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GDCh-Advisory Committee
on Existing Chemicals of
Environmental Relevance (BUA)

Tetrachloroethylene

BUA Report 139

(April 1993)



S. Hirzel

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Tetrachloroethylene

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S. Hirzel

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Foreword

The German Chemicals Act (Chemikaliengesetz - ChemG) of 1980 stipulates that certain existing chemicals must be reported to the competent authority, if they exhibit properties which indicate that they may be hazardous, either alone or in combination with other substances.

In the summer of 1982, an Advisory Committee on Existing Chemicals of Environmental Relevance (BUA) was set up by the German Chemical Society (Gesellschaft Deutscher Chemiker - GDCh). It brings together representatives from the scientific community, the chemical industry and the governmental authorities. This Advisory Committee is responsible for elaborating appropriate solutions for substances of relevance for health and the environment on the basis of voluntary measures. It selects and examines existing chemicals from the aforementioned angles. The testing and evaluation are based on scientific criteria alone.

It was, therefore, necessary to develop priority setting procedures. In a first phase reports were only prepared for priority chemicals. Within the framework of a first priority setting procedure, chemicals were compiled from several priority lists and 135 chemicals were selected for detailed substance reports.

In a second priority setting procedure the survey of the German Chemical Industry Association (VCI) on all substances with a production volume of more than 10 tons per year was used as a starting list. Since this survey covered 4,600 chemicals, BUA decided to process the corresponding list in several stages. The first stage included approx. 1,050 substances with a production volume of more than 1,000 tons per year.

Detailed reports are drawn up on chemicals suspected of having a hazard potential and abridged reports on those presenting only a minor hazard potential, according to the current state of knowledge.

The detailed BUA reports take in both the published literature and data from industry. If data for the evaluation of the chemicals are not available, additional studies are recommended and the results are published as updates to the reports. The reports serve as a basis for the instigation of administrative measures, when there are indications of risks to health or the environment.

Tübingen, May 1993

Ernst Bayer
Chairman of the Advisory Committee
on Existing Chemicals
of Environmental Relevance

Contents

Summary and Conclusions	XI
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Recommendations	XXII
------------------------------	-------------

Tetrachloroethylene

1. Chemistry of Tetrachloroethylene	1
1.1 Chemical Identity	1
1.2 Composition of the Technical Product, Purity	3
1.3 Chemical Properties	3
2. Physical Properties	5
3. Analytical Methods	9
3.1 Determination in Air	9
3.2 Determination in Water	15
3.3 Determination in Soil, Sediment and Biological Material	21
4. Emissions into the Environment through Production, Processing, Use and Waste Disposal	28
4.1 The Production Process	28
4.2 Manufacturers, Processors, Export, Import, Total Consumption.....	31
4.3 Processing, Use and Amounts Consumed	38
4.3.1 Processing	38
4.3.2 Direct Use	39
4.3.3 Pattern of Use	42
4.4 Emissions into the Atmosphere	44
4.4.1 Emissions through Production and Processing	44
4.4.2 Emissions through Direct Use	45
4.5 Emissions into the Hydrosphere	46
4.5.1 Emissions through Production and Processing	46
4.5.2 Emissions through Direct Use	46
4.6 Emissions into the Geo- and Biosphere	47
4.7 Emissions from Waste and Waste Treatment	47
4.7.1 Recycling und Reprocessing	48
4.8 Summary of Emissions into the Environment	49

