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INTERNATIONAL LABOUR ORGANISATION
WORLD HEALTH ORGANIZATION

INTERNATIONAL PROGRAMME ON CHEMICAL SAFETY

ENVIRONMENTAL HEALTH CRITERIA 187

White Spirit (Stoddard Solvent)

This report contains the collective views of an international group of experts and does not necessarily represent the decisions or the stated policy of the United Nations Environment Programme, the International Labour Organisation, or the World Health Organization.

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The International Programme on Chemical Safety (IPCS), established in 1980, is a joint venture of the United Nations Environment Programme (UNEP), the International Labour Organisation (ILO), and the World Health Organization (WHO). The overall objectives of the IPCS are to establish the scientific basis for assessment of the risk to human health and the environment from exposure to chemicals, through international peer-review processes, as a prerequisite for the promotion of chemical safety, and to provide technical assistance in strengthening national capacities for the sound management of chemicals.

The Inter-Organization Programme for the Sound Management of Chemicals (IOMC) was established in 1995 by UNEP, ILO, the Food and Agriculture Organization of the United Nations, WHO, the United Nations Industrial Development Organization and the Organisation for Economic Co-operation and Development (Participating Organizations), following recommendations made by the 1992 UN Conference on Environment and Development to strengthen cooperation and increase coordination in the field of chemical safety. The purpose of the IOMC is to promote coordination of the policies and activities pursued by the Participating Organizations, jointly or separately, to achieve the sound management of chemicals in relation to human health and the environment.

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NOTE TO READERS OF THE CRITERIA MONOGRAPHS

Every effort has been made to present information in the criteria monographs as accurately as possible without unduly delaying their publication. In the interest of all users of the Environmental Health Criteria monographs, readers are requested to communicate any errors that may have occurred to the Director of the International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland, in order that they may be included in corrigenda.

A detailed data profile and a legal file can be obtained from the International Register of Potentially Toxic Chemicals, Case postale 356, 1219 Châtelaine, Geneva, Switzerland (Telephone No. 9799111).

* * *

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Environmental Health Criteria

PREAMBLE

Objectives

In 1973 the WHO Environmental Health Criteria Programme was initiated with the following objectives:

- (i) to assess information on the relationship between exposure to environmental pollutants and human health, and to provide guidelines for setting exposure limits;
- (ii) to identify new or potential pollutants;
- (iii) to identify gaps in knowledge concerning the health effects of pollutants;
- (iv) to promote the harmonization of toxicological and epidemiological methods in order to have internationally comparable results.

The first Environmental Health Criteria (EHC) monograph, on mercury, was published in 1976 and since that time an ever-increasing

number of assessments of chemicals and of physical effects have been produced. In addition, many EHC monographs have been devoted to evaluating toxicological methodology, e.g., for genetic, neurotoxic, teratogenic and nephrotoxic effects. Other publications have been concerned with epidemiological guidelines, evaluation of short-term tests for carcinogens, biomarkers, effects on the elderly and so forth.

Since its inauguration the EHC Programme has widened its scope, and the importance of environmental effects, in addition to health effects, has been increasingly emphasized in the total evaluation of chemicals.

The original impetus for the Programme came from World Health Assembly resolutions and the recommendations of the 1972 UN Conference on the Human Environment. Subsequently the work became an integral part of the International Programme on Chemical Safety (IPCS), a cooperative programme of UNEP, ILO and WHO. In this manner, with the strong support of the new partners, the importance of occupational health and environmental effects was fully recognized. The EHC monographs have become widely established, used and recognized throughout the world.

The recommendations of the 1992 UN Conference on Environment and Development and the subsequent establishment of the Intergovernmental Forum on Chemical Safety with the priorities for action in the six programme areas of Chapter 19, Agenda 21, all lend further weight to the need for EHC assessments of the risks of chemicals.

Scope

The criteria monographs are intended to provide critical reviews on the effect on human health and the environment of chemicals and of combinations of chemicals and physical and biological agents. As such, they include and review studies that are of direct relevance for the evaluation. However, they do not describe every study carried out. Worldwide data are used and are quoted from original studies, not from abstracts or reviews. Both published and unpublished reports are considered and it is incumbent on the authors to assess all the articles cited in the references. Preference is always given to

published data. Unpublished data are only used when relevant published data are absent or when they are pivotal to the risk assessment. A detailed policy statement is available that describes the procedures used for unpublished proprietary data so that this information can be used in the evaluation without compromising its confidential nature (WHO (1990) Revised Guidelines for the Preparation of Environmental Health Criteria Monographs. PCS/90.69, Geneva, World Health Organization).

In the evaluation of human health risks, sound human data, whenever available, are preferred to animal data. Animal and *in vitro* studies provide support and are used mainly to supply evidence missing from human studies. It is mandatory that research on human subjects is conducted in full accord with ethical principles, including the provisions of the Helsinki Declaration.

The EHC monographs are intended to assist national and international authorities in making risk assessments and subsequent risk management decisions. They represent a thorough evaluation of risks and are not, in any sense, recommendations for regulation or standard setting. These latter are the exclusive purview of national and regional governments.

Content

The layout of EHC monographs for chemicals is outlined below.

- * Summary - a review of the salient facts and the risk evaluation of the chemical
- * Identity - physical and chemical properties, analytical methods
- * Sources of exposure
- * Environmental transport, distribution and transformation
- * Environmental levels and human exposure
- * Kinetics and metabolism in laboratory animals and humans
- * Effects on laboratory mammals and *in vitro* test systems

- * Effects on humans
- * Effects on other organisms in the laboratory and field
- * Evaluation of human health risks and effects on the environment
- * Conclusions and recommendations for protection of human health and the environment

- * Further research
- * Previous evaluations by international bodies, e.g., IARC, JECFA, JMPR

Selection of chemicals

Since the inception of the EHC Programme, the IPCS has organized meetings of scientists to establish lists of priority chemicals for subsequent evaluation. Such meetings have been held in: Ispra, Italy, 1980; Oxford, United Kingdom, 1984; Berlin, Germany, 1987; and North Carolina, USA, 1995. The selection of chemicals has been based on the following criteria: the existence of scientific evidence that the substance presents a hazard to human health and/or the environment; the possible use, persistence, accumulation or degradation of the substance shows that there may be significant human or environmental exposure; the size and nature of populations at risk (both human and other species) and risks for environment; international concern, i.e. the substance is of major interest to several countries; adequate data on the hazards are available.

If an EHC monograph is proposed for a chemical not on the priority list, the IPCS Secretariat consults with the Cooperating Organizations and all the Participating Institutions before embarking on the preparation of the monograph.

