overall average of 200 ng/l (Fillibeck *et al*, 1995);
- monthly means of 50 to 350 ng/l in Zürich and 0 to 350 ng/l in a rural location in Switzerland (Reimann *et al*, 1996);

- mean concentrations in Zürich and Dübendorf (Switzerland) of 280 and 320 ng/l, respectively (Müller *et al*, 1996);
- 26 values varying from 0 to 55 ng/l in the Russian tundra and in northern Norway and Sweden, i.e. at latitudes of 63 - 78°N (Grimvall *et al*, 1995);
- levels of 0 to 45 ng/l for 4 samples taken in British Columbia, at 50 - 52°N (Grimvall *et al*, 1995);
- 6 values ranging from 20 to 120 ng/l in Antarctica (Grimvall *et al*, 1995).

While the TCA concentrations in rain over central Europe are broadly consistent with the assumption that TCA is formed from atmospheric PER with a yield of approximately 5%, the values observed in both the high-latitude northern hemisphere and in British Columbia are lower than one would expect on this basis, while the values observed in Antarctica are higher.

More detailed modelling than the rough “hemispheric-average” calculation performed here would be required to confirm the possible relationship between PER and TCA.

The extremely high TCA levels in soil reported by Frank (1988), namely 20 - 400 μg/kg at 20 cm depth in southern Germany, could in no way be explained either by input from rainfall or production from the degradation of PER, if these levels were typical of soils in general. This can be demonstrated by the following conservative calculation. Assuming that:

- TCA, at a steady-state concentration of 100 μg/kg, is physically confined to the top 20 cm-layer of soil (unlikely for a fully-ionised, hydrophilic, substance);
- TCA is microbially or chemically degraded in soil with a lifetime of 90 days (upper limit given by Worthing and Walker, 1987);
- annual rainfall is 80 cm and soil density is 2,000 kg/m^3;

then the rainwater concentration necessary to sustain the reported soil concentration would be approximately 100 μg/l, i.e. roughly 1,000 times greater than the levels actually observed in rainwater, and corresponding (if TCA is present in northern hemisphere precipitation alone and is uniformly distributed) to a total deposition flux of 50 Mt TCA/y.

APPENDIX B. AQUATIC FATE OF TETRACHLOROETHYLENE (ABIOTIC PROCESSES)

The abiotic processes which may be expected, a priori, to contribute to removal of PER from aqueous media are: volatilisation, chemical (or photochemical) reaction and sorption. However, in confined groundwater, neither volatilisation nor photodegradation will occur.

B.1. VOLATILISATION

Owing to its high Henry's Law constant (Table 1), PER present in surface waters will partition preferentially into the ambient air. Application of a Mackay Level 1 model leads to the conclusion that 99.45% of PER partitions to the air compartment (Ballschmiter, 1992). The rate of volatilisation is discussed below.

B.1.1 Laboratory Studies

Dilling *et al* (1975) and Dilling (1977) carried out experiments with pure water containing 1 mg/l of PER, stirred at 200 rpm in an open beaker in the presence of still air. The fall-off in the aqueous-phase concentration followed a first-order rate law and the evaporation half-life of the solute was approximately 0.4 hours at 25°C and 0.6 hours at 1 - 2°C. Addition of various contaminants (clay, limestone, sand, salt, peat moss, etc.) to the water had relatively little effect on the evaporation or disappearance rates of the PER. When the aqueous solution was stirred only intermittently (15 s every 5 min), the volatilisation half-life increased to over 1.5 hours.

Chiou *et al* (1980) performed laboratory experiments in a shallow dish (height 1.6 cm, diameter 5.2-cm) With initial concentrations of 180 and 0.1 mg/l, respective volatilisation half-lives were 3.2 and 7 minutes when the aqueous solution was stirred at 100 rotations/min (1.67 Hz) at 25°C. Without stirring (at the lower concentration) the half-life increased to 69 minutes. Chiou *et al* (1980) provided a theoretical model showing how, for relatively volatile solutes such as PER, mixing enhances the rate of volatilisation by reducing the liquid layer concentration gradient.

Smith *et al* (1980) devised a method for predicting environmental volatilisation rates of chemicals such as PER, from laboratory measurements. This method relies on measuring, in the laboratory, the ratio R of the evaporation rate constant to the oxygen re-aeration rate constant. In experiments carried out in stirred 1-litre or 2-litre beakers, PER volatilisation half-lives of 7.5 to 50 minutes were measured. The ratio R was shown to be constant at 0.52 over a wide range of conditions. The PER volatilisation rate constant in a natural water body can be obtained by measuring or estimating the oxygen re-aeration rate constant under the relevant environmental conditions and multiplying by the factor R.

Matter-Müller *et al* (1980, 1981) adopted a similar approach. Using a mechanically-stirred, surface-aerated, 3-litre vessel at 25°C, they measured volatilisation half-lives of 14 and 47 min at 800 and 600 rotations/min (1,334 and 1000 Hz) respectively and showed that the ratio R of the mass-transfer rate constant of PER to that of oxygen was 0.56. The presence of various types of surfactants was shown to have little effect on this ratio.

Roberts and Dändliker (1983) operated with 7.3 litres of 5 mg/l aqueous solutions of PER at 20°C and showed not only that the fall-off in concentration obeyed a first-order rate law, but that the overall mass-transfer rate constant increased almost linearly with the specific power input to the agitator once the turbulent regime was attained. Under the latter conditions, typical rather of mechanical aerators than of environmental situations, half-lives between 3 minutes and 1 hours were measured. The ratio R was found to be 0.61, practically independent of the mixing intensity.

Ince and Inel (1989) found R to be 0.53; they obtained a good correlation between the measured overall liquid transfer coefficient and the one estimated from the two-film model.

Zytner *et al* (1989b) studied volatilisation of PER from unstirred aqueous solutions containing 19 to 75 mg/l of PER, in beakers having surface/volume ratios varying between 2 and 81 m^{-1}, at 22°C. An air velocity of 10 km/h was maintained above the solutions. The evaporation half-lives were found to increase with decreasing surface/volume ratio; they ranged from 2 to 16 hours.

Chodola *et al* (1989) reported overall liquid-film transfer coefficients for PER at the water-air interface.

B.1.2 Large-Scale Experiments and Observations

Ruf and Scherb (1977a,b) reported on practical trials carried out by introducing mg/l levels of PER into a 1 km long, 18 cm deep artificial stream, (flow 0.5 m/s, water temperature 15-19°C). Samples were taken at various points downstream of the injection point and half-lives were calculated from first-order plots of the fall-off of the PER concentration. Although there was much scatter in the data, the half-lives were in the range 0.2 to 3.6 hours.

Wakeham *et al* (1983) carried out measurements on solutions of a few mg/l of PER in an experimental ecosystem or “mesocosm”, i.e. a tank containing 13 m^3 of sea-water and its associated planktonic and microbial communities. The tank was regularly mixed (4 x 2h/day). Half-lives of between 12 and 25 days were measured and differences were attributed to variations in wind stress regime. It was concluded that volatilisation appeared to be the dominant process and that biodegradation and sorption onto particles were probably not important. In further mesocosm experiments of this type, but using ^{14}C-labelled PER, Wakeham *et al* (1986) confirmed that biodegradation was not a significant process.

Namkung and Rittmann (1987) observed loss of volatile organic compounds from two waste-water treatment plants using an activated sludge process with diffused aeration. They concluded that volatilisation was the main loss process, adsorption being negligible (biodegradation was assumed from other studies to be insignificant).