5.	Occurrence in the Environment.....	50
5.1	Atmosphere	50
5.1.1	Ambient Air	51
5.1.1.1	Smokeless Zones	51
5.1.1.2	German Cities	52
5.1.1.3	Areas with High Level of Air Pollution	56
5.1.1.4	Europe	57
5.1.1.5	Ocean, North and Southern Hemispheres	58
5.1.2	Soil Air	60
5.1.3	Indoor Air	62
5.1.3.1	Indoor Air with normal background Pollution	62
5.1.3.2	Indoor Air with High Level of tetrachloroethylene Pollution	65
5.1.4	Workplace Air	67
5.2	Hydrosphere	68
5.2.1	Surface Waters	68
5.2.1.1	Sea Water	69
5.2.1.2	Lakes and Reservoirs	70
5.2.1.3	Rivers	71
5.2.1.4	Rain Water	86
5.2.2	Sediments	88
5.2.3	Ground Water and Drinking Water	89
5.2.3.1	Bank Filtrate and Drinking Water Treatment	94
5.2.4	Landfill Water and Leachate	95
5.2.5	Effluent	97
5.2.6	Activated Sludge	98
5.3	Geosphere	99
5.4	Biosphere	99
5.4.1	Tetrachloroethylene Levels in Humans	99
5.4.2	Tetrachloroethylene Levels in Animals	105
5.4.3	Plants	108
5.4.4	Foodstuffs	108
5.5	Natural Sources	120
6.	Environmental Behaviour	121
6.1	Transformation, Degradation and Degradation Products	121
6.1.1	Biological Degradation	121
6.1.1.1	Metabolism	121
6.1.1.2	Aerobic Degradation with Activated Sludge or Effluent as Inoculum	127
6.1.1.3	Aerobic Degradation with Water Samples as Inoculum	129

6.1.1.4	Anaerobic Degradation	129
6.1.2	Hydrolytic Degradation	133
6.1.3	Photochemical Degradation	134
6.1.3.1	Photochemical Degradation in Air	134
6.1.3.1.1	Direct Photochemical Degradation in Air	134
6.1.3.1.2	Indirect Photochemical Degradation in Air	134
6.1.3.2	Photochemical Degradation in Water	141
6.1.3.3	Photodegradation on Particle Surfaces	141
6.2	Accumulation	142
6.2.1	Bioaccumulation	142
6.2.2	Geoaccumulation	145
6.3	Distributional Behaviour and Transport Processes within and between Environmental Compartments	146
6.3.1	Henry's Law Constant	146
6.3.2	n-Octanol/Water Partition Coefficient	149
6.3.2.1	Other Partition Coefficients	149
6.3.3	Coefficient of Soil Sorption	150
6.3.3.1	Distribution between Air and Soil	156
6.3.4	Distribution between Air and Foodstuffs and between Air and other Material	159
6.4	Fate in the Environment	160
7.	Ecotoxicology	162
7.1	Effect on Aquatic Organisms	162
7.1.1	Microorganisms	162
7.1.2	Plants	164
7.1.3	Invertebrates	166
7.1.4	Vertebrates	170
7.2	Effects on Terrestrial Organisms	176
7.2.1	Microorganisms	176
7.2.2	Plants	177
7.2.3	Invertebrates	178
7.2.4	Vertebrates	178
7.3	Effects on Ecosystems	178
8.	Toxicity in Mammals	182
8.1	General Effects	182
8.2	Mode of Action	184
8.3	Toxicokinetics and Metabolism	185
8.3.1	Absorption	186
8.3.2	Distribution in Tissues	186

8.3.3	Biotransformation.....	189
8.3.4	Binding to Macromolecules	193
8.3.5	Elimination	194
8.4	Acute Toxicity.....	197
8.5	Skin and Eye Irritation/Corrosion	203
8.6	Sensitisation.....	204
8.7	Subacute, Subchronic and Chronic Toxicity	204
8.8	Genotoxicity	210
8.9	Carcinogenicity	223
8.10	Reproduction Toxicity	233
8.11	Effects on the Immune System	240
8.12	Other Effects.....	240
8.13	Effects on Man	250
8.13.1	Acute h.....	250
8.13.1.1	Oral Uptake.....	250
8.13.1.2	Dermal Exposure	251
8.13.1.3	Inhalation Exposure	251
8.13.2	Subacute, Subchronic and Chronic Intoxication.....	253
8.13.3	Epidemiological Data	257
8.13.3.1	Field Experience of the Effects of Tetrachloroethylene on Parenchymatous Organs	257
8.13.3.2	Epidemiological Data in Respect to Neurotoxicity.....	260
8.13.3.3	Epidemiological Data in Respect to Genotoxicity.....	263
8.13.3.4	Epidemiological Data in Respect to Carcinogenicity	265
8.13.3.5	Epidemiological Data in Respect to Reproduction Toxicity	271
8.13.3.6	Epidemiological Data in Respect to Effects on the Immune System.....	280
8.13.4	Metabolism, Toxicokinetics in Humans	280
8.13.4.1	Absorption.....	280
8.13.4.2	Distribution in Tissues.....	281
8.13.4.3	Biotransformation.....	281
8.13.4.4	Elimination	283
9.	Substance-Specific Regulations	285
10.	Literature	290