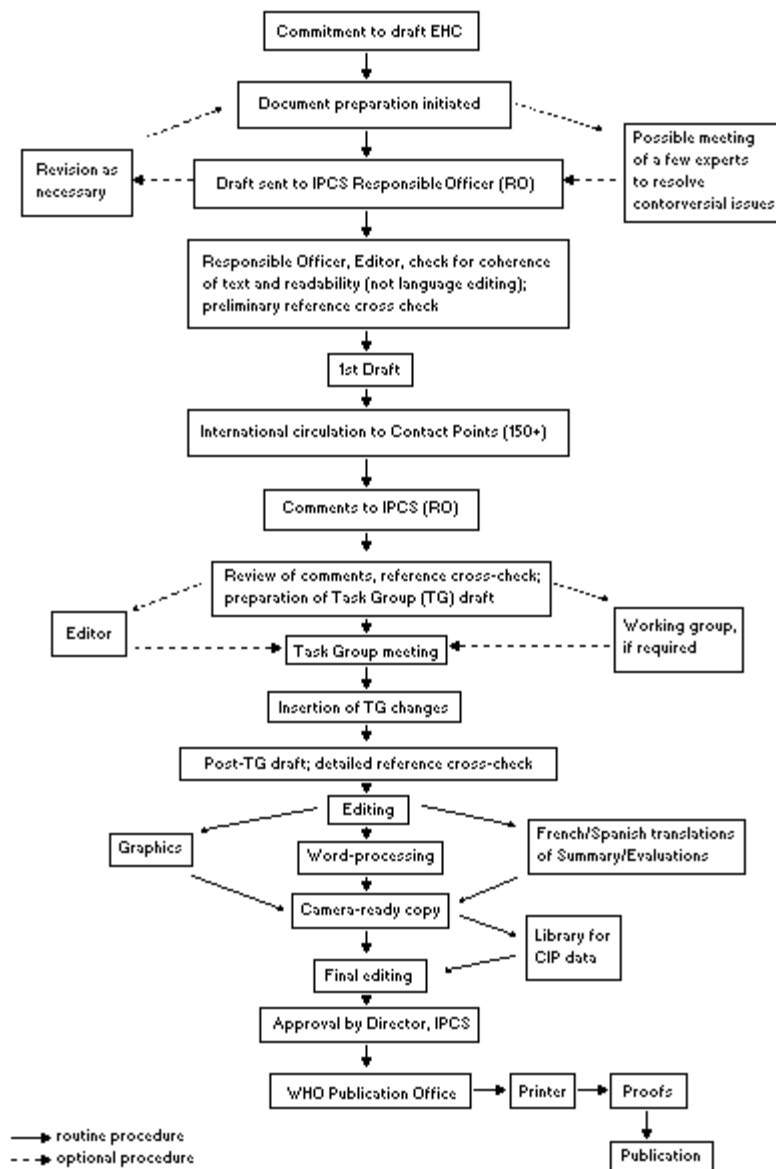
Procedures

The order of procedures that result in the publication of an EHC monograph is shown in the flow chart. A designated staff member of IPCS, responsible for the scientific quality of the document, serves as Responsible Officer (RO). The IPCS Editor is responsible for layout and language. The first draft, prepared by consultants or, more usually, staff from an IPCS Participating Institution, is based initially on data provided from the International Register of Potentially Toxic Chemicals, and reference data bases such as Medline and Toxline.

The draft document, when received by the RO, may require an initial review by a small panel of experts to determine its scientific quality and objectivity. Once the RO finds the document acceptable as a first draft, it is distributed, in its unedited form, to well over

150 EHC contact points throughout the world who are asked to comment on its completeness and accuracy and, where necessary, provide additional material. The contact points, usually designated by governments, may be Participating Institutions, IPCS Focal Points, or individual scientists known for their particular expertise. Generally

EHC PREPARATION FLOW CHART



some four months are allowed before the comments are considered by the RO and author(s). A second draft incorporating comments received and approved by the Director, IPCS, is then distributed to Task Group members, who carry out the peer review, at least six weeks before their meeting.

The Task Group members serve as individual scientists, not as representatives of any organization, government or industry. Their function is to evaluate the accuracy, significance and relevance of the information in the document and to assess the health and environmental risks from exposure to the chemical. A summary and recommendations for further research and improved safety aspects are also required. The composition of the Task Group is dictated by the range of expertise required for the subject of the meeting and by the need for a balanced geographical distribution.

The three cooperating organizations of the IPCS recognize the important role played by nongovernmental organizations. Representatives from relevant national and international associations may be invited to join the Task Group as observers. While observers may provide a valuable contribution to the process, they can only speak at the invitation of the Chairperson. Observers do not participate in the final evaluation of the chemical; this is the sole responsibility of the Task Group members. When the Task Group considers it to be appropriate, it may meet *in camera*.

All individuals who as authors, consultants or advisers participate in the preparation of the EHC monograph must, in addition to serving in their personal capacity as scientists, inform the RO if at any time a conflict of interest, whether actual or potential, could be perceived in their work. They are required to sign a conflict of interest statement. Such a procedure ensures the transparency and probity of the process.

When the Task Group has completed its review and the RO is satisfied as to the scientific correctness and completeness of the document, it then goes for language editing, reference checking, and preparation of camera-ready copy. After approval by the Director, IPCS, the monograph is submitted to the WHO Office of Publications for printing. At this time a copy of the final draft is sent to the

Chairperson and Rapporteur of the Task Group to check for any errors.

It is accepted that the following criteria should initiate the updating of an EHC monograph: new data are available that would substantially change the evaluation; there is public concern for health or environmental effects of the agent because of greater exposure; an appreciable time period has elapsed since the last evaluation.

All Participating Institutions are informed, through the EHC progress report, of the authors and institutions proposed for the drafting of the documents. A comprehensive file of all comments received on drafts of each EHC monograph is maintained and is available on request. The Chairpersons of Task Groups are briefed before each meeting on their role and responsibility in ensuring that these rules are followed.

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ENVIRONMENTAL HEALTH CRITERIA FOR WHITE SPIRIT

A WHO Task Group on Environmental Health Criteria for White Spirit met at BIBRA Toxicology International, Carshalton, United Kingdom, from 13 to 17 November 1995. Dr P.G. Jenkins, IPCS, welcomed the participants on behalf of Dr M. Mercier, Director, IPCS, and the three IPCS cooperating organizations (UNEP/ILO/WHO). The Group reviewed and revised the draft monograph and made an evaluation of the risks for human health and the environment from exposure to white spirit.

The first draft of the monograph was prepared by Dr P.B. Larsen, National Food Agency of Denmark, Ministry of Health, Søborg, Denmark. He also prepared the second draft, incorporating comments received

following circulation of the first draft to the IPCS contact points for Environmental Health Criteria monographs.

Dr P.G. Jenkins, IPCS, was responsible for both the overall scientific content and the technical editing.

The efforts of all who helped in the preparation and finalization of the monograph are gratefully acknowledged.

ABBREVIATIONS

AEP	auditory evoked potential
CBF	cerebral blood flow
CNS	central nervous system
CT	computerized tomography
EEG	electroencephalography
EMG	electromyography
ENG	electroneurography
FID	flame ionization detector
GC	gas chromatography
IR	infrared
LAWS	low aromatic white spirit
LEI	lifetime exposure intensity
MS	mass spectrometry
MTE	mild toxic encephalopathy
NCV	nerve conduction velocity
OR	odds ratio
PEG	pneumoencephalography
POS	psycho-organic syndrome
RR	relative risk
TLV	threshold limit value
TST	temperature sensitivity
VER	visual evoked response
VTR	vibration threshold

1. SUMMARY

1.1 Properties of white spirit

White spirit is a clear colourless solvent with very low water solubility and a characteristic odour (odour threshold: 0.5-5 mg/m³).

The most common variety of white spirit is a mixture of saturated aliphatic and alicyclic C₇-C₁₂ hydrocarbons with a content of 15-20% (by weight) of aromatic C₇-C₁₂ hydrocarbons and a boiling range of 130-230°C. The C₉-C₁₁ hydrocarbons (aliphatics, alicyclics and aromatics) are most abundant, constituting $\geq 80\%$ (by weight) of the total. This ordinary white spirit is designated *white spirit, type 1, regular grade*, as three different types and three different grades exist. The type refers to whether the solvent has been subjected to hydrodesulfurization (removal of sulfur) alone (type 1), solvent extraction (type 2) or hydrogenation (type 3). The hydrodesulfurized type contains less than 25% aromatic hydrocarbons, the solvent-extracted less than 5%, and the hydrogenated less than 1%. Each type comprises three different grades: low flash grade (flash point: 21-30°C; initial boiling point: 130-144°C), regular grade (flash point: 31-54°C; initial boiling point: 145-174°C), and high flash grade (flash point: $\geq 55^\circ\text{C}$; initial boiling point: 175-200°C). The grade is determined by the crude oil used as the starting material and the conditions of distillation. Type 0 white spirit is defined as a distillation fraction with no further treatment, consisting predominantly of saturated C₉-C₁₂ hydrocarbons with a boiling range of 140-220°C. The low flash grade possesses the highest vapour pressure of approximately 1.4 kPa (10.5 mmHg) at 20°C.

A USA variety of type 1 is called Stoddard solvent and is a petroleum distillate defined according to its boiling range of 149-204°C and the absence of rancid or objectionable odours.

1.2 Uses and sources of exposure

1.2.1 Production

The various types and grades of white spirit are produced from straight-run naphtha and straight-run kerosene, which are refinery streams obtained from the distillation of crude oil. These fractions are subjected to fractional distillation into appropriate boiling ranges and to different kind of treatments (referred to in section 1.1) to obtain the desired type of white spirit. The composition of the solvents may vary due to variation in the composition of the crude oil and also because of the differences in refinery processing. White spirit may, therefore, have changed over time because of changes in manufacturing processes. Quantitative data are not available, but

there is a trend towards increased use of low aromatic white spirit in Europe.

1.2.2 Uses and emission into the environment

White spirit is used mainly in paints and varnishes, in cleaning products and as a degreasing and extraction solvent. Details of the solvents used in paints are not available, but white spirit is a common component of the solvent in a wide variety of paints. It is also used by both amateur and professional painters as a diluent. The proportion of the total solvent represented by white spirit varies between paints. Estimates of white spirit as a percentage of total paint solvents are approximately 45% for Europe and 25% for the USA. White spirit may be present as a minor constituent of water-based paints.

Although exact figures of white spirit consumption in the paint industry are not available, the following figures of the consumption of aliphatic and aromatic hydrocarbons give some impression of the usage of white spirit, as it constitutes a large part of the total hydrocarbons (Table 1).