B.1.3 Field Observations

Zoeteman *et al* (1980) pointed out that evaporation is generally much slower in real surface waters than in laboratory experiments. In fact liquid-phase resistance to evaporation dominates the mass transfer rate for most hydrophobic pollutants. In rivers, the vertical transport of pollutants in the water phase is mainly determined by eddies caused by the interaction of the current with the river bottom and thus depends on the depth of the river. In lakes the turbulence originates from the atmosphere and the wind speed is probably the dominant parameter. Field observations made by Zoeteman *et al* (1980) in Rhine water in the Netherlands gave half-lives for PER (initial concentration around 1 μg/l) of approximately 10 days in river water and 1 month in lake water.

Somewhat lower half-lives in rivers (4 - 6 d) resulted from field observations on PER concentrations (1.4 - 3.6 μg/l) in the River Main (Germany) carried out in 1982 (Brüggemann and Trapp, 1988). The authors of this study presented an equation, involving wind speed, water speed and river depth, for calculating the evaporation rate. They concluded that volatilisation was the main loss process, chemical degradation and burial with sediment being orders of magnitude slower. Subsequent measurements of PER in the Main, carried out in 1989-1990, showed that the concentrations were then lower (0.05 - 0.3 μg/l), but the calculated half-life was similar (3 - 5 d) (Trapp *et al*, 1992). Trapp and Harland (1995) derived, from the 1990 Main observations, a half-life for PER of 2 days. These authors also compared the experimental results with those provided by four theoretical volatilisation models.

Dyrssen *et al* (1990) performed measurements of PER concentrations (up to 0.4 μg/l) along the estuary of the River Elbe, showing that PER was supersaturated in the water and that evaporation to the atmosphere was a rapid and favoured process.

Schwarzenbach *et al* (1979) measured PER concentrations (0.03 - 0.07 μg/l) as a function of depth in Lake Zurich. The authors concluded that volatilisation was the dominant process for the removal of PER and they estimated the transfer flux to the atmosphere.

B.2. CHEMICAL REACTION

The rate, mechanism and products of the hydrolysis of PER in aqueous solution have not been well characterised. The existing data show, however, that PER reacts very slowly.

McConnell *et al* (1975) and Pearson and McConnell (1975) reported an estimated (extrapolated) half-life of 6 years, at an unspecified temperature. They stated that the rate of hydrolysis is not significantly pH-dependent (at least in the neutral to acid range) and speculated that the observed degradation may have occurred in the gas phase of the test bottles and may have been due to the presence of oxygen.

Dilling *et al* (1975) carried out reactivity studies with 1 mg/l of PER dissolved in water previously purged with air, so that the molar ratio of dissolved oxygen to PER was over 40. Samples were maintained for up to one year, either in sealed Pyrex tubes at approximately 25°C in the laboratory (and in the dark), or in quartz tubes at approximately –20 to + 40°C outdoors (exposed to daylight). In each case there was a large air space above the liquid in the tubes. The observed half-life was found to be approximately 9 months for the dark experiments and 6 months for the solutions exposed to daylight. It is quite probable that reaction was not purely hydrolytic, but at least partly (photo)oxidative and may have occurred in the head-space.

Jensen and Rosenberg (1975) measured the fall-off of the concentrations of PER dissolved at initial levels of 0.1 to 1 mg/l in sea-water and maintained in the dark or in daylight in various open or closed systems at 11 - 12°C. After 8 days the decrease in concentration was found to be 25 - 50%. In the case of sterilised de-ionised water, on the other hand, there was no significant decrease after 8 days at 4 - 20°C. It was speculated that the difference in behaviour may have been due to “inorganic or biological factors”.

Chodola *et al* (1989) carried out hydrolysis experiments in sealed vials with no head-space and observed losses of up to 14% after 7 days at 50°C and pH 9.2.

Jeffers *et al* (1989) measured hydrolysis rate constants for PER between 130 and 170°C and at pHs of 2 to 14. Apparently no special precautions were taken to exclude traces of oxygen. Only a basic attack was observed (first order in PER and first order in hydroxide ion); no evidence was found for a “neutral” reaction (attack by H_2O molecules) or for a process catalysed by the hydrogen ion. When the results were extrapolated to 25°C and pH 7, the estimated half-life was found to be as long as 10^9 years.

Miyamoto and Urano (1996) maintained neutral aqueous solutions containing 0.1 - 1 mg/l of PER for 48 hours at 80°C and reported that the conversion was less than 10%. On the basis of an assumed activation energy for hydrolysis (110 kJ/mol), they calculated a half-life of greater than 170 years at 15°C.

The above results suggest that PER might be very persistent in closed aqueous systems such as groundwater, unless biodegradation is an important breakdown pathway.

On the other hand, Kohno *et al* (1995) monitored PER present in groundwater, over a period of more than 5 years, and observed disappearance of this compound according to first-order kinetics, with a half-

life of only 344 days. The physical, chemical or microbial processes contributing to removal of PER from the groundwater were not identified.

As far as the nature of the hydrolysis products is concerned, little is known, but review articles report TCA to be a product (Hardie, 1964; Callahan *et al*, 1979). This is somewhat surprising: if nucleophilic substitution of the vinylic chlorine atoms occurs by attack of OH^- or H_2O and elimination of Cl^- ,one would expect it to be followed by an enol to keto tautomerisation to dichloroacetyl chloride and rapid hydrolysis of the latter to dichloroacetic acid. TCA may have resulted from gas-phase oxidation to TCAC (Section A.3.2), followed by hydrolysis of the latter.

For lack of experimental data, no in-depth attempt has been made here to assess the possible importance of degradation reactions of PER in sunlit surface waters due either to direct photolysis or to "indirect photolysis", i.e. reactions initiated by humic or fulvic materials acting as photosensitisers or by various species of photochemical origin, such as the hydrated electron, the hydroxyl radical, alkylperoxy and alkoxy radicals, electronically excited (singlet) molecular oxygen and the superoxide ion.

Mabey *et al* (1982) concluded that direct photolysis is not an environmentally significant degradation process in aquatic media. They made a rough evaluation of the rate constants for the reactions of PER with singlet molecular oxygen and with alkylperoxy radicals. According to their data, these two processes would have half-lives of many thousands of years. Chodola *et al* (1989) conducted experiments simulating photolysis in the aqueous environment and concluded that this process is negligible. Mertens and Von Sonntag (1995) carried out a detailed study of the photo-oxidation of PER in aqueous solution at 254 nm, but such short wavelengths are not present in the sunlight that reaches the Earth's surface.

B.3. SORPTION

B.3.1 Laboratory Studies

Some early observations on the sorption of PER by mineral substances, peat moss and natural sediments were reported by Dilling *et al* (1975), McConnell *et al* (1975) and Pearson and McConnell (1975).

Values for the partition coefficient of PER from water to the organic carbon of soils (K_{oc}), published by various authors are listed in Table 1; log K_{oc} lies in the range 1.9 - 2.6.

Wakeham *et al* (1983, 1986) calculated that for Narragansett Bay sea-water, any PER present should be mainly dissolved in the aqueous phase and hardly bound at all to suspended particulate matter.

Using the procedure adopted by Smith and Dragun (1984), but adopting a log K_{oc} of 2.4, one can calculate that for a water-saturated subsoil containing 1% of organic carbon and low levels of PER, roughly 10% of this solute will be present at equilibrium in the aqueous phase and 90% on the soil.

The low K_{oc} values and the above calculation on the partitioning to soils suggest that PER is fairly mobile in soil/water systems. The mobility of PER was studied experimentally, in soil-column experiments, by Wilson *et al* (1981), Bouwer *et al* (1981a) and Bates *et al* (1991).