BUA Report on Tetrachloroethene

Summary and conclusions

Ecological aspects

Occurrence and distribution in the compartments

Since the 1950's tetrachloroethene (PER) is the most important solvent used in the dry-cleaning of textiles and in the degreasing of metals. It is also used as starting material in the production of trichloroethene and chlorofluorocarbons (CFCs). Due to restricting legislation (FCKW-Halon-Verbotsverordnung) passed in 1991, the production of these CFCs has been curbed or terminated.

In 1990 production capacity for PER in the Federal Republic of Germany (old federal states) was 165,000 tonnes per annum, while actual production volume was 114,842 tonnes per annum. Exports of PER amounted to 84,332 tonnes per annum. No PER was imported into the Federal Republic of Germany by the manufacturers.

In 1990 consumption of PER in the Federal Republic of Germany was 33,913 tonnes per annum (without regenerates). The discrepancy between production volume and sales (consumption plus exports) is accounted for by the reduction of existing stock.

Between 1974 and 1990, West German production of PER was subject to strong - presumably economic - fluctuations. A declining trend is apparent, which is probably a consequence of the closure of two of the three German production plants in 1991. A further strong reduction in German PER production can be reckoned with in the coming years, since apart from the 2nd Air Pollution Act (BImSchV) of 1990, in 1987 the Enquête Commission of the German Bundestag, on the basis of the Montreal Protocol, decided to recommend a reduction of at least 95 % in the production and consumption of CFCs and halogenated hydrocarbons by the mid-1990's. The European Union aims to end production of these substances by the end of the century. As alternatives of PER in the metal-working industry, neutral, water-based cleaners, alkaline or acid cleaners or flammable solvents are available. Light gasoline and water-based solvents are under discussion as substitutes for PER as dry-cleaning agent.

In 1990, thanks to waste-air treatment in West German production and processing plants, emissions of PER into the atmosphere amounted to only 4.6 tonnes per annum, while 29 tonnes per annum were emitted from the manufacturers' internal use of PER.

According to estimates, by the use of PER about 65 - 70 % of the production volume are emitted into the atmosphere, which for 1991 corresponds to about 60,000 - 64,000 tonnes per annum.

Indirect emissions into surface waters and soil, which in 1987 were estimated to amount to about 250 tonnes per annum, can occur as a result of rainout from the atmosphere.

In 1990, following waste-water treatment, discharges of PER into the hydrosphere from production, processing and internal use by manufacturers in the Federal Republic of Germany amounted to about 0.28 tonnes per annum.

On account of its diverse pattern of use and processing (e.g. as solvent, dry-cleaner, surface-treatment agent, extracting agent, intermediate in CFCs production), as well as its non-defined use by private consumers, estimation of total emissions into atmosphere, hydrosphere and geosphere is not possible.

In the atmosphere, PER can be detected world-wide. Considered globally, the main sources of emissions into the atmosphere are the production and processing plants located in the northern hemisphere. This results in significant differences in concentration between the northern and southern hemisphere, as well as between polluted continental regions and non-polluted ("rural") regions and the oceans. In the spring of 1983, global PER pollution was found to be about $0.55 \mu\text{g PER/m}^3$ in the northern hemisphere and about $0.24 \mu\text{g PER/m}^3$ in the southern hemisphere.

In 1988, typical but not routinely monitored atmospheric concentrations of PER in the Federal Republic of Germany fluctuated between 0.5 and $2 \mu\text{g PER/m}^3$ in rural areas and between 2 and $15 \mu\text{g PER/m}^3$ (means: $5 \mu\text{g PER/m}^3$) in areas of urbanisation. Analyses carried out in the Federal Republic of Germany between the spring of 1986 and 1987, showed isolated concentrations of up to $71 \mu\text{g PER/m}^3$ in a urbanized area such as Hamburg.