Table 1. Solvent consumption in the paint industry
(in thousands of tonnes)

	Europe 1987	USA 1985
Aliphatic hydrocarbons	695	433
Aromatic hydrocarbons	435	572
Other solvents, e.g., alcohols, ketones, glycol ethers, esters	470	935
Total solvent consumption	1600	1940

In 1985 the annual sale of white spirit in the USA was 7.17×10^5 tonnes, and consumption in 1986 in western Europe amounted

to 7.5×10^5 tonnes.

The major part of the manufactured white spirit is released to the environment and largely partitions to the atmosphere.

1.3 Environmental transport, distribution and transformation

The environmental transport and transformation of white spirit constituents will depend on the physico-chemical and biological properties of the constituents. The lower molecular weight alkanes and aromatics tend to volatilize and undergo photodegradation in the

atmosphere. The higher molecular weight alkanes and cycloalkanes tend to be sorbed to organic matter in soil or water. Biodegradation is expected to be the primary fate of white spirit in soil and water. Biodegradation of C_7 to C_{12} hydrocarbons is expected to be significant under environmental conditions favourable to microbial oxidation. Ready biodegradability has been demonstrated in laboratory tests using sewage sludge. The low water solubility and moderate vapour pressure of white spirit suggest that volatilization and subsequent photooxidation are important for abiotic degradation. Reported octanol/water partition coefficients ($\log P_{ow}$) of 3.5 to 6.4 indicate a moderate potential for bioaccumulation. However, the degradability and lowered bioavailability following sorption would reduce the likelihood of bioconcentration in the field.

1.4 Environmental levels and human exposure

There are few data on white spirit in air, water or soil. Monitoring at a site contaminated with spilt white spirit (Stoddard solvent) revealed soil levels of up to 3600 mg/kg and deep soil water levels of up to 500 mg/litre. Biodegradation led to a 90% reduction in soil concentration over a 4-month period following remediation.

Humans are predominately exposed to white spirit through the inhalation of vapour. The general population is exposed during the domestic use of paints and lacquers containing white spirit. Mean exposure concentrations during amateur painting have not been estimated but would be expected to be similar to those encountered by professionals. Exposure concentrations for humans in recently painted rooms would be expected to be lower, but no estimated values are

available. Occupationally exposed humans would be exposed to similar concentrations during house painting. Spray-painting could lead to higher exposures and exposure to aerosols. An 8-h average exposure level of 150-240 mg/m³ has been estimated for painters in ventilated rooms. Peak concentrations in closed or poorly ventilated rooms may be as high as 6200 mg/m³, particularly at high temperatures.

Vehicle washers using products containing white spirit showed measured time-weighted average (TWA) exposures ranging from 5 to 465 mg/m³ for automobiles and 45 to 805 mg/m³ for heavy vehicles. TWA measurements of between 90 and 210 mg/m³ were made in dry cleaning plants using white spirit (Stoddard solvent). The highest reported exposure concentration was for workers in airline hangars, with a short-term value of up to 8860 mg/m³.

1.5 Kinetics and metabolism

White spirit vapour is readily absorbed by inhalation. In humans 59% of the aliphatic and alicyclic hydrocarbons and 70% of the aromatic hydrocarbons were absorbed at a white spirit vapour level of 1000 mg/m³. The hydrocarbons are distributed from blood to other

tissues, and a human fat:blood partition coefficient of 47 has been calculated. White spirit is widely distributed throughout the body in humans. Experiments performed with single hydrocarbon exposure to rats revealed higher brain:blood partition ratios for aliphatics and alicyclics than for aromatic hydrocarbons.

White spirit is eliminated from the blood in a biphasic manner after exposure. After an initial and very short distribution phase with rapid elimination from the blood, a long phase with a considerably slower elimination (half-life of about 46 h) follows. Thus, white spirit has been detected in blood 66 h after a single inhalation exposure. The half-life in adipose tissue has been estimated to be 46-48 h.

Only sparse data on elimination and metabolism of white spirit exist, but urinary excretion of metabolites and elimination of parent compounds through expiration have been demonstrated in humans.

1.6 Effects on laboratory animals and in vitro systems

White spirit possesses low acute toxicity for mammals. Thus an LC_{50} for rats was not achieved with 8-h exposure to 8200 mg/m^3 (1400 ppm). In a group of four cats, all were killed at $10\,000 \text{ mg/m}^3$ (vapour and aerosols). The general signs were irritation, loss of coordination, tremor and clonic spasms. No mortality was found after oral administration (gavage) of 5000 mg/kg to rats. In rabbits loss of appetite and hypoactivity followed a single dermal exposure of $2000\text{-}3000 \text{ mg/kg}$, and death occurred in 1 out of 16 exposed animals.

In skin irritation tests white spirit was determined to be a slight to moderate irritant.

In short- and long-term toxicity studies on white spirit, the central nervous system (CNS), respiratory system, liver and kidney were generally found to be the target of white spirit toxicity.

Irritation of the respiratory tract has been observed following inhalation exposure, and histopathological signs from irritation have been observed in rats exposed nose-only to 4-h exposures for 4 days at 214 mg/m^3 .

Guinea-pigs were the most sensitive of five species tested with long-term exposure. There was increased mortality following 90 days of continuous exposure to levels of 363 mg/m^3 or more. During postmortem examinations pulmonary irritation was found.

Rats exposed to 4800 mg/m^3 , 8 h daily, for 26 weeks exhibited reduced nerve conduction velocity in the tail axon. Neurobehavioural tests indicated only mild effects and only immediately after a daily exposure.

Rats exposed to 2290 and 4580 mg/m^3 , 6 h daily, for 3 weeks or 6 months were found to develop increases in the levels of catecholamines and serotonin in the brain and reduced protein content in synaptosomes isolated from the animals. No effects were noted in neurobehavioural tests.

Neurophysiological recordings have shown changes in sensory evoked potentials in the brain of rats measured 2 months after a 6-month period of exposure to either 2339 or 4679 mg/m^3 (400 or

800 ppm) of dearomatized white spirit. Three weeks of exposure to this solvent also resulted in increased levels of reactive oxygen species in brain tissue from the rats.

In several inhalation studies, male rats developed the so-called "alpha₂-microglobulin nephropathy".

Repeated dermal exposure of rabbits caused reduction in weight gain and liver toxicity at dose levels of 2000 mg/kg, given 3 times weekly for 4 weeks.

There have been three developmental toxicity studies, all of which reported essentially negative findings. However, insufficient data are available for a comprehensive assessment.

White spirit was not found to be genotoxic in assays using *Salmonella typhimurium* and *Saccharomyces cerevisiae*, a mouse lymphoma mutation assay, mouse and rat bone marrow cytogenic tests, and rodent (rat and mouse) dominant lethal tests.

No carcinogenicity studies have been performed with experimental animals exposed to white spirit. Related heavier and lighter refinery distillation streams such as kerosene, straight-run and light straight-run naphtha have induced skin tumours in mice after 80 weeks of skin application.

1.7 Effects on humans

The odour threshold of white spirit is quite low, and vapours can be detected at levels of 0.5-5 mg/m³. Tolerance of the odour may be developed.

Eye irritation has been reported in connection with acute exposure down to a level of 600 mg/m³ (100 ppm). At higher levels respiratory irritation and more pronounced eye irritation occur. Acute CNS symptoms such as headache, "drunkenness", dizziness and fatigue have been reported in several cases of occupational exposure.

Controlled 7-h exposure to levels of 600 mg/m³ or more resulted in impaired balance during walking and to an increased reaction time. Exposure to 4000 mg/m³ for 50 min resulted in impaired performance in

tests for perceptual speed and short-term memory.

One case of cyanosis, apnoea and cardiac arrest after excessive inhalation exposure during painting has been reported.

Ingestion of white spirit has been reported to produce gastrointestinal irritation with pain, vomiting and diarrhoea. Lesions of the mucous membranes in the oesophagus and the gastrointestinal tract followed the oral exposure.

Owing to its low viscosity and low surface tension, white spirit poses a risk of aspiration into the lungs following oral exposure. A few ml of solvent aspirated into the lungs are able to produce serious bronchopneumonia and 10-30 ml may be fatal.

Prolonged dermal exposure to white spirit, e.g., resulting from wearing clothes that have been soaked or moistened by white spirit for hours, may produce irritation and dermatitis.

Single cases of acute toxicity to the kidney, liver and bone marrow have been reported following exposure to white spirit at high levels. However, owing to lack of details and the sporadic nature of the reportings, the relevance of these findings is unclear.