Piwoni and Banerjee (1989) showed that sorption of PER onto low-carbon aquifer materials (C < 0.1%) is several times greater than would be predicted on the basis of partitioning to organic carbon alone; they attributed this to an additional mechanism involving adsorption on the mineral surfaces. Mokrauer and Kosson (1989) postulated that electrostatic attraction between negatively-charged clay particles and the positively-charged carbon atoms of organic chlorine compounds such as PER is the driving force for sorption onto a sandy loam.

Grathwohl (1990) showed that sorption of non-ionic compounds such as PER depends not only on the organic carbon content of the soils and sediments, but also on the nature of the organic matter. This author gave log K_{oc} values of 2.6, 3.3 and 4.0 for different adsorbents and presented a correlation equation for calculating K_{oc} from P_{ow} and the hydrogen/oxygen atomic ratio of the organic matter.

Schwarzenbach and Westall (1981) found that sorption to a variety of materials was reversible at the low concentrations of PER typical of the environment; they noted however that sorption kinetics may have an effect on transport of PER over the range of flow velocities encountered in aquifers.

Doust and Huang (1992) concluded that the sorption of PER to soils, clays and sands is rapid and reversible, following pseudo-first-order kinetics with a half-time of approximately 4 hours.

Pignatello (1990a,b) describes the formation of “slowly reversible” sorbed fractions of PER in soils. Such fractions were found to increase with sorption equilibration time and applied concentration. This work shows that even compounds normally regarded as labile in the environment by their volatility and weak equilibrium sorption tendencies can generate kinetically slowly sorbed residues.

Rate-limited, non-equilibrium sorption of PER was also investigated by Brusseau and Reid (1991) and Brusseau *et al* (1991).

A mathematical model was developed by Biswas *et al* (1992) to predict sorption, desorption and leaching of PER, in various soil environments. This model has been critiqued by Kuo (1993).

B.3.2 Field Observations

As reported by Kußmaul *et al* (1978), bank infiltration of Rhine water did not lead to any reduction in the concentration of PER, showing that sorption and any other removal processes such as biological degradation were negligible under these conditions.

Analogous conclusions on bank infiltration were published by Schwarzenbach *et al* (1983) and Giger *et al* (1983) for two sites in Switzerland. The similar average concentrations in the rivers and in the groundwater showed that PER was not significantly affected by any elimination process. Furthermore, the strong response in the groundwater to concentration changes in the river suggested that during infiltration PER was not strongly retained in the ground.

Apparently contradictory conclusions have been published on the efficiency of dune infiltration of Rhine water. Zoeteman *et al* (1980) reported results showing a 10-fold reduction in the PER concentration. On the other hand, Piet *et al* (1981) observed no such reduction.

Tomson *et al* (1981) published results on the efficiency of removal of PER from a secondary sewage effluent applied to a rapid infiltration site, by sorption and possibly other processes.

APPENDIX C. MODELLING OF CANCER RISK - A CRITICAL EVALUATION

A number of quantitative cancer risk assessments exist for exposure to PER, both from the environment and during occupational use of the chemical. The majority of these have been prepared by, or on behalf of, the US Federal and State regulatory authorities. It is the practice in the USA to use mathematical extrapolation from animal data to provide numerical power estimates of risk in humans. However, in other countries this methodology is rejected because it is imprecise and the risk estimates are subjected to substantial variation by defering assumptions used in the calculations. In the extreme case, the variation can be 5 orders of magnitude between the 95% upper confidence limit (UCL) of the multistage model and the maximum likelihood estimate (MLE) using other estimates. Thus risk assessments of this type must take into account this systematic variability.

The published risk assessments are based on the tumour incidences seen in the 2-year studies (NCI, 1977; NTP, 1986) and use either mouse liver tumours, rat mononuclear cell leukaemias, or both, as the basis of the assessment. Male rat kidney tumours, seen in one of the animal bioassays (NTP, 1986), have not been used. The risks were calculated using applied dose or metabolised dose, body weight or body surface area, for extrapolation between species, or using physiologically-based pharmacokinetic (PBPK) models for both dose and species extrapolation, followed by the application of linearised multistage or the Weibull statistical models for extrapolation from high to low dose.

Most of the existing risk assessments that pre-date the mechanistic studies define the mode of action of PER as a carcinogen. Consequently, the role of peroxisome proliferation, protein droplet nephropathy and activation by the GSH β-lyase pathway are not considered, either in the calculation of risk, or in the choice of animal model or tumour type on which the risk assessment is based. In the absence of these data the risk assessments were based on the highest incidences of tumours in the most sensitive animal species.

The US-EPA in their Health Assessment Document (US-EPA, 1985), based the risk calculations on the mouse liver tumours observed in the NCI gavage study (NCI, 1977). Dose was expressed either as applied dose or metabolised dose, with the linearised multistage model used for high to low dose extrapolation. When metabolised dose was used, estimates of metabolism were obtained from published papers (Bolanowska and Golacka, 1972; Fernandez *et al*, 1976; Schumann *et al*, 1980; Buben and O'Flaherty, 1985). Species to species scaling was based on either surface area extrapolation or metabolised dose. Although a number of different methods and data sets were used to produce a range of results, the preferred (by EPA) upper-bound estimates (95% UCL) of the incremental risk were as follows. For inhalation, the lifetime risk from exposure to a concentration of 1 mg PER/m^3 (0.15 ppm) was 4.8×10^{-7}, and for drinking water the risk associated with ingestion of 1 mg PER/l was 1.5×10^{-6}.

The Health Risk Assessment of PER in California Drinking Water prepared by Bogen *et al* (1987) contains a full review of the toxicology of PER and its environmental fate, in addition to a risk assessment, which is compared with the EPA approach described above. As in most risk assessments of PER, the toxic and carcinogenic effects are assumed to result from metabolites of PER. This concept is not further defined other than by reference to "reactive intermediates or epoxides". Metabolised dose is therefore preferred over applied dose and is determined by Simple Steady State Pharmacokinetics based on the Michaelis-Menten equation and published experimental studies. Risks are calculated using either the mouse liver tumours seen in the NCI gavage study (NCI, 1977) or in the NTP inhalation study (NTP, 1986), or the rat mononuclear-cell leukaemias seen in the NTP study (NTP, 1986). The linearised multistage model was used throughout to predict the risks at very low dose levels, and inter-species scaling was based on both bodyweight and body surface area. A large number of potency values (128) are given comparing the California approach with that of the EPA for both metabolised and applied dose. These values have an 84-fold range for metabolised dose and a 447-fold range for applied dose.

A number of PBPK models have been developed for PER (Hattis *et al*, 1986; Bogen and McKone, 1987; Ward *et al*, 1988; Travis *et al*, 1989). All of these models are suggested as an approach to risk assessment but only two include risk calculations (Hattis *et al*, 1986; Travis *et al*, 1989). Of the two publications that do include risk calculations, one (Hattis *et al*, 1986) was prepared on behalf of NIOSH and describes the risks at occupational exposure levels, the other (Travis *et al*, 1989) is based on continuous lifetime exposure to environmental levels. Both models assume a genotoxic mode of action for PER. Hattis *et al* (1986) calculate risks based on mouse liver tumours and rat leukaemias, and give a range of values. For example, a working lifetime exposure to 100 ppm (689 mg/m^3) PER is predicted to cause an increased cancer incidence in the range 52 - 65% (UCL) or 4.5 - 27% (MLE), depending upon the tumour type.