Extensive studies of the general anthropogenic occurrence of PER in soil air carried out in North Rhine Westfalia in the years 1987/1988 revealed mean concentrations of $10 \mu\text{g PER/m}^3$.

Data are available for the year 1978 on the occurrence of PER in soft air at various altitudes above mean sea level and at different soil depths for both the west and east slopes of the Black Forest. On the west slope, at a soil depth of 15 cm, concentrations of 8.6, 38 and 96 $\mu\text{g PER/m}^3$ respectively, were measured at Rhine level, 300 m and 500 m above sea level. For the east slope the corresponding values were 5.2, 13.9 and 17.9 $\mu\text{g PER/m}^3$.

Between 1978 and 1980 in the Rhine-Main area of Germany, mean soil air PER concentrations of 5.9 $\mu\text{g PER/m}^3$ were measured in agricultural and forestry land remote from industry and commerce, while in areas in the vicinity of industry and commerce 18.7 $\mu\text{g PER/m}^3$ and in areas directly affected 198 $\mu\text{g PER/m}^3$ were found.

In various samples of landfill gas taken near ground level at a landfill for industrial sludge in the years 1983 - 1988, PER concentrations between 505 and 83,500 $\mu\text{g PER/m}^3$ were detected.

A study of indoor air published by the Federal Health Office (Bundesgesundheitsamt) in 1988 showed that in 90 % of the 500 randomly selected domiciles subject to normal background pollution, concentrations of PER were below 15 $\mu\text{g PER/m}^3$.

Indoor air is nearly always found to contain a higher concentration of PER than that of the ambient air. In 1987 and 1988 PER concentrations were measured in highly industrialized areas and in clean-air areas in southern Germany. In this isolated study, mean concentrations of 2.19 $\mu\text{g PER/m}^3$ were found in the ambient air of an industrial area, while mean indoor concentrations of 22.4 $\mu\text{g PER/m}^3$ were measured. In a clean-air area, outside air was found to have a mean PER concentration of 1.26 $\mu\text{g PER/m}^3$ and indoor air a mean concentration of 9.14 $\mu\text{g PER/m}^3$.

In plants processing or using PER the range of concentrations measured in the air is very great, depending, among other things, on conditions at the particular plant. The granting of an operating licence is based on a Federal Health Office (Bundesgesundheitsamt) guideline for living space of 5,000 $\mu\text{g PER/m}^3$ and a MAK value of 345,000 $\mu\text{g PER/m}^3$.

In the period 1987 - 1989, the concentration of PER found in surface water sediments was 2 to 300 $\mu\text{g PER/kg}$.

PER concentrations of 0.01 µg PER/l were found in the open ocean, while in coastal waters a maximum concentration of 0.15 µg PER/l was measured.

In the years 1981 - 1990, PER concentrations of 0.5 - 1.5 µg PER/l were measured in the great West German rivers.

In studies carried out in the 1980's PER was detected in just about all German waters (springs, streams, ground water). In ground water, concentrations ranged from < 0.1 to > 1,000 µg PER/l, in drinking water from < 0.1 to > 100 µg PER/l and in surface waters from < 0.1 to 1,300 µg PER/l (mean value: 0.5 µg PER/l).

Between 1983 and 1984, depending on depth, PER concentrations of 0.7 - 4 µg PER/kg dry substance were detected in soil and sediment samples taken from various soil horizons in the foothills of the Harz mountains.

In humans, PER uptake occurs mainly via inspired air and ingested food. The relative proportions are: ca. 1 % from drinking water, 33 - 97 % from the air and 2 - 66 % from food. Studies carried out in 1981, 1982 and 1983 revealed daily uptake values of 50 - 240 µg PER. Analyses of body tissues showed the following average PER contents, based on wet weight: subcutaneous fat tissue, 21 µg PER/kg; renal capsule fat and liver parenchyma, 20 µg PER/kg; lung tissue, 11 µg PER/kg; muscle tissue, 10 µg PER/kg.

In 1982 in the Netherlands, PER concentration in the alveolar air of exposed school children was found to be 24 µg PER/m³ while in a control group 2.8 µg PER/m³ was measured. The alveolar air by exposed teachers contained 11 µg PER/m³ while in the control group 2 µg PER/m³ was measured.