There have been few reports concerning the haematological or biochemical effects of white spirit. However, clinical studies reveal decreased erythrocyte, leukocyte and platelet counts, and increased mean corpuscular volume in exposed workers. Similar haematological changes have been observed in animal studies. There are no consistent serum biochemical changes; reduced aspartate aminotransferase and lactate dehydrogenase activity and elevated creatinine kinase activity have been observed.

Numerous epidemiological studies have been performed involving painters with long-term exposure to white spirit. Increased incidence of complaints of memory impairment, fatigue, impaired concentration, irritability, dizziness, headache, anxiety and apathy have been demonstrated in several cross-sectional studies. Studies including neuropsychological tests have shown impaired ability in performing some of the tests. In some studies an overall reduction in cognitive functioning was noted to a degree that corresponded to a diagnosis of

chronic toxic encephalopathy (see section 8.2.1). In a few studies a dose-response relationship was established. This was the case in a comprehensive study in which painters predominantly exposed to white spirit were compared with non-exposed bricklayers. Painters with low solvent exposure were comparable to non-exposed bricklayers with

regard to neuropsychological test results. However, the prevalence of impaired functioning increased with increasing exposure in the groups of painters with medium and high exposure.

Similar complaints and neuropsychological test results, although more severe, were reported from clinical studies in which painters predominantly exposed to white spirit had been referred to occupational medical clinics for detailed examinations because of health complaints and suspected chronic toxic encephalopathy due to the long-term solvent exposure.

In case-control studies, increased odds ratios for the award of disability pension because of mental disturbances were found for painters compared to other occupational groups not exposed to white spirit or other solvents.

Several case-control studies have shown a high risk of glomerulonephritis among painters. Even though cross-sectional studies using early markers of nephropathy were inconclusive, they are consistent with the hypothesis that painters have an increased risk of glomerulonephritis and renal dysfunction.

Several minor studies concerning reproductive effects in humans have been undertaken. In one of the most extensive studies, reproductive parameters were compared between members of a union for painters and members of a union for electricians. No firm conclusion in this or in the other studies could be drawn as no significant differences occurred. Nevertheless, there is a suggestion that parental exposure to solvents may have an untoward effect on the offspring. However, there is no adequately reported information directly related to white spirit.

Few epidemiological studies of cancer in humans exposed solely to white spirit are available. Increased risks of respiratory, pancreatic and kidney cancer have been reported in three studies on

dry cleaners where white spirit was the predominant cleaning solvent. For painters, an occupational group widely exposed to white spirit, evidence has been found of increased cancer risks, particularly in the lung and bladder.

There was no increase in sister-chromatid exchange in a group of painters with long-term solvent exposure. However, there were some small increases in cytogenetic damage in a small number of humans exposed mainly to petroleum vapours.

1.8 Effects on other organisms in the laboratory and field

Few studies on the toxicity of white spirit to organisms other than laboratory mammals have been reported.

Reports of inhibitory effects on growth of the fungus *Aspergillus niger* have been made, although concentrations of the white spirit in the growth medium were difficult to assess. No effects were found on mycorrhizal fungi in a single study. Increased oxygen uptake by excised plant root tips has been reported; the significance of this finding is doubtful for actual exposure in the field.

The few studies on the aquatic toxicity of white spirit and related hydrocarbon mixtures indicate moderate toxicity to freshwater and marine organisms. The toxicity is probably due to the dissolved fraction and leads to 96-h LC₅₀ values of the order of 0.5 to 5.0 mg/litre.

These results are likely to overestimate the effects of white spirit in the field, given its volatility and lowered bioavailability following sorption to soil/sediment.

2. IDENTITY, PHYSICAL AND CHEMICAL PROPERTIES, AND ANALYTICAL METHODS

Appraisal

White spirit is a petrochemical solvent containing mainly C₇ to C₁₂ aliphatic, alicyclic and aromatic hydrocarbons with a boiling range of 130-220°C. Different qualities exist and are defined according to different kinds of treatment (hydro-

desulfurization, solvent extraction and hydrogenation) or according to their boiling range or flash-point. The ordinary and most widely used quality of white spirit contains 80-85% (by weight) aliphatic and alicyclic alkanes and 15-20% (by weight) aromatic hydrocarbons. This quality is denoted as white spirit type 1 in Europe and Stoddard solvent in the USA.

2.1 Identity

White spirit is a mixture of saturated aliphatic and alicyclic C₇-C₁₂ hydrocarbons with a maximum content of 25% of C₇-C₁₂ alkyl aromatic hydrocarbons (Henriksen, 1980).

Molecular formulae:	C_nH_{2n+2} (<i>n</i> -alkanes and isoalkanes) C_nH_{2n} (cycloalkanes) ^a C_nH_{2n-6} (aromatics), <i>n</i> >6
Relative molecular mass:	150 (approximate average value) 92-170 (for single constituents) (CEFIC, 1989)
Common synonyms:	Lacknafta (Sweden); Lakkibensiini (Finland); Mineral Spirit; Mineral Turpentine; Mineralsk Terpentin (Denmark); Mineralterpentin (Sweden); Petroleum Spirits; Solvent Naphtha; Stoddard Solvent; Terpentin (Denmark); Testbenzin (Germany), Turpentine Substitute (Henriksen, 1977; Hass & Prior, 1986; IARC, 1989a).
Common trade name:	B.A.S.; C.A.S.; Clairsol; Dilutine; Exxsol; Halpasol; Hydrosol; Indusol; Sane; Kristalloel; Laws; Ragia; Solfina; Sangajol; Shellsol; Solfina; Solnap; Solvesso; Spezialbenzin; Spirdane; Spraysol; Stoddard Solvent; Supersol; Terpentina; Tetrasol; Thersol; Varnolene; Varsol; W.S.; White Spirit (CEFIC, 1989; IARC, 1989a).

^a Aliphatic alkanes are also known as "paraffins", while

"naphthenes" is a commonly used term for cycloalkanes.

CAS registry number: 8052-41-3 (Stoddard solvent);
64742-82-1 (white spirit type 1);
64741-92-0 (white spirit type 2);
64742-48-9 (white spirit type 3);
64742-88-7 (white spirit type 0)
(CEFIC, 1989)

EINECS number: 232-489-3 (Stoddard solvent);
265-185-4 (white spirit type 1);
265-095-5 (white spirit type 2);
265-150-3 (white spirit type 3);
265-191-7 (white spirit type 0)
(CEFIC, 1989)

2.1.1 Technical specifications

The content of white spirit can vary, because of differences in the raw material (crude oil) and in the production processes. The different kinds of white spirit are defined according to physico-chemical properties rather than exact chemical composition. The specifications for white spirit in different countries are listed in Table 2.

White spirit is a complex mixture containing mainly C₇-C₁₂ hydrocarbons with a boiling range of 130-220°C. The various types are produced as distillation fractions from naphtha and kerosene components of crude petroleum. The composition of the various types of white spirit depends on the production process.

Type	Description	Aromatics (% by weight)	Benzene (% by weight)
1	hydrodesulfurized	< 25	< 0.1
2	solvent extracted	< 5	< 0.02
3	hydrogenated (hydrotreated)	< 1	< 0.002

White spirit types 1, 2 and 3 are defined as follows (CEFIC, 1989):

Type 1: Naphtha (petroleum), hydrodesulfurized heavy
 A complex combination of hydrocarbons obtained from a catalytic hydrodesulfurization process. It consists of hydrocarbons having carbon numbers predominantly in the 7-12 range and boiling in the range of approximately 90 to 230°C (194 to 446°F).

Table 2. Specifications for white spirit in selected countries and internationally (from: IARC, 1989a)

Country, product and Colour Aromatic content specification reference (Saybolt) (% by volume)	Distillation IBP/FBP ^a (°C)	Flash-point (°C)	Kauri-butanol value (min/max)	Sulfur content (% by weight)
Germany Testbenzine (white spirit) max (Hazen - (DIN 51632) colour number)	130 min/ 220 max	21 min	-	- +20
United Kingdom Mineral solvent (white spirit, darker than < 25 type A) (BS 245: 1976) standard colour solution	approx. 130/ 220 max	above 32	-	- not
Mineral solvent (white spirit, darker than 25-50 type B) (BS 245: 1976) standard colour solution	approx. 130/ 220 max	above 32	-	- not
USA Mineral spirit type 1 - regular min -	149 min/	38 min	29/45	- ^c +25

(Stoddard solution)
(ASTM D235-83)^b

208 max

International standard

Mineral solvent for paint

(technically identical to BS

245: 1976)

- white spirit, etc. (ISO 1250)

^a IBP = initial boiling point; FBP = final boiling point

^b Also includes specifications for high flash-point (60 °C min), odourless (Kauri-butanol value, 29 max) and low dry-point (185 max)

types of mineral spirit

^c Bromine number, max 5

Type 2: Naphtha (petroleum), solvent-refined heavy

A complex combination of hydrocarbons obtained as the raffinate from a solvent extraction process. It consists predominantly of aliphatic hydrocarbons having carbon numbers predominantly in the 7-12 range and boiling in the range of approximately 90 to 230°C (194 to 446°F).