The approach taken by Travis *et al* (1989) assumes that there are two metabolic pathways for PER, one a saturable pathway leading to TCA, the other a linear but undefined pathway invoked to explain an apparent imbalance between uptake of parent chemical and production of metabolites. Metabolic rate constants for each species were determined by fitting model predictions to the same experimental data used in the previous risk assessments. The incidences of mouse liver tumours in the NCI (1977) and NTP (1986) studies were combined with those for male rats in the NTP study, even though the latter were not statistically significant. Data from the inhalation bioassay (NTP, 1986) were converted to a mg/kg/d dose so that they could be combined with the data from the gavage study (NCI, 1977). The relationship between metabolised dose and these tumour incidences was obtained using a least squares fit of the data. As in some of the previous risk assessments, comparisons were made between the PBPK approach and the conventional approach using applied dose and allometric scaling between species. At very low dose levels, the PBPK method gave a reduction in risk of 1.6-fold, exposure to PER in air at a concentration of 1 mg/m^3 (0.15 ppm) giving a risk of 3.1×10^{-7} by the PBPK method and 5.1×10^{-7} using the

applied dose. The reduction in risk given by the PBPK method increased at higher dose levels (118-fold at 500 ppm; 3,445 mg/m^3) when metabolic saturation was taken into account by one method (PBPK) but not the other.

In addition to the numerical, mathematically-based risk assessments, the US-EPA published an exposure and risk assessment for PER in 1982 (US-EPA, 1982), including a major review of the chemical, its fate in the environment and its effects on various biological systems. The quantitative aspects concerning the environment are now 10 years old and may no longer be correct. The risk assessment was largely superseded by that in the Health Assessment Document of 1985 (US-EPA, 1985). Several groups have commented on the various PBPK models used for PER risk assessments, both on the statistical precision of the models (Farrar *et al*, 1989; Bois *et al*, 1990), and on the values of some of the biological parameters used in the models (Reitz and Nolan, 1986).

Alternative approaches to risk assessment using mechanistic data from different species produce a totally different picture (see below and ECETOC, 1990).

The uncertainties in human risk assessments based on animal data are apparent from the wide range of risks predicted for PER by the various methodologies used. These arise from the choice of animal tumour data, the selection of dose and the models used for dose and species extrapolation. Because of a lack of knowledge (at the time) of the mechanism of action and pharmacokinetics of PER, there is little or no guidance as to the most appropriate form of these risk assessments. For example, rat leukaemias are frequently used even though most reviewers considered these tumours inappropriate for human risk assessment (NTP, 1986; HSE, 1987; ECETOC, 1990). There appears to be general agreement that metabolised dose is preferable to applied dose, although the assumptions made in the calculation of these doses vary widely and are frequently based on inadequate data. There is little agreement on the use of physiology, body weight or body surface area for species to species extrapolation.

The wide range of risks predicted by these assessments fail to provide accurate guidance for establishing safe levels of PER either during occupational use or in the environment. Some of the risks predicted are exceptionally high: e.g. Hattis *et al* (1986) suggest a 65% increase in tumours for occupational exposure to 100 ppm (689 mg/m^3); the US-EPA (1985) predict the potency of PER to be 8-fold higher than that of vinyl chloride. However, occupational experience of PER over several decades clearly suggests that these predictions are unrealistic, which leads to the conclusion that key pieces of information were either ignored or were unavailable when these risk assessments were published.

More recent studies of the various mechanisms involved in the induction of cancer in rodents exposed to PER have revealed both qualitative and quantitative differences between rats and mice, and between these species and humans. As a result, the tumours seen in rats and mice exposed to PER

are now considered to be an inappropriate endpoint on which to base human risk assessments (ECETOC, 1990).

APPENDIX D. REVIEW OF MUTAGENICITY TESTS

The details of mutagenicity assays of PER are summarised in Tables D.1-D.18.

D.1 GENE MUTATION

Bacterial Assays

Studies using bacterial assays are summarised in Table D.1.

The ability of PER to cause gene mutations in bacteria has been investigated in *Salmonella typhimurium* and *Escherichia coli*. In several plate-incorporation assays negative results were obtained, either with or without pre-incubation, using *S. typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538 and two additional strains which are not DNA repair deficient (UTH 8413 and 8414). Toxicity was observed at 224 - 333 mg/plate. Metabolic activation was achieved with liver S9 fractions obtained from rats, mice or hamsters induced by phenobarbital or Aroclor (Margard, 1978 as quoted in US-EPA, 1985; Bartsch *et al*, 1979; Kringstad *et al*, 1981; Haworth *et al*, 1983; Connor *et al*, 1985).

PER in the vapour phase has been tested on different *S. typhimurium* strains (see Table D.1). PER of high purity and containing low concentrations of stabilisers gave negative results in these assays up to levels which were toxic to the organisms in the absence or presence of Aroclor induced rat, mouse or hamster liver S9 fractions (SRI International, 1983 as quoted in US-EPA, 1985; Williams and Shimada, 1983 as quoted in US-EPA, 1985; Milman *et al*, 1988; Warner *et al*, 1988).

Positive responses in both plate incorporation and vapour phase Ames assays have been obtained with certain commercial and technical preparations of PER but only at toxic concentrations. No dose-response relationship was established in these tests. Furthermore, non-stabilised, highly pure PER gave a negative response in these studies (Margard, 1978; Williams and Shimada, 1983, both as quoted in US-EPA, 1985). The positive findings may be due to the presence of mutagenic contaminants and/or added stabilisers such as cyclohexene oxide and epichlorohydrin; both contaminants gave positive results with *Salmonella typhimurium* TA100 at concentrations greater than 0.25 ppm (1.72 mg/m^3 vapour), and *Salmonella typhimurium* TA1535 at 0.2 mg/ml agar (Bridges, 1978; Koorn, 1987).

PER of undefined purity was tested in a spot test, using *S. typhimurium* strains TA98, TA100, TA1535, TA1950, TA1951 and TA1952. Mutagenic activity was shown in all strains. A dose-dependent response was observed only in strain TA100 (Cerná and Kypenová, 1977). Insufficient details were provided for an assessment of this study.

A screening test on the ability of PER to induce survival repair mechanisms (SOS chromotest) in *E. coli* PQ37 was negative (Von der Hude *et al*, 1988).

PER caused no increase in the frequency of forward or reverse mutations in a bacterial assay with *E. coli* K12, in the presence or the absence of mouse liver S9 fractions (Greim *et al*, 1975).

D.1.1 Yeast Assays (Table D.2)

PER did not induce mutagenic activity in a yeast culture of *Saccharomyces cerevisiae* D7 in stationary phase in the absence or the presence of an exogenous activation system (Bronzetti *et al*, 1983).

PER has also been studied in *S. cerevisiae* D7 and D4 strains using log-phase cultures (Callen *et al*, 1980; Koch *et al*, 1988). The results were positive but were not reliable because of poor survival. The purity of the PER used was incompletely described.

D.1.2 *Drosophila* Assay (Table D.2)

Sex-linked recessive lethal tests in *Drosophila melanogaster* in which PER was administered by inhalation, feeding or injection showed no mutagenic effect (Beliles *et al*, 1980; Valencia *et al*, 1985).

D.1.3 Host-mediated Assays (Table D.3)

Oral administration of PER of high purity (99.5%) to CD-1 mice for 5 days gave negative results in a host-mediated assay using stationary *S. cerevisiae* D7 as the indicator organism (Bronzetti *et al*, 1983). The protocol, which involved intravenous injection, was unusual and as no positive control was used, interpretation of this study is impossible.