In 1982, the concentration of PER found in the alveolar air of two employees in a dry-cleaning facility tended to increase and accumulate during the course of the working week (62,000 - 103,000 µg PER/m³ and 103,400 - 296,300 µg PER/m³ respectively).

The concentration of PER in the blood of someone living in a large city is given as ranging from 0.1 to 3.4 µg PER/l whole blood (median: 0.4 µg PER/l), while concentrations in the blood of employees in a dry-cleaning facility were found to be as high as 2,497 µg PER/l. PER has been detected in human milk.

PER has been detected in marine organisms such as molluscs and fish. In the muscles of the common whelk (*Buccinum undatum*) 39 µg PER/kg dry weight were found, while in the muscles of the conger eel (*Conger conger*) 1 µg PER/kg dry weight and in the cod (*Gadus morhua*) 2 µg PER/kg dry weight were measured. In the liver of the dogfish (*Scylliorhinus canicula*) and the pout (*Trisopterus luscus*) 0.3 µg and 9 µg PER/kg dry weight, respectively, were found. In muscle tissue of one group of freshwater fish 35 - 8,328 µg PER/kg and in another group 0.3 - 7.1 µg PER/kg wet weight were detected. The corresponding concentrations found in the liver were 102 - 7,011 and n.d. - 5.2 µg PER/kg wet weight, respectively. In spruce needles (*Picea abies excelsa*) up to 12 µg PER/m³ needles were found.

Owing to its good solubility in fat, depending on fat content, ambient air and the length of time and conditions under which the food is kept, PER can contaminate and accumulate in food.

In non-polluted areas, PER concentrations found in food were below 10 µg/kg. In beer, for example, 0.008 µg PER/l were detected and in eggs < 2 µg PER/l. On the other hand, the eggs of hens which had received feed contaminated with PER were found to contain 600 µg PER/kg. In eggs which had been kept for several days in a flat exposed to emissions from dry-cleaning facilities, PER concentrations of 440 µg PER/kg were detected.

The dependency of PER accumulation in food on the concentration in indoor air is demonstrated by the case of a fatty doughnut ("Berliner"), which, following 24 hours exposure in a flat in the vicinity of a dry-cleaning facility, was found to contain 4,200 µg PER/kg.

There are no known natural sources of PER.

Degradability

The most important route of PER degradation is its photodegradation in the atmosphere. Depending on OH-radical concentration, temperature and the intensity of illumination, half-lives of 16 to 160 days have been calculated for the degradation of PER through OH-radicals in the atmosphere.

For the elimination of PER from water, the most important degradation route is anaerobic biodegradation by adapted microorganisms. Under anaerobic, methanogenic conditions in an 8-week experiment in batch culture, following an adaptation period of 19 days, PER was almost

completely eliminated after 2 days detention time.

Biodegradation of PER under aerobic conditions has not been demonstrated.

On account of its physicochemical properties, under environmentally relevant conditions hydrolytic degradation of PER is not to be expected.

Accumulation

Based on an experimentally determined $\log P_{OW}$ of 2.53 - 2.88, moderate bioaccumulation of PER is to be expected.

Geoaccumulation of PER is not to be expected. On account of its water solubility and its low degree of sorption in soil, PER can enter the ground water, where, depending on conditions, it may be subject to anaerobic degradation or may persist over a period of several years. Compared to its concentration in soil leachate and ambient air, PER is enriched in soil air, in which it can be transported in a vertical or horizontal direction.

Ecotoxicology

Based on the production of sewage gas, bacteria from the activated sludge of a municipal sewage plant were inhibited to 50 % following 5 weeks incubation with 3 mg PER/g dry substance.

In the cell multiplication inhibition test with *Pseudomonas putida*, an 18-h EC_{10} of 51 mg PER/l was determined, while in the Microtox system, for *Photobacterium phosphoreum* a 50 % reduction in luminescence was produced following 5 minutes exposure to a concentration of 8.6 mg PER/l. PER had an inhibitive effect on cell division in the green algae *Scenedesmus subspicatus*. A toxic threshold concentration of > 250 mg PER/l was determined for an exposure period of 7 days. In a test of inhibition of oxygen production with the algae *Haematococcus pluvialis*, a 4-h EC_{10} of 36 mg PER/l was determined.