Type 3: Naphtha (petroleum), hydrotreated heavy

A complex combination of hydrocarbons obtained by treating a petroleum fraction with hydrogen in the presence of a catalyst. It consists of hydrocarbons having carbon numbers predominantly in the 6-13 range and boiling in the range of approximately 65 to 230°C (149 to 446°F).

The naphtha and kerosene fractions from crude petroleum are first subjected to hydrosulfurization, followed by fractional distillation into the appropriate boiling ranges. In the case of type 3 white spirit, hydrogenation (treatment with hydrogen over a catalyst, also termed hydrotreatment) is carried out on the fraction of hydrodesulfurized white spirit. The sequence of fractionation and hydrogenation may be reversed.

Hydrogenation converts the unsaturated aromatics into saturated cycloalkanes. Consequently, hydrogenated white spirit contains straight- and branched-chain aliphatics (*n*- and iso-alkanes), a relatively large fraction of cycloalkanes (naphthenes) and practically no aromatics.

White spirit that has not been treated beyond the process of distillation is termed straight-run white spirit (type 0). Stoddard solvent is a USA term for white spirit which corresponds to a type 1, hydrodesulfurized solvent. Types 1, 2 and 3 are further divided into three technical grades which are defined by flash point (see also section 2.2).

- "low flash" white spirit, flash point 21-30°C
 boiling point 130-144°C
- "regular flash" white spirit flash point 31-54°C
 boiling point 145-174°C
- "high flash" white spirit flash point > 55°C
 boiling point 175-200°C

2.1.2 Chemical composition

The chemical composition of white spirit depends on the type and grade (for the distinction between different grades see section 2.2). However, the traditional white spirit type 1, regular grade has a complex but a well-defined chemical content. Tables 3 and 4 present overall results from analytical analysis of white spirit type 1, regular grade from different parts of the world.

Table 3. Content of aliphatic and cyclic alkanes in white spirit

Molecular size spirit (Stoddard solvent) ^b		North European white spirit ^a		USA white
monocyclic alkanes (% v/v)	alkanes dicyclic alkanes (% w/w) ^c (% v/v)	monocyclic alkanes (% w/w)	dicyclic alkanes (% w/w)	alkanes (% v/v)
C ₆	-	0.01	-	-
-	-			
C ₇	0.10 (0.064)	0.17	-	-
2.4	-			

	C ₈	0.88 (0.58)	1.4	-	0.9
4.3	-	-	-	-	-
	C ₉	10 (7.4)	8.7	1.7	9.5
5.0	2.7	-	-	-	-
	C ₁₀	17 (11)	11	3.5	21
8.4	4.7	-	-	-	-
	C ₁₁	8.4 (4.0)	3.8	3.2	13
5.0	3.2	-	-	-	-
	C ₁₂	0.58 (0.58)	0.65	0.46	3.4
1.0	1.0	-	-	-	-
	C ₆ -C ₁₂	37 (23)	26	8.9	48
26	12	-	-	-	-
	C ₆ -C ₁₂		total alkanes		total
alkanes 85%			72% specified (+ 12% unspecified)		

^a Varnolene (boiling range: 162-198 °C), white spirit from the Danish market (Henriksen, 1980)

^b Stoddard solvent (boiling range: 152-194 °C), white spirit from the USA market (Carpenter et al., 1975a)

^c The values in parentheses indicate the percentage by weight of n-alkanes
Table 4. Aromatic content of white spirit

Molecular size	Substance	Northern Europe ^a (% w/w)	Russia ^b (% w/w)	USA ^c (% v/v)
C ₆	benzene	0.001	0	0.1
C ₇	toluene	0.005	0.20	0.4
C ₈	ethylbenzene	0.2	0.25	
	o-xylene	0.34	1.2	
	m-xylene	0.49	2.4	
	p-xylene	0.22	0.54	
	total C ₈ aromatic hydrocarbons	1.3	4.4	1.4
C ₉	n-propylbenzene	0.97	0.29	

	isopropylbenzene (cumene)	0.21	0.14	
	1-methyl-2-ethylbenzene	0.60	0.44	
	1-methyl-3-ethylbenzene	1.2	1.4	
	1-methyl-4-ethylbenzene	0.66	0.72	
	1,2,3-trimethylbenzene (henimellitene)	0.62	0.08	
	1,2,4-trimethylbenzene (pseudocumene)	2.1	2.5	
	1,3,5-trimethylbenzene (mesitylene)	0.83	1.6	
	trans-1-propenylbenzene	0.40	-	
	total C ₉ aromatic hydrocarbons	7.6	7.1	7.6
C ₁₀	n-butylbenzene	0.97	0.29	
	isobutylbenzene	0.37	0.44	
	sec-butylbenzene	-	0.08	
	tert-butylbenzene	-	0.25	
	1-methyl-2-isopropylbenzene (o-cymene)	0.06	0.07	
	1-methyl-3-isopropylbenzene (m-cymene)	0.47	0.29	
	1-methyl-4-isopropylbenzene (p-cymene)	0.62	0.70	
	1,2-diethylbenzene	0.13	-	
	1,3-diethylbenzene	0.25	0.10	
	1,4-diethylbenzene	0.13	-	
	1,2-dimethyl-3-ethylbenzene	0.08	0.06	
	1,2-dimethyl-4-ethylbenzene	0.25	0.15	
	1,3-dimethyl-2-ethylbenzene	-	0.07	
	1,3-dimethyl-4-ethylbenzene	0.26	0.15	
	1,3-dimethyl-5-ethylbenzene	0.38	0.37	
	1,4-dimethyl-2-ethylbenzene	0.28	0.14	
	1,2,3,4-tetramethylbenzene (prebnitene)	0.16	0.08	
	1,2,3,5-tetramethylbenzene (isodurene)	0.14	0.12	

Table 4. (Con't)

Molecular size	Substance	Northern Europe ^a (% w/w)	Russia ^b (% w/w)	USA ^c (% v/v)
C ₁₀	1,2,4,5-tetramethylbenzene (durene)	0.34	0.08	
	tetralin	0.08	-	
	total C ₁₀ aromatic hydrocarbons	5.2	4.0	3.7

C ₁₁	total C ₁₁ aromatic hydrocarbons	1.2	-	0.9
C ₁₂	total C ₁₂ aromatic hydrocarbons	0.12	-	0.1
-	indans + tetralins			0.5
C ₆ -C ₁₂	total aromatic hydrocarbons	15.4	15.4	14.7

^a Varnolene (boiling range: 162-198°C), white spirit from the Danish market (Henriksen, 1980)

^b White spirit (boiling range: 165-200°C) from the Russian market (Leont'ev et al., 1974). The values were originally given as percentage by weight of the total aromatic fraction but were transformed to percentage by weight of total hydrocarbon fraction by Henriksen (1980)

^c White spirit (Stoddard solvent; boiling range: 152-194°C) from the USA market (Carpenter et al., 1975a)

Tables 3 and 4 show that saturated aliphatic and cyclic hydrocarbons constitute about 85% of the content of white spirit and aromatic hydrocarbons about 15% (by weight). Nearly all the hydrocarbons are in the C₇-C₁₂ range. The C₉-C₁₁ fractions of aliphatic and alicyclic hydrocarbons predominate with a total content of 67-73% of the products, of which half is made up by the C₁₀ fraction. The aromatic fraction is dominated by C₉ and C₁₀ isomers, amounting to 7.1-7.6% and 3.7-5.2% of the total content, respectively.

Henriksen (1980) detected a total of 208 different substances (87.5% of the content, 12.5% not specified as single compounds) when analysing a northern European (Danish) white spirit type 1, regular grade (Varnolene). For a high-flash white spirit (Varsol HF) almost the same aliphatic/aromatic hydrocarbon distribution was found, but the dominant fractions were substances with higher relative molecular mass (*n*-decane, *n*-undecane, *n*-dodecane and *n*-tridecane).

For low-flash solvents, higher contents of the more volatile low molecular weight hydrocarbons are expected. In de-aromatized solvents, the content of aromatic hydrocarbons has been reduced either by solvent extraction (removal) or by hydrogenation (catalytic conversion). The hydrogenated solvents have a higher content of

cycloalkanes as a result of the conversion of aromatic hydrocarbons (CEFIC, 1989).