Using *S. typhimurium* strains TA1950, TA1951 and TA1952 as indicators, an increase in mutagenicity was observed in a host-mediated assay with PER of unknown purity administered to female ICR mice. No dose dependence was found (Cerná and Kypenová, 1977). In another host-mediated assay using *S. typhimurium* strain TA98, PER administered to female mice by inhalation at concentrations of 100 and 500 ppm (689 and 3,445 mg/m^3) yielded a clear (four-fold) increase in mutations at the highest concentration (Beliles *et al*, 1980). The material used was of low purity (91.43%) but it was negative when tested with TA98 in the presence of an S9 fraction.

The results obtained from the host-mediated assays are un-interpretable because of the absence of suitable controls or the use of an unconventional route of administration.

D.1.4 Mammalian System (Table D.4)

A study of gene mutation *in vitro* in a mouse lymphoma cell line (L5178Y/TK+/-), in the presence of an induced rat liver S9 fraction, gave negative results up to concentrations which were toxic to the cells (NTP, 1986).

Table D.1: Gene Mutation in Bacteria

Test system	Protocol	Purity (% w/w) / Source	Concentrations tested	Metabolic activation	Result	Comment	Reference
Ames / *Salmonella* TA98, TA100 TA1535, TA1537	Vapour-phase airtight 8 h, 37°C	> 99% Aldrich	0.025, 0.05, 0.1, 0.5, 1.0 and 1.5 ml added to Petri plate at bottom of desiccator (9 l)	± Aroclor 1254 induced rat S9 liver (F + M) and mouse S9 liver (F + M)	**–ve**	1.5 ml toxicity	SRI International, 1983 as quoted in US-EPA, 1985; Milman *et al,* 1988
Ames / *Salmonella* TA100	Tedlar vaporisation desiccator technique	Unknown	Unknown	± induced hamster S9 liver	**–ve**	Toxic levels achieved	Warner *et al,* 1988
Ames / *Salmonella* TA98, TA100, TA1535, TA1537, TA1538	Vapour-phase airtight 18 h, 37°C	99.93% PPG Industries, Perchlor 200[a]	1% (v/v) TA98, TA1538 and TA1537 0.1, 1.0, 2.5, 5.0, 7.5 and 10% (v/v) TA100 and TA1535	± Aroclor 1254 induced rat S9 liver	**+ve** (2.5%) TA100 TA1535	2.5% : (> 97% toxic) 3-6 fold response ± activation, dose-response not established	Williams and Shimada 1983 in US-EPA, 1985; Shimada *et al*, 1985
Ames / *Salmonella* TA98, TA100, TA1535, TA1537, TA1538	Vapour-phase airtight 18 h, 37°C	99.80% PPG industries, Perchlor 230[b]	1% (v/v) TA98, TA1538 and TA1537 0.1, 1.0, 2.5, 5.0, 7.5 and 10% (v/v) TA100 and TA1535	± Aroclor 1254 induced rat S9 liver	**+ve** (2.5%) TA100 TA1535	2.5% : (> 98% toxic) 3 - 10 fold response ± activation, dose-response not established	Williams and Shimada 1983 in US-EPA, 1985; Shimada *et al*, 1985
Ames / *Salmonella* TA100, TA1535	Vapour-phase airtight 18 h, 37°C	99.98% PPG Industries, high purity perchlor[c]	0.1, 1.0 and 2.5% (v/v)	± Aroclor 1254 induced rat S9 liver	**–ve**	2.5% : toxic	Williams and Shimada 1983 in US-EPA, 1985; Shimada *et al,* 1985
Ames / *Salmonella* TA98, TA100, TA1535, TA1537	Pre-incubation 20 min 37°C plate-test	Technical grade Fisher 772783	3, 10, 33, 100 and 333 µg / plate in DMSO[e]	± Aroclor 1254 induced rat S9 liver and hamster S9 liver	**–ve**	333 µg/plate toxic	Haworth *et al*, 1983

Table D.1: Gene Mutation in Bacteria (continued)

Test system	Protocol	Purity (% w/w) / Source	Concentrations tested	Metabolic activation	Result	Comment	Reference
Ames / *Salmonella* TA97a, TA98, TA100, TA102	Pre-incubation plate-test	Unknown	Unknown	± S9	**–ve**	Doubtful response in TA97A, insufficient details for proper evaluation	Calandra *et al*, 1987
Ames / *Salmonella* TA100	Plate-test	99.7% Merck-Darmstadt	0 - 1,791 μg/plate in DMSO[e] (4mM)	Phenobarbital induced mouse S9 liver, with and without NAPD+, G6P	**–ve**	> 224 μg/plate 0.5 mM toxic)	Bartsch *et al*, 1979
Ames / *Salmonella* TA1535	Plate-test	99.0% E. Merck	100 μg/plate in ether	Absent	**–ve**		Kringstad *et al*, 1981
Ames / *Salmonella* TA98, TA100, UTH8414, UTH8413	Plate-test	Purity unknown Eastman Kodak	50, 100, 500, 1,000 and 2,000 μg/plate in DMSO[e]	± Aroclor induced male rat S9 liver	**–ve**		Connor *et al*, 1985
Ames / *Salmonella* TA98, TA100, TA1535, TA1537, TA1538	Plate-test Airtight	High purity Detrex Chemical Industries, non stabilised	0.04, 0.05 and 0.1 ml/plate (16 - 160 mg/plate)	± Aroclor 1254 induced rat S9 liver	**–ve**		Margard, 1978[f]
Ames / *Salmonella* TA98, TA100, TA1535, TA1537, TA1538	Plate-test airtight	99.84% Detrex Chemical Industries, stabilised[d]	0.01, 0.05 and 0.1 ml/plate (16 - 160 mg/plate)	± Aroclor 1254 induced rat S9 liver	(**+ve**)- S9 **+ve**+S9 (0.1 ml) TA100 (?)	0.1 ml : (> 90%) toxicity 10 - 17 fold increase with activation, 2 fold without activation	Margard, 1978[f]

Table D.1: Gene Mutation in Bacteria (continued)

Test system	Protocol	Purity (% w/w) / Source	Concentrations tested	Metabolic activation	Result	Comment	Reference
Ames / *Salmonella* TA98, TA100, TA1535, TA1538, TA1952, TA1951, TA1950	Spot-test	Unknown	1 and 10% in 0.05 ml DMSO[e] or undiluted (= 0.01, 0.1, 1 mg/ml)	Absent	**+ve**	Mutagenic activity of undiluted compound in all strains, dose dependence in TA100 only. Insufficient details for proper evaluation	Cerná and Kypenová, 1977
E. coli K 12 arg+ nad+ gal+ MTR	Liquid 2 h at 37 °C	Analytical grade Merck-Darmstadt	0.6 mM (= 150 μg/ml)	± Phenobarbital induced mouse S9 liver ± NADPH cofactors	**–ve**	99% survival	Greim *et al*, 1975

[a] Stabilised with 0.012% hydroquinone monomethylether (HQMME)
[b] Stabilised with 0.07% cyclohexeneoxide, 0.05% β-ethoxyproprionitrile, 0.011% HQMME
[c] Stabilised with 0.01% HQMME
[d] Stabilised with 0.7% β-hydroxypropionitrile, 0.1% hydroquinone monoethylether, 0.07% epichlorohydrin, 0.007% *n*-methylmorpholine
[e] DMSO, dimethyl sulphoxide
[f] As quoted in US-EPA, 1985