At a nominal concentration of 2 mg PER/l, a significant, 13 % inhibition of 14 was found in various algae from brackish water (*Chlorophyceae*, *Cyanophyceae* and *Bacillariophyceae*). A 24-h LOEC (lowest-observed-effect concentration) of 2 mg PER/l was determined.

In the test of acute toxicity with the water flea *Daphnia magna*, according to DIN 38412, Part 11, a 24-h EC_{50} of 22 mg PER/l and a

24-h EC₁₀₀ of 988 mg PER/l were determined. However, no details are given as to whether the concentrations were nominal or effective. The toxic effects of PER were investigated in a field experiment, in the ecosystem of an experimental pond, conducted under static conditions over a period of 11 weeks. Although the tested PER concentrations of 1.6 and 0.8 mg PER/l were chosen so that even the higher value was only 10 % of the LC/EC₅₀ determined in laboratory tests for the water flea *Daphnia magna*, in the experimental pond the population became extinct within the first days of the experiment. No details are given as to whether the concentrations were nominal or effective. In a dynamic *Daphnia* test carried out in the upper course of the river Ruhr, a concentration of 12 µg PER/l was found to have a marked effect on the animals' activity. However, none of the available studies gives any indication of the reason for the difference between the results obtained from laboratory experiments and those obtained from field experiments (comp. Chap. 7.1.3 and 7.3).

In a chronic, 28-day test of reproduction toxicity with *Daphnia magna*, in which a negative effect on growth of the maternal animals was observed, a LOEC of 1.1 ± 0.48 mg PER/l was determined. The NOEC (no-observed-effect concentration) was 0.51 ± 0.25 mg PER/l.

For the rainbow trout (*Oncorhynchus mykiss*, former name: *Salmo gairdneri*) a 96-h EC₅₀, based on abnormal swimming behaviour and disturbance of balance, of 4.86 mg PER/l was determined.

In an embryo-larval test with the fathead minnow *Pimephales promelas* (no further details), a toxic threshold concentration of 0.5 - 1.4 mg PER/l and a chronic-toxic concentration of 0.84 mg PER/l were determined.

In a static, 60-day toxicity test, adult toothcarps (*Poecilia sphenops*) were exposed to PER concentrations of 8.1 and 1.62 mg PER/l. After 34 days exposure, 5 of 6 fish in each group had died. In the 8.1 mg PER/l group, the 6th fish died on day 59, while in the other group the 6th fish survived. At both dose levels, body weight of the fish was reduced by about 40 % during the course of the test.

In a test on the toxic effect of PER towards the soil oligochaete *Aelosoma hemprichi*, an EC₅₀ of 13 mg PER/l was determined. The worms were incubated for several days (no further details) in sealed bottles in the dark at 20 °C.

For spruce trees (*Picea abies excelsa*) exposed to PER in exposure chambers, an acute toxicity of about 130 µg PER/m³ was determined. This finding confirms the findings from field experiments, in which yellowing and loss of needles were observed following exposure to PER.

Toxicological aspects

PER is readily taken up by man and animals through inhalation, skin absorption and from the intestinal tract, and is exhaled largely unaltered. On account of PER's lipophilic properties, it mainly accumulates in fatty tissues. For man, a half-life for elimination of 144 hours has been determined.

Only a very small amount of absorbed PER is metabolized, either by oxidation (via mixed-function oxidases) or by reduction (through conjugation with glutathione). Metabolites are eliminated in the urine. The main product of oxidative biotransformation is trichloroacetic acid. Additional metabolites, small amounts of which have also been identified in the urine, are oxalic acid, oxalylethanol amide (products of oxidative metabolism), as well as 1,1,2-trichlorovinyl-N-acetyl cysteine and traces of dichloroacetic acid (products of reductive metabolism).

The rate of oxidative PER biotransformation shows saturation behaviour. The degree of reductive metabolism via glutathione is low at low PER concentrations, but increases significantly following saturation of oxidative metabolism via cytochrome P-450.