It is important to bear in mind that the composition of white spirit may have changed over the years. Firstly, the content may vary because of different origins of the crude oil used for the production. Secondly, the refinery processes that determine the content of the final products may have undergone changes over the years (see section 3.2).

2.2 Physical and chemical properties

White spirit is a clear, colourless, non-viscous solvent with a characteristic odour. For each of the three types of white spirit there exist three different technical grades of white spirit (CEFIC, 1989):

- Low-flash grade
- Regular grade
- High-flash grade

Physical properties of the three different grades are given in Table 5.

The *n*-octanol/water partition coefficient ($\log P_{ow}$) for white spirit (17% v/v aromatics) was determined by reverse-phase HPLC to range from 3.5 to 6.4, indicating a moderate potential for bioaccumulation (Coveney, 1985).

2.3 Conversion factors

1 ppm white spirit = 5.25-6.0 mg/m³
1 mg/m³ = 0.17-0.19 ppm
(based on the ppm-mg/m³ relationship given in Table 8)

2.4 Analytical methods

Different ways of sampling and different analytical methods may be utilized for the measurement of white spirit vapour in air. Trapping of vapour on charcoal tubes is a widely used technique for the sampling of volatile hydrocarbons, and this method is recommended by NIOSH for the measurement of the time-weighted average exposure for

naphthas in the occupational environment (NIOSH, 1984).

Table 5. Physical properties of white spirit

	Low flash	Regular	High flash
Initial boiling point (IBP) (°C) ^a	130-144	145-174	175-200
Final boiling point (°C) ^a		IBP+21, max. 220	
Average relative molecular mass ^a	140	150	160
Relative density (15°C) ^b	0.765	0.780	0.795
Flash point (°C) ^a	21-30	31-54	≥ 55
Vapour pressure (kPa, 20°C) ^b	1.4	0.6	0.1
Volatility (n-butyl acetate=1) ^b	0.47	0.15	0.04
Autoignition temperature (°C) ^b	240	240	230
Explosion limits (% by volume in air) ^b	0.6-6.5	0.6-6.5	0.6-8
Vapour density (air=1) ^c	4.5-5	4.5-5	4.5-5
Refractive index (at 20°C) ^c	1.41-1.44	1.41-1.44	1.41-1.44
Viscosity (cps, 25°C) ^c	0.74-1.65	0.74-1.65	0.74-1.65
Solubility (% by weight in water) ^c	< 0.1	< 0.1	< 0.1
Kauri-butanol value ^c	29-33	29-33	29-33
Aniline point (°C) ^c	60-75	60-75	60-75

Reactivity^c react with strong oxidizing agents

Odour threshold (mg/m³)^d - 0.5-5 4

^a CEFIC (1989); ^b FDKI (1986); ^c IARC (1989a);

^d Carpenter et al. (1975a,b)

Sampling of air for the measurements of instantaneous occupational concentrations (e.g., peak concentrations) or concentrations in expired air (alveolar air) may be performed by the use of gas pipettes or flexible bags (Aastrand et al., 1975; Cohr & Stockholm, 1979b).

Analytical measurements in air may be conducted by directly reading infrared (IR) instruments, which yield quantitative results for total content of hydrocarbons (Lundberg, 1987). Qualitative results can be obtained by gas chromatographic (GC) separation of the sample and detection by flame ionization (FID) or mass spectrometry (MS) (Aastrand et al., 1975; Carpenter, 1975a,b; Cohr & Stockholm, 1979b; NIOSH, 1984).

Einarsson et al. (1990) have proposed a computerized GC-MS method for the measurement of white spirit vapour in workplace air and for the calculation of the hygienic effect from the single hydrocarbon components.

Various analytical methods are summarized in Table 6.

Table 6. Analytical methods for determining white spirit

Medium limit	Sampling Reference	Analytical method	Range (recommended or used)	Detection
Air Einarsson et al. (1990)	charcoal tube, extraction with carbon disulfide	GC-MS	-	-

Air NIOSH (1984)	charcoal tube, extraction with carbon disulfide	GC-FID	100-2000 mg/m ³ approx. 0.5-10 mg/sample	-
Air µg/sample	charcoal/silica gel, extraction McDermott (1975) with hexane	GC-FID	-	0.4
Air µg/sample	gas-tight syringe Carpenter (1975a)	GC-FID	-	0.5
Air µg/sample	gas-tight syringe Carpenter et al. (1975b)	GC-FID	-	0.025
Air mg/m ³	direct measurement Lundberg (1987)	IR	-	approx. 1
Alveolar air Astrand et al. (1975)	gas pipette	GC-FID	280-1500 mg/m ³	-
Blood Astrand et al. (1975)	headspace of sample	GC-FID	1-4 mg/kg	-
Fat Pedersen et al. (1984)	vapours from heated sample trapped on charcoal and extracted with 1,2-dichloroethane	GC-FID	10-40 mg/kg	-

3. SOURCES OF HUMAN AND ENVIRONMENTAL EXPOSURE

3.1 Natural occurrence

White spirit does not occur naturally. However the single chemical substances in white spirit are present in crude oil.

3.2 Production

An overview of the production of the different types of white spirit is given in Fig. 1 (IARC, 1989a).

White spirit type 1 (the traditional white spirit) with a content

of up to 25% of aromatics is produced from straight-run naphtha and straight-run kerosene, which are refinery process streams obtained from the distillation of crude oil. These fractions are subjected to fractional distillation into the appropriate boiling ranges of white spirit (130-220°C). A hydrodesulfurization process (removal of sulfur) is carried out either before or after the fractional distillation.

White spirit type 2 is produced by solvent extraction of the kerosene and naphtha fractions followed by a fractional distillation. The extraction process for removal of the aromatic hydrocarbons can be undertaken with sulfolane, sulfur dioxide, or *N*-methylpyrrolidone. Hydrodesulfurization may occur (CEFIC, 1989; IARC, 1989a).

To obtain white spirit type 3, the ordinary type 1 white spirit is subjected to hydrogenation (treatment with hydrogen over a catalyst). The hydrogenation converts the aromatics into saturated alicyclic hydrocarbons. The hydrogenation process may be performed before the fractional distillation.

In 1985, the total amount of the various white spirit solvents produced in the USA was 922 000 tonnes. This was made up of odourless white spirit (236 000 tonnes), Stoddard solvent (324 000 tonnes) and 140 Flash solvent (362 000 tonnes) (IARC, 1989a).

3.3 Uses

White spirit is used as an extraction solvent, as a cleaning solvent, as a degreasing solvent, and as a solvent in aerosols, paints, wood preservatives, asphalt products, lacquers and varnishes. In western Europe about 60% of the total white spirit consumption is used in paints, lacquers and varnishes; white spirit is the most widely used solvent in the paint industry (IARC, 1989a; CEC, 1990). About 45% of the white spirit sold in the USA in 1985 was used in the paint and coating industry. The total amount sold was 717 000 tonnes of white spirit (IARC, 1989a).

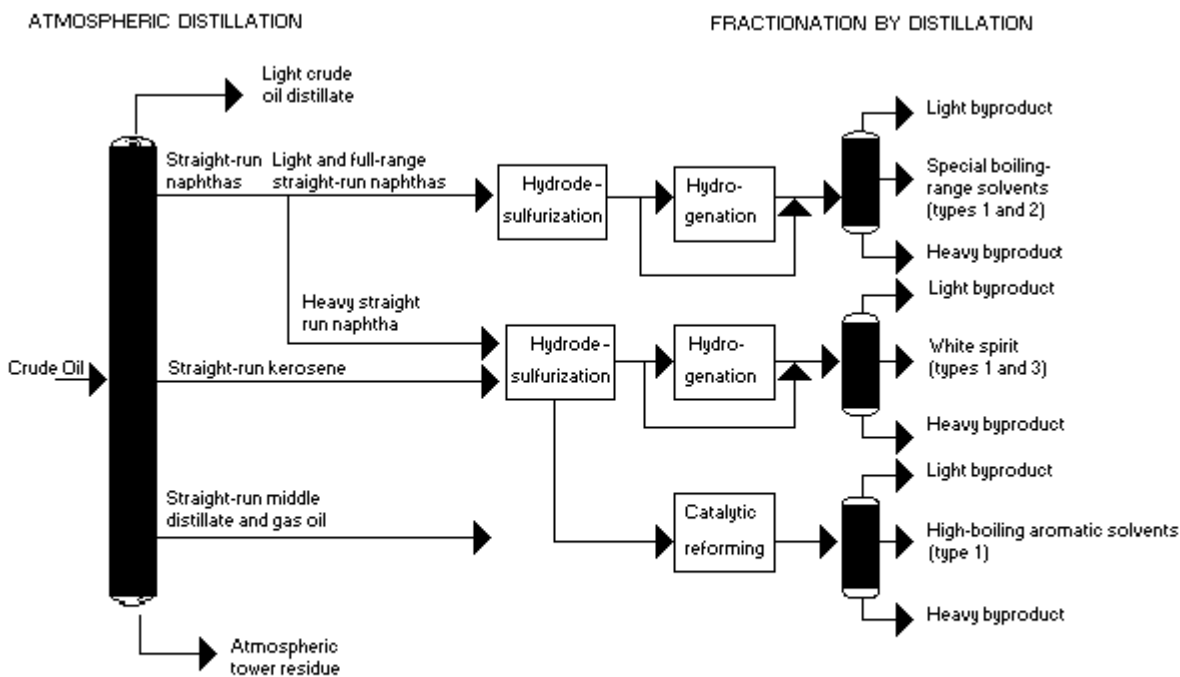


Fig. 1. Simplified flow scheme for the production of white spirit and other petroleum distillates (IARC, 1989a)