Table D.2: Gene Mutation and Recombination in Yeast and *Drosophila*

Test system	Protocol	Purity (% w/w) / Source	Concentrations tested	Metabolic activation	Result	Comment	Reference
Saccharomyces cerevisiae D7 ilv-1 (reverse mutation) trp-5 (mitotic gene conversion) ade-2 (mitotic recombination)	2 h, 37°C suspension	99.5% purity 0.01% thymol Carlo Erba	5, 10, 20, 60, 85 mM (0 -14.1 mg/ml) in DMSO[a]	Stationary phase; ± phenobarbital and β-naphtoflavone induced mouse S9 liver	**–ve**	Significantly decreased survival from 10 mM	Bronzetti *et al*, 1983
S. cerevisiae D7 ilv-1 (reverse mutation) trp-5 (mitotic gene conversion) ade-2 (mitotic recombination)	1 h	Not specified purity, 0.01% thymol Eastman Kodak	813 μg/ml (4.9 mM) ilv-1 813 and 1,094 μg/ml (4.9 - 6.6 mM) trp-5, ade-2	Log phase	**–ve** ilv **–ve** trp ade	+ve at 1,094 μg/ml 42% toxicity (1459 μg/ml 100%). No +ve control	Callen *et al*, 1980
S. cerevisiae D7 liv 1 - 92 (reverse mutation) trp-5 (mitotic gene conversion)	2 h, 30 °C	Analytical grade EGA Chemie	9.8, 14.7 mM in phosphate buffer	Late log phase or stationary phase; ± Aroclor 1254 induced mouse liver S9	Unknown	No evaluation possible due to high toxicity (70% at 9.8 mM)	Koch *et al*, 1988
Drosophila melanogaster SLRL	7-h inhalation	91.43% purity North Strong LBI No 2537	100, 500 ppm (689, 3,445 mg/m^3)	Absent	**–ve**	Only small sample size examined	Beliles *et al*, 1980
D. melanogaster Canton-S SLRL	3 d feeding or injection (0.3 μl)	Technical grade Fisher 772783	4,000 ppm (feeding) 1,000 ppm (injection) in 10% ethanol	Absent	**–ve**		Valencia *et al*, 1985; NTP, 1986

[a] DMSO, dimethyl sulphoxide

Table D.3: Gene Mutation in Host–mediated Assays

Test system	Protocol	Purity/Source (% w/w)	Concentrations tested	Metabolic activation	Result	Comment	Reference
Host-mediated *Salmonella typhimurium* TA1950, TA1951, TA1952	Unknown	Unknown	0.5 LD_{50}, LD_{50}	ICR mice (F)	**+ve**	No dose dependence, insufficient details for proper evaluation	Cerná and Kypenová, 1977
Host-mediated *S. typhimurium* TA98	I.p. after last exposure (inhalation, 5 d, 7 h/d) 3-h incubation	91.43% purity North Strong LBI No 2537	100, 500 ppm (689, 3,445 mg/m^3)	Swiss CD-1 mice (F + M)	**+ve** 500 ppm **+ve** male 100 ppm	+ve control (0.8 mg/kgbw 2-aminoanthracene, 1 mol/l) ineffective. –ve in S9 activated Ames plate incorporation assay (TA98). Low purity.	Beliles *et al*, 1980
Host-mediated *Saccharomyces cerevisiae* D7 stationary phase trp-5 (mitotic gene conversion) ilv-1 (reverse mutation)	Retro-orbital sinus injection direct before (final) oral exposure, 4-h incubation (liver, lungs, kidneys)	99.5% purity 0.01% thymol Carlo Erba	11,000 mg/kgbw or 26,000 mg/kgbw (total of 12 administrations over 3 wk)	SwissCD-1 mice (M)	**–ve**	No +ve control, unusual protocol	Bronzetti *et al*, 1983

Table D.4: Gene Mutation in *In Vitro* in Mammalian System

Test system	Protocol	Purity (% w/w) / Source	Concentrations tested	Metabolic activation	Result	Comment	Reference
Mouse lymphoma L5178Y/TK+/-	4 h, 37°C	Unknown	12.5, 25, 50 nl/ml (6.25, 100 nl/ml for + S9) (75, 150 nl/ml for –S9)	+ Aroclor 1254 induced rat liver S9	**–ve**	Growth was inhibitor at top dose level	NTP, 1986

D.2 CHROMOSOMAL EFFECTS

D.2.1 *In Vitro* Mammalian Systems (Tables D.5 and D.6)

PER did not induce chromosomal aberrations or sister chromatid exchanges (SCEs) in an *in vitro* study on Chinese hamster ovary cells, in the presence or absence of rat liver S9 metabolic activation (NTP, 1986; Galloway *et al*, 1987).

D.2.2 *In Vivo* Mammalian Systems (Table D.7)

Administration of PER to rats at concentrations up to 600 ppm (4,134 mg/m^3) for 12 months and by single or repeated i.p. injection to mice did not reveal exposure related chromosome aberrations in bone marrow (Cerná and Kypenová, 1977; Rampy *et al*, 1978; Beliles *et al*, 1980).

A dominant lethal study in which male rats were exposed (7 h/d) to 100 - 500 ppm (689 - 3,445 mg/m^3) PER by inhalation, for 5 days showed no mutagenic effects (Beliles *et al*, 1980).

D.2.3 Non-Mammalian Systems (Tables D.8 and D.10)

An inhalation study of the mutagenic activity of PER (100 - 500 ppm for 7 h) in *Drosophila melanogaster* failed to demonstrate effects on chromosomes, including sex chromosome loss (Beliles *et al*, 1980).

D.2.4 *In Vivo* Human Systems (Tables D.6 and D.9)

Studies on lymphocytes from 10 factory workers occupationally exposed to PER for 3 months to 18 years showed no significant dose-related differences in numerical or structural chromosomal aberrations, SCE rate, the proportion of M2 and M3 metaphases and mitotic index (Ikeda *et al*, 1980). The study is of limited value because the workers studied were not matched to the control group with regard to age, sex, race or social-economic status. No record was available of the medical histories of the subjects.

Table D.5: Chromosomal Aberrations in *In Vitro* Mammalian System

Test system	Protocol	Purity (% w/w) / Source	Concentrations tested	Metabolic activation	Result	Reference
Chinese hamster ovary cells	2 h (+S9) 8 - 10 h (-S9) 37 °C	Unknown	17, 34, 68 µg/ml in DMSO[a] (+ 136 µg/ml, – S9)	± Aroclor 1254 induced rat liver S9	**–ve**	NTP, 1986; Galloway *et al*, 1987

[a] DMSO, dimethyl sulphoxide

Table D.6: SCE in *In Vitro* Mammalian System

Test system	Protocol	Purity / Source (% w/w)	Concentrations tested	Metabolic activation	Result	Reference
Chinese hamster ovary cells	2 h, 37°C	Unknown	16.4, 54.5, 164.0 µg/ml DMSO[a] (– S9) 80.4, 109.9, 124.6 µg/ml DMSO[a] (+S9)	± Aroclor 1254 induced rat liver S9	**–ve**	NTP, 1986; Galloway *et al*, 1987