PER's toxic effects presumably result largely from the interaction of its metabolites with macromolecules: The reactive intermediates of oxidative metabolism (tetrachloroxirane, trichloroacetyl chloride) and reductive biotransformation (1,1,2-trichlorovinyl cysteine, trichlorovinyl thiol) can bind covalently to proteins and nucleic acids (to DNA and more strongly to RNA).

Values for acute oral toxicity (LD₅₀) towards the rat are about 2,600 mg/kg body weight, while for the mouse values between 8,850 and 10,900 mg/kg body weight have been determined. For inhalation exposure, a 6-h LC₅₀ of 28,249 mg/m³ and an 8-h LC₅₀ of 34,200 mg/m³ have been found for rats, while for mice a 4-h LC₅₀ of 35,828 mg/m³ was determined.

The symptoms of acute oral or parenteral PER intoxication are characterized by functional disturbances of as well as by damage to both liver (swelling, deposition of fat, necrosis, cellular atrophy, degeneration, vacuolisation of centrilobular hepatocytes) and kidneys (swelling, atrophy of tubule cells, tubular calcification, dilation of ducti renales). Depression of the central nervous system is also observed. By acute inhalation exposure, symptoms of prenarctic intoxication and a narcotic effect dominate.

Direct contact of PER with the skin induces severe irritation and can cause erythema and oedema formation as well as degenerative changes in the epidermis. In the eye, liquid PER causes reversible blepharospasm and mild damage to the cornea.

PER vapour is also an irritant of mucous membranes and in high concentrations causes pulmonary oedema.

A "split-adjuvans" test with guinea pigs produced no indication of PER having any sensitizing potential.

The main target organs following repeated inhalation exposure to PER are the liver (deposition of fat, hepatomegaly, congestion, leucocytic infiltration, degeneration, centrilobular necrosis) and the kidneys (swelling of tubule epithelia, tubular karyomegaly, impairment of glomerular filtration and tubular excretion, hyaline droplet nephropathy).

Following subacute oral administration or subacute, whole body inhalation exposure to high levels of PER, induction of peroxisome proliferation was only observed in the liver and kidneys of B6C3F1 mice but not in F344 rats.

From the results of animal experiments involving repeated inhalation exposure of rats, rabbits and monkeys to PER, a NOEL (no-observed effect level) of 2,756 mg/m³ was deduced (exposure for 7 h/day, 5 days a week over a period of 26 to 32 weeks).

In various in vitro tests of mutagenicity carried out with pure PER, negative results were obtained with both eukaryotic and prokaryotic organisms.

Numerous in vivo tests with *Drosophila melanogaster* (recessive lethal mutations and loss of sex chromosomes), mice (chromosome aberration

rate) and rats (dominant lethal mutations, unscheduled DNA synthesis and chromosome aberration rate) provided no indication of PER having a mutagenic or genotoxic effect. A damaging effect of PER on chromosomes was found for mice, in the form of a dose-dependent induction of single-strand breaks in liver and kidney cell DNA but not in lung cell DNA.

In *in vitro* tests, however, the reactive metabolites of both oxidative and reductive PER metabolism (tetrachloroxirane, 1,1,2-trichlorovinyl cysteine, 1,1,2-trichlorovinyl-N-acetyl cysteine) have been clearly shown to produce point mutations.

In two long-term inhalation studies into the carcinogenic potential of PER, carried out according to current guidelines with B6C3F1 mice and F344 rats, increases in the spontaneous tumour rates were observed. In male and female mice a significant increase in hepatocellular carcinomas was found, while in male and female rats the frequency of mononuclear cell leucemia was increased, although there was no clear dose dependency. In addition, rats of both sexes - males stronger than females - showed signs of damage to the renal tubules, which can be considered to be a pathogenetic preliminary stage of tumour formation.

Available data obtained from animal experiments in respect to the carcinogenic effect of PER seem to result from species specific mechanisms which are probably not applicable to humans.

Studies of reproduction toxicity with mice, rats and rabbits, involving inhalation exposure to PER, provided no indication of an embryotoxic or teratogenic effect. The increased frequency of variation/retardation found in mice was probably due to the maternal toxicity of the PER concentration to which the animals were exposed. It was not possible to draw any conclusions about fertility.