In some countries white spirit in paint has been replaced by other kinds of solvents in recent years. In Denmark the professional use of paint containing white spirit has been regulated.

A trend towards higher consumption of hydrogenated white spirit can be seen from the consumption pattern in Europe (Table 7).

Table 7. Consumption of white spirit in western Europe in thousands of tonnes (IARC, 1989a)

Type	1972	1986
------	------	------

Type 1 (hydrodesulfurized)	670	540
Type 2 (solvent extracted)	30	40
Type 3 (hydrogenated)	50	120
Total	750	700

4. ENVIRONMENTAL TRANSPORT, DISTRIBUTION AND TRANSFORMATION

White spirit (Stoddard solvent) may be released to the environment during its use as a solvent in dry-cleaning plants or as an industrial degreasing agent (ATSDR, 1993). It may also enter water or soil as a result of storage leaks (Schmitt et al., 1991) or spills during use or transportation (ATSDR, 1993).

There are few data specific to the transport and transformation of Stoddard solvent in the soil/groundwater systems. However, the environmental transport and transformation of white spirit (Stoddard solvent) constituents will depend on the physico-chemical and biological properties of the constituents. Some constituents dissolve more quickly in percolating groundwater and are sorbed less strongly onto soils, thus being transported more rapidly, and may or may not be susceptible to degradation (USAF, 1989).

4.1 Transport and distribution between media

The lower molecular weight alkanes and aromatics tend to volatilize and undergo photodegradation in the atmosphere. The higher molecular weight alkanes and cycloalkanes tend to be sorbed to organic matter in soil or water. The lower molecular weight alkanes may also be sorbed in to organic matter if volatilization is not rapid (ATSDR, 1993). Jones & McGugan (1978) studied the evaporation of white spirit from a shallow pool (1 m² in area) and a waste site (0.5 m deep; 1 m² in area). The more volatile components evaporated rapidly from the pool, volatilization decreasing over the first 10 to 20 min. The linear release rate for the less volatile components was 0.29 kg/m² per h. The initial release rate from the waste site was much higher than from the pool; however, the rate in the waste site had fallen to less than that of the pool within 3 h. The subsequent release rate was 0.105 kg/m² per h based on nonane.

The primary pathway of concern from the soil/groundwater system is the contamination of groundwater resulting from large spills of white spirit (Stoddard solvent) or leaking underground storage tanks. The vapour from leaked or spilled solvent may diffuse through soil. Spills of white spirit would result in the evaporative loss of the more highly volatile components; the fraction remaining in the soil would be expected to be relatively mobile and moderately persistent. In deep soil and groundwater the persistence may be higher. The downward migration of weathered surface spills and subsurface discharges represent a potential threat to underlying groundwater. Large surface spills or subsurface discharges may result in a separate organic phase on the surface of the groundwater. Migration of the organic phase may be very different from that of the groundwater itself (USAF, 1989).

Schmitt et al. (1991) reported soil and soil water contamination by white spirit from underground storage tanks. The highest concentrations in the soil (3500 mg/kg) and in soil water (500 mg/litre) were found immediately below the site of the tanks.

4.2 Transformation

4.2.1 Biodegradation

Biodegradation is expected to be the primary fate process for white spirit (Stoddard solvent) in soil and water. The rate and extent of biodegradation are dependent on the ambient temperature, the presence of a sufficient number of microorganisms capable of metabolizing the hydrocarbons and the concentration of white spirit in or on the soil or water (ATSDR, 1993).

Biodegradation of C₇ to C₁₂ hydrocarbons is expected to be significant under environmental conditions favourable to microbial oxidation. Naturally occurring hydrocarbon-degrading microorganisms have been isolated from polluted soil and, to a lesser extent, non-polluted soil (USAF, 1989).

Stone & Watkinson (1982) conducted two tests for ready biodegradability of low aromatic white spirit (no details of composition given) using OECD test guidelines 301B and 301D. The

formula of the white spirit was considered as $C_{10}H_{22}$ (relative molecular mass, 142), leading to a theoretical oxygen demand of 3.49 mg oxygen per mg and a theoretical carbon dioxide evolution of 3.10 mg CO_2 per mg. The white spirit was degraded by 55-63% in the Stum test (guideline 301B) and 12-13% in the closed bottle test (guideline 301D). Neither test was ideally suited to the white spirit. The Strum test results were probably conservative, owing to the volatility of the test substance. Low dispersion-limiting organism-substrate interaction was considered to be the cause of the low result in the Closed Bottle test. White spirit was considered to be readily degradable.

Schmitt et al. (1991) studied the bioremediation of a site contaminated with white spirit (Stoddard solvent) (up to 3500 mg/kg soil) from an underground storage facility. The authors reported 99% removal of white spirit by biological treatment to a concentration below the limit of detection within 4 months.

4.2.2 Abiotic degradation

The low water solubility and moderate vapour pressure of white spirit (Stoddard solvent) suggest that volatilization and subsequent photooxidation are important processes for abiotic degradation in the atmosphere (USAF, 1989).

4.2.3 Bioaccumulation

The octanol/water partition coefficient ($\log P_{ow}$) of white spirit (17% v/v aromatics) has been found to be 3.5 to 6.4 (section 2.2). This indicates a moderate potential for bioaccumulation by organisms from water and a likelihood of partitioning to fat within organisms. The sorption to soil/sediment in the environment will tend to reduce bioavailability and, therefore, uptake of white spirit components. There are no studies quantifying bioconcentration factors for white spirit. No information is available on the bioconcentration of white spirit directly. However, organisms have been found to accumulate the hydrocarbons present in fuel oils, some of which occur in white spirit (ATSDR, 1993).

5. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

5.1 Environmental levels

The detection of white spirit (Stoddard solvent) in soil and water requires collection of a representative field sample and laboratory analysis for the specific major components. However, the relative concentrations of the white spirit constituents will vary with time and distance from the site of initial contamination. Therefore, there are few data specifically related to environmental levels.

5.1.1 Air

White spirit is not monitored in air as a hydrocarbon mixture, but its volatile components (low molecular weight alkanes and aromatics) are monitored (ATSDR, 1993).

5.1.2 Water

There is little information regarding the levels of white spirit as a hydrocarbon mixture in surface or groundwater. Many monitoring studies have revealed the hydrocarbon constituents of white spirit; however, it is unclear whether these resulted from white spirit release or that of any other hydrocarbon mixture or compound (ATSDR, 1993). Schmitt et al. (1991) measured white spirit levels in soil water at a site contaminated by underground storage tanks in 1987. A concentration of 500 mg/litre was detected immediately below the site of the tanks, but the contamination was localized and no solvent had migrated off-site.

5.1.3 Soil

There have been few monitoring studies for white spirit as a hydrocarbon mixture in soil (ATSDR, 1993). Schmitt et al. (1991) monitored a site contaminated with white spirit from underground storage tanks and found levels of up to 3500 mg/kg in the immediate vicinity of the storage tanks. However, the lateral extent of soil contamination was rather limited. Levels of up to 2200 mg/kg were measured in the vicinity of the underground pipes which connected the tanks to a former dry-cleaning facility.

5.1.4 Waste sites

White spirit has been identified in at least 7 of the 1300 hazardous waste sites on the US EPA National Priorities List (NPL). However, it is not known whether there have been releases to the environment from these sites (ATSDR, 1993).

5.2 General population exposure

A major part of the manufactured white spirit is released to the air, owing to its extended use as a solvent and as the volatile ingredient in paints, varnishes and lacquers. Henriksen (1977) estimated that, out of a total consumption in Denmark of 236 000 tonnes in 1975, more than 15 000 tonnes (> 63% of the consumption) might have been emitted into the atmosphere.

The general population may be regularly exposed to white spirit, because of its extensive use in lacquers, paints and cleaning solvents. People who do home maintenance work or a lot of hobby work may be particularly exposed via inhalation of vapour or skin contact with the solvent. Exposure peak concentrations can be very high if there is a lack of occupational protection equipment, inadequate ventilation or little attention towards the possible danger of chemical exposure. However, the total life exposure from these activities will usually be much lower than for people occupationally exposed to white spirit. Section 5.3 includes descriptions of some situations in which exposure levels of white spirit have been measured during painting.

5.3 Occupational exposure

5.3.1 Considerations concerning vapour exposure

The components of white spirit do not all have the same volatility, and so white spirit vapour does not have the same composition as the solvent. Both the gaseous phase and the liquid phase change during volatilization because of rapid evaporation of the most volatile components and slower evaporation of the less volatile ones. An exception to this is flash evaporation from a hot surface in which the total liquid phase is evaporated instantaneously. Thus the evaporation rate and the composition of the gaseous phase depend on temperature, air pressure, diffusion and convection properties.

Aerosols formed during work will increase the surface area of the liquid and increase the evaporation rate (Hass & Prior, 1986).

5.3.2 Exposure levels

Cohr & Stokholm (1979b) investigated the working conditions of 14 house painters during 19 days of work. Air samples from the inhalation zone collected on charcoal tubes revealed a geometric mean exposure level of 929 mg/m³ white spirit vapour. The paint work was mainly done by rolling or spraying. In 24 out of 30 samples the levels exceeded 600 mg/m³. Short-term peak exposures estimated from air samples collected on gas pipettes while paint was being sprayed showed a geometric mean of 4038 mg/m³ (95-100% of the total organic volatile compounds was estimated to be white spirit).

Hansen (1988) measured the exposure level in the inhalation zone during paint work done by brush in six different but realistic everyday scenarios. The conditions varied with respect to the painted area, ventilation, room volume, temperature, etc. The white spirit vapour levels in the different scenarios ranged from 270 to 6140 mg/m³.

Riala et al. (1984) measured the exposure resulting from indoor house painting at 92 work situations in 18 different buildings. They found that the exposure from alkyd paint (white spirit content of 30-50%) varied greatly depending on the actual situation. Thus the exposure level correlated with the amount of paint used (i.e. treated surface area), the volume of the room and the ventilation rate. An average exposure level of 1260 mg/m³ (210 ppm) was found from painting of large surfaces (21 samples), while an average value of 210 mg/m³ (35 ppm) was found from painting of small surfaces (14 samples). From these measurements and from questionnaires answered by 231 painters, it was estimated that the yearly inhalation dose in the 1960s and early 1970s for an average painter amounted to 0.53 kg of white spirit, corresponding to a daily 8-h continuous level of 240 mg/m³ (40 ppm). However, painters working after 1977 were found to have been exposed to a somewhat lower yearly level of 0.32 kg of white spirit, corresponding to a daily 8-h level of 150 mg/m³ (25 ppm).

Gill et al. (1991a) investigated the concentration of white

spirit vapour in the breathing zone of one person engaged in domestic painting in 25 inside and 6 outside different painting scenarios. Two paint products were applied by brush and contained white spirit concentrations of 23.5% and 32%. Time-weighted average exposure levels of 18-136 mg/m³ (3.1-23.7 ppm) and 37-372 mg/m³ (6.4-65.1 ppm) were measured for the outdoor and the indoor scenarios.

Car washers using spray liquid containing white spirit were exposed to time-weighted average levels ranging from 5 to 465 mg white spirit/m³ during the washing of automobiles and from 45 to 805 mg/m³ during the washing of heavy vehicles. The study covered a total of 11 washes, and 97 charcoal air samples from 27 workers were analysed. Both ordinary white spirit (type 1; boiling range 145-200°C) and high-flash white spirit (boiling range: 185-200°C) were used (Niemelä et al., 1987).

Oberg (1968) measured the level of white spirit (Stoddard solvent) at 30 different dry-cleaning plants in Detroit City. The cleaning plants utilized Stoddard solvent 105, -120 or -140 (respective flash points of 40°C, 49°C and 60°C). Peak exposures of 1500-4500 mg/m³ (250-750 ppm) were measured during the cleaning cycle at the plants using the most volatile solvent, while peak exposures at plants using Stoddard solvent -140 never exceeded 1200 mg/m³

(200 ppm). The 8-h average exposures on ordinary working days were calculated to be 210 mg/m³ (35 ppm), 150 mg/m³ (25 ppm) and 90 mg/m³ (15 ppm) in plants using Stoddard solvent 105, -120, or -140, respectively.

NIOSH has made several surveys of white spirit (Stoddard solvent/mineral spirit) in various occupational environments. The following levels have been determined in samples taken in the breathing zone of workers: maintenance painters, 33-761 mg/m³ (NIOSH, 1973); workers in airline hangars, 363-8860 mg/m³ (NIOSH, 1975a); workers in screen cleaning processes, 137-385 mg/m³ (NIOSH, 1975b); workers at a washing machine for automobile parts, 43-594 mg/m³ (NIOSH, 1975c); manufacture of catapult cylinders, 2615 mg/m³ (spraying solvent), and up to 275 mg/m³ for painting operations (NIOSH, 1975d); ski boots finishing, 345-451 mg/m³ (NIOSH, 1975e); telephone cable assembly, 79-244 mg/m³ (NIOSH, 1980).

5.3.3 Exposure limit values

Threshold limit values (TLV) for white spirit (Stoddard solvent) in various countries are given in Table 8.

Table 8. Occupational exposure limits for white spirit

Country	Threshold Limit Value (time-weighted average)	
	(mg/m ³)	(ppm)
Australia ^a	790	-
Belgium ^a	525	100
Canada ^b	525	100
Denmark ^c	145	25
Netherlands ^b	575	100
Norway ^d , (≤ 22% aromatics)	275	50
(> 22% aromatics)	120	25
Sweden ^a , (petroleum spirit)	300	50
United Kingdom ^e	575	100
(short term, 15 min)	720	125
USA (ACGIH) ^a	525	100

^a ILO (1991)

^b IRPTC (1991)

^c Directorate of National Labour Inspection Service (1994)

^d Norwegian Labour Inspection Service (1991)

^e UK Health and Safety Executive (1994)

6. KINETICS AND METABOLISM IN LABORATORY ANIMALS AND HUMANS

Appraisal

Since white spirit is a mixture of many chemicals, the study of the toxicokinetics is complex. Generally speaking, the relative percentage of the single compounds and their different physical and chemical properties greatly affect the toxicokinetics of white spirit. White spirit is readily absorbed following inhalation

exposure. The inhalation absorption of white spirit depends on several factors including concentration in the inspired air, blood partition coefficient, pulmonary ventilation and pulmonary blood flow. White spirit is widely distributed throughout the body in humans. Studies in rats indicate that white spirit is distributed in brain, kidney, liver and fat. Aromatic components are generally more soluble in blood than aliphatic and alicyclic hydrocarbon components. Biotransformation of white spirit occurs, although no adequate information on white spirit metabolism is available. White spirit is mainly excreted in urine and partly in expired air.

6.1 Absorption

6.1.1 Inhalation

6.1.1.1 Human exposure

Astrand et al. (1975) showed that white spirit is readily absorbed by inhalation. Human volunteers were exposed for 30 min during rest or during exercise to 1250 and 2500 mg/m³ of white spirit (boiling range, 150-200°C; 83% aliphatics and alicyclics, 17% aromatics). At the end of the exposure period the concentration of aliphatics and aromatics in alveolar air was found to be about 25% and 15%, respectively, of the concentration in the inspired air. With exposure during exercise (load of 50 watts, corresponding to light work), the pulmonary ventilation tripled and the concentrations of the aliphatics and the aromatics in the alveolar air increased to about 50% and 20%, respectively, of the concentrations in the inspired air. However, the total amount of retained vapour was considerably increased because of the three-fold rise in pulmonary ventilation. Measurements of the concentrations in venous and arterial blood were found to reflect the exposure level quite well. Thus the amount in blood doubled as the exposure level doubled. Exposure to 1250 mg/m³ during hard exercise (load of 150 watts) resulted in a seven-fold rise in pulmonary ventilation