[a] DMSO, dimethyl sulphoxide

Table D.7: Chromosomal Aberrations in *In Vivo* Mammalian Systems

Test system	Protocol	Purity / Source (% w/w)	Concentrations tested (ppm)	(mg/m^3)[a]	Result	Comment	Reference
Rat bone marrow	Inhalation, 6 h/d, 5 d/w, 12 months	99.9% purity 3 ppm trichloroethylene 2 ppm carbontetrachloride 44 ppm 4-methylmorpholine	300, 600	2,067, 4,134	**–ve**	Very low number of metaphases scored in females	Rampy *et al*, 1978
Rat bone marrow	Inhalation, 7 h BM cells 6, 24, 48 h	91.4% purity North Strong LBI No 2537	100, 500	689, 3,445	**–ve**	Weak clastogenic effects (breaks, fragments, deletions, aneuploid cells) in 500 ppm males at 24 h	Beliles *et al*, 1980
Rat bone marrow	Inhalation 7 h/d, 5 d BM cells 6 h	91.4% purity North Strong LBI No 2537	100, 500	689, 3,445	**–ve**	Slight increase of aberrations in females at 100 ppm	Beliles *et al*, 1980
Mouse bone marrow	I.p. injection single dose	Unknown	0.5 x LD_{50}		**–ve**		Cerná and Kypenová, 1977
Mouse bone marrow	I.p. injection 1 x/d, 5 d	Unknown	0.16 x LD_{50}		**–ve**		Cerná and Kypenová, 1977
Human lymphocites	Workers of a degreasing workshop	Technical grade	92 (30 - 220) and 10 - 40	634 (207 - 1,516) and 68.9 - 275.6	**–ve**		Ikeda *et al*, 1980

[a] Converted values

Table D.8: Chromosome Loss - Non Mammalian Systems

Test system	Protocol	Purity/Source (% w/w)	Concentrations tested (ppm)	(mg/m^3)[a]	Result	Reference
Drosophila melanogaster	Inhalation, 7 h	91.4% purity North Strong LBI No 2537	100, 500	689, 3,445	**–ve**	Beliles *et al*, 1980

[a] Converted values

Table D.9: SCE and Mitotic Index - *In Vivo* Mammalian Systems

Test system	Protocol	Purity/Source (% w/w)	Concentrations tested (ppm)	(mg/m^3)[a]	Result	Reference
Human lymphocytes	Workers from degreasing workshop	Technical grade	92 (30 - 220) and 10 - 40 for 3 months to 10 years	634 (207 - 1,516) and 68.9 - 245.6	**–ve**	Ikeda *et al*, 1980

[a] Converted values

Table D.10: Dominant Lethal - *In Vivo* Mammalian Systems

Test system	Protocol	Purity/Source (% w/w)	Concentrations tested (ppm)	(mg/m^3)[a]	Result	Reference
Male rats	Inhalation 7 h/d, 5 d	91.4% purity North Strong LBI No 2537	100, 500 ppm	689, 3,445	**–ve**	Beliles *et al*, 1980

[a] converted values

D.3 DNA DAMAGE

D.3.1. Unscheduled DNA Synthesis (Tables D.11 to D.12)

Unscheduled DNA synthesis (UDS) is a measure of reparative (rather than replicative) synthesis resulting from damage to DNA. PER of varying purity has been evaluated *in vitro* by means of UDS test systems using human fibroblasts and rat or mouse hepatocytes. No effects indicative of DNA damage were observed (Beliles *et al*, 1980; Williams, 1983 as quoted in US-EPA, 1985; Williams and Shimada, 1983 as quoted in US-EPA, 1985; Costa and Ivanetich, 1984; Milman *et al*, 1988). In assays conducted in the vapour phase, weak positive responses were observed at levels that killed more than 25% of cells (Williams and Shimada, 1983 as quoted in US-EPA, 1985). The PER used in this study was stabilised (see Table D.11) and gave a positive response in a *Salmonella* assay (see Table D.1). In an *in vivo/in vitro* rat kidney cell UDS assay, in which PER was administered orally (1,000 mg/kgbw), reparative DNA synthesis was not induced (Goldsworthy *et al*, 1988).

D.3.2 Single-Strand DNA Breaks (Table D.13)

Single-strand DNA breaks were found in cells of the liver and kidney, but not of the lungs, of mice 1 hour after i.p. administration of PER; the sensitivity of detection was 1 single-strand break per $5x10^6$ nucleotides. All damage was repaired by 24 hours (Walles, 1986). The origin of the single-strand breaks induced by PER as is not clear. No studies are available from which to evaluate the effects of prolonged administration of PER on the persistence of these single-strand breaks.

D.3.3 DNA Binding (Tables D.14 and D.15)

The ability of PER to bind covalently to DNA was studied *in vivo* in mice following inhalation (600 ppm, 4,134 mg/m^3 for 6 h) and oral administration (500 mg/kgbw) (Schumann *et al*, 1980). No evidence of alkylation was found; the study had a power to detect 1 alkylation in 105 nucleotides. DNA binding was reported to occur in mouse liver *in vivo* following i.p. injection of PER and in calf thymus DNA under certain metabolic conditions *in vitro* (Mazzullo *et al*, 1987). An unusual pattern of binding in the *in vivo* study was reported, the level bound to RNA being significantly higher than that bound to protein or DNA. No distinction was drawn between covalent binding and the incorporation of radioactivity through the C-1 pool, making interpretation of the results impossible.

D.3.4 Evaluation

In conclusion, although PER produced a low incidence of single-strand breaks, the limited studies of DNA damage failed to provide evidence of DNA alkylation. PER did not induce UDS either *in vitro* or *in vivo*.

Table D.11: Unscheduled DNA Synthesis *In Vitro*

Test system	Protocol	Purity / Source (% w/w)	Concentrations tested	Metabolic activation	Result	Comment	Reference
Human fibroblast (diploid WI-38)	Liquid phase	91.4% purity North Strong LBI No 62537	0.1, 0.5, 5, 1, 5 µl/ml DMSO[a]	± Aroclor induced rat liver S9	**–ve** (e)	Toxic at 5 µl/ml +ve controls gave weak responses	Beliles *et al*, 1980
Rat hepatocytes	Liquid phase, 3 h, 18 h	Perchlor 200[b] 99.93% purity PPG Industries	0.0001, 0.001, 0.1, 1.0% (v/v)	None	**–ve**		Williams and Shimada, 1983 in US-EPA, 1985
Rat hepatocytes	Liquid phase, 3 h, 18 h	Perchlor 230[c] 99.80% purity PPG Industries	0.0001, 0.001, 0.1, 1.0% (v/v)	None	**–ve**		Williams and Shimada, 1983 in US-EPA, 1985
Rat hepatocytes	Vapour phase, 3 h, 18 h	Perchlor 230[b] 99.80% purity PPG Industries	0.1, 1.0, 2.5% (v/v) - target	None	**+ve** 0.1%	Toxicity (25 - 50%) at 0.1%; toxicity (100%) at 1.0 and 2.5%	Williams and Shimada, 1983 in US-EPA, 1985; Shimada *et al*, 1985
Rat hepatocytes	Vapour phase, 3 h, 18 h	Perchlor 200[b] 99.93% purity PPG Industries	0.1, 1.0, 2.5% (v/v) - target	None	**+ve** 0.1% (3 h)	Toxicity (75%) at 0.1%; toxicity (100%) at 1.0 and 2.5%	Williams and Shimada, 1983 in US-EPA, 1985; Shimada *et al*, 1985
Rat, mouse hepatocytes	Liquid phase 18 h	99+% purity Aldrich Chemical Company	0.00001, 0.0001, 0.001, 0.01, 0.1% (v/v)	None	**–ve**	Toxic at 0.01%	Williams, 1983 in US-EPA, 1985; Milman *et al*, 1988
Rat hepatocytes	Liquid phase 2.5 h, 37°C airtight	Merck-Darmstadt	2.5 mmol in ethanol	Phenobarbital	**–ve**	Viability of hepatocytes affected at > 2.5 mmol	Costa and Ivanetich, 1984

[a] DMSO, dimethyl sulphoxide
[b] Stabilised with 0.012% HQMME
[c] Stabilised with 0.011% HQMME, 0.07% cyclohexeneoxide, 0.05% β-ethoxyproprionitrile