No findings are available from animal experiments on the possibility of PER having an effect on the immune system.

In respect to the neurotoxic effects of PER vapour on Fischer 344 rats (functional disturbances of behaviour, electrophysiological parameters, neuropathological findings), a NOEL of 1,378 mg/m³ and a NOAEL (no-observed-adverse-effect level) of 5,519 mg/m³ were deduced (exposure for 6 h/day, 5 days/week over a period of 13 weeks).

As do all halogenated hydrocarbons, PER sensitizes the heart for sympathetic stimulation and for stimulation from adrenergics, including adrenaline.

PER intoxication in humans is known from its therapeutic use as an anthelmintic: Initial toxicopathy following a single oral dose of between 1 and 8 ml per person is characterized by local symptoms and symptoms involving the central nervous System; temporary loss of consciousness can rapidly occur, as can deep anaesthesia or even coma followed by death.

Apart from irritation of mucosa, respiratory tract and eyes, in humans acute intoxication through inhalation of PER predominantly causes depression of the central nervous system. The threshold concentration for irritation of mucosa following 1 - 4 minutes exposure to PER is about 520 mg/m³. Autopsy of a fatal case of exposure to an unknown concentration of PER revealed multiple haemorrhage of internal organs and pulmonary oedema.

The main effects of chronic inhalation exposure in humans also involve the central nervous system. Pathological findings in Internal organs are rare, but when observed usually involve functional disturbances of and damage to the liver, as well as subclinical impairment of renal function, which may be indicative of very slight kidney damage.

For the exposure of workers to PER vapour, in respect to neurotoxic symptoms and a possible functional disturbance of liver, kidney or muscle tissue a NOEL of 145 mg/m³ was deduced from a study on employees in dry-cleaning facilities (time-weighted concentration for an average of 6.4 years occupational exposure).

From the results of a study carried out by the Federal Environmental Office (Umweltbundesamt) on 28 test persons, a NOEL of between 68.9 and 344.5 mg/m³ can be deduced for Inhalation exposure to PER (4 h/day on 4 consecutive days).

One study, requiring clarification, provided evidence of a clastogenic effect in humans.

Design and results of available epidemiological studies into carcinogenic risk for humans are inadequate for establishing a causal relationship between exposure to PER and the occurrence of cancer.

On account of study design or the small number of cases involved, up to the present existing epidemiological studies of occupational exposure, as a whole, cannot be adequately evaluated in respect to PER-related impairment of fertility or of the course of pregnancy.

Recommendations

Ecology

Available studies on the toxicity of PER towards *Daphnia* show that in field experiments effective concentrations are well below those found in the laboratory. Thus, to facilitate a detailed assessment of the toxic potential of PER in the aquatic environment, a long-term *Daphnia* test in the field, with accompanying chemical analyses would be useful. However, the need for research into the effects of PER on terrestrial systems is greater, since, for evolutionary-genetical reasons, their structure and the sensitivity of the individual species involved is far greater.

It has been known for some considerable time that PER, especially in combination with UV-light, causes damage to conifers. Since large amounts of PER are released into the atmosphere, a detailed assessment of the concentration-effect relationship for the terrestrial environment is absolutely necessary. To this end, a fumigation test with the herbaceous plants *Brassica rapa ssp. rapa* and *Avena sativa* should be carried out.

Toxicology

One study, requiring clarification, produced evidence of a clastogenic effect in humans. Clarification through a further study would be useful. The study should be carried out on a larger number of test persons, since the former high exposure levels are no longer encountered. Considering our present knowledge of PER's toxicological properties, the revealed findings in exposed humans are unexpected. Thus, animal experiments should also be carried out. It is recommended that an *in vivo* micronucleus test and, as additionally

suggested by the Federal Health Office (Bundesgesundheitsamt), an *in vitro* chromosome aberration test should be carried out.

In animal experiments PER has been shown to possess carcinogenic properties. Toxicokinetic studies on rats and mice are currently being carried out and evaluated in order to clarify the contradictory findings of animal experiments in respect to their applicability to humans.

On the basis of available data, PER cannot be evaluated in respect to reproduction toxicity. To this end a multigeneration study is currently being conducted, the evaluation of which is awaited.