Table D.12: Unscheduled DNA Synthesis *In Vivo* / *In Vitro*

Test system	Protocol	Purity / Source (% w/w)	Concentrations tested	Result	Reference
Male rats kidney	Oral 12, 24-h incubation	Unknown	1,000 mg/kgbw	**–ve**	Goldsworthy *et al*, 1988

Table D.13: Single-Strand DNA Breaks *In Vivo*

Test system	Protocol	Purity / Source (% w/w)	Concentrations tested	Result	Comment	Reference
Mouse (M) liver, kidney, lungs	I.p. 1-h and 24-h incubation[a]	99.8% purity Merck-Schuchardt	4 - 8 mmol /kgbw in Tween - 80	**+ve** (liver, kidney 1 h)	No damage in lung DNA after 1 h All damage repaired within 24 h	Walles, 1986

[a] Detection limit: 1 single-strand break / 5 x 10^6 nucleotides

Table D.14: DNA Binding *In Vivo*

Test system	Protocol	Purity / Source (%w/w)	Concentrations tested	Result	Comment	Reference
Mouse (liver)	Inhalation (6 h) or oral single exposure	Dowper, 99+% purity 56 ppm 4-methylmorpholine	600 ppm inhalation 500 mg/kgbw oral	**–ve**	Binding less than 10 - 14.5 alkylations per 10^6 nucleotides	Schumann *et al*, 1980
Rat, mouse (liver, lung, kidney, stomach)	I.p. > 22 h incubation detection limit 0.13 - 0.94/10^6 nucleotides	^{14}C-labeled, 97% purity (hexachloroethane) specific activity 14.6 mCi/mmol	8.70 µmol/kgbw	**+ve** (mouse liver)		Mazzullo *et al*, 1987

Table D.15: DNA Binding *In Vitro*

Test system	Protocol	Purity / Source (%w/w)	Concentrations tested	Metabolic Activation	Result	Comment	Reference
Calf (thymus)	90 min, 37°C	^{14}C-label, 97% purity (hexachloroethane) specific activity 14.6 mCi/mmol	2.5 μCi	± Phenobarbitone induced rat, mouse liver S9 or cytosol	**+ve**	Cytosol enzymes more effective than S9	Mazzullo *et al*, 1987

D.4 MISCELLANEOUS TEST SYSTEMS

D.4.1 Cell Transformation (Table D.16)

PER has been tested for its ability to induce transformation in various cell systems. No effects were observed in BHK21/C13 and BALB/C-3T3 mouse cells (Longstaff and Ashby, 1978; Tu *et al*, 1985; Milman *et al*, 1988). Transformed cell colonies were induced in an unusual test system using Rauscher leukaemia virus-infected F344/N rat embryo cells (Price *et al*, 1978). Conflicting results from different cell transformation test systems is common and makes uncertain their relevance to, and reliability in, predicting carcinogenic activity.

D.4.2 Germ Cell Effects (Table D.17)

Effects on germ cells were studied in a sperm head abnormality test in mice and rats (Beliles *et al*, 1980). PER of low purity, which also produced weakly positive responses in other test systems, induced an increase in the proportion of sperm with aberrant morphology in mice but not in rats. As sperm morphology can be affected by non-genetic mechanisms, no conclusions regarding germ cell mutagenicity can be drawn from these findings.

Table D.16: Cell Transformation

Test system	Protocol	Purity/Source (% w/w)	Concentrations tested	Metabolic activation	Result	Comment	Reference
Rat embryocells F 1706 p 108	48-h incubation	99.9% Eastman Kodak 755428	97 - 970 µmol/l (=16.1 - 161 µg/ml)	None	**+ve**	Cytotoxic at 97 µM; positive control: 3-methylcholantrene	Price *et al*, 1987
BALB/C-313 mouse		97 - 99% purity Aldrich	0 - 250 µg/ml	None	**–ve**	Cytotoxic at 250 µg/ml (4% survival)	Tu *et al*, 1985; Milman *et al*, 1988
Hamster BHK 21/C13	Vapour phase	Purity unknown ICI MD 516	Unknown	+ Aroclor induced rat liver S9	**–ve**		Longstaff and Ashby, 1978

Table D.17: Germ Cell Effects *In Vivo*

Test system	Protocol	Purity (% w/w) / Source	Concentrations tested (ppm)	(mg/m^3)[a]	Result	Comment	Reference
Rat, mouse sperm head abnormality	Inhalation (7 h/d, 5 d/wk) for 1, 4 and 10 wk	91.4% purity North Strong LBI No 2537	100, 500	689 - 3,4455	**–ve** (rat) **+ve** (mouse)	500 sperm/animal examined damage to spermatocytes, spermatogenia	Beliles *et al*, 1980

[a] Converted values

D.5 METABOLITES OF PER

The general lack of genotoxicity of PER has been discussed above. In addition, its metabolites from the cytochrome P-450 pathway - tricholoroacetylchloride (Reichert *et al*, 1983) oxalic acid (Sayato *et al*, 1987) TCA (Andersen *et al*, 1972; Waskel, 1978) and trichloroethanol (Bignami *et al*, 1980) - have been shown to be non-mutagenic (Table D.18). It is noted, however, that TCA has been demonstrated to cause chromosome aberrations and spermhead abnormalities in mice following i.p. administration of 500 mg/kgbw (Bhunya and Behera, 1987).

D.5.1. Evaluation

These observations are consistent with the hypothesis that the mouse liver tumours arise through a non-genotoxic mechanism. Although the GSH-pathway may produce a genotoxic metabolite in rats, it does so only in the kidneys and it is therefore not relevant to the formation of mouse liver tumours. For details, see ECETOC (1990).

Table D.18: Mutagenicity of Metabolites of PER

Test compound	Test system	Protocol	Metabolic activation	Result	Reference
PER oxide	Ames / *Salmonella typhimurium* TA1535	Pre-incubation 20 min, 37°C	None	**+ve**	Kline *et al*, 1982
Trichloroacetylchloride	Ames / *S. typhimurium* TA98, TA100	Pre-incubation 90 min, 37°C	± Aroclor 1254 induced rat liver S9	**–ve**	Reichert *et al*, 1983
TCA	Ames / *S. typhimurium* TA98, TA100, TA1535	Plate incorporation	± Aroclor 1254 and phenobarbital induced rat liver S9	**–ve**	Waskell, 1978; Andersen *et al*, 1972
Trichloroethnol	Ames / *S. typhimurium* TA100, TA1535	Spot and plate incorporation	± Aroclor 1254 induced rat liver S9	**–ve**	Bignami *et al*, 1980
Oxalic acid	Ames / *S. typhimurium* TA97, TA98, TA100, TA102, TA104	Plate incorporation, preincubation 20 min, 37°C	± Phenobarbital and 5,6-benzoflavone induced rat liver S9	**–ve**	Sayato *et al*, 1987
1,1,2-Trichlorovinylcysteine	Ames / *S. typhimurium* TA100	Plate incorporation	± Aroclor 1254 induced rat kidney S9	**+ve**	Green and Odum, 1985
	Ames / *S. typhimurium* TA98, TA100, TA2638	Pre-incubation 120 min, 37°C	± Rat liver and kidney S9 or cytosol	**+ve** except TA2638	Dekant *et al*, 1986
1,1,2-Trichlorovinyl-*N*-acetylcysteine	Ames / *S. typhimurium* TA100	Unknown	± Rat kidney cytosol	**+ve**	Vamvakas *et al*, 1987
TCA	Mouse *in vivo*	500 mg/kg i.p.	None	Sperm head abnormalities chromosome aberrations	Bhunya and Behera, 1987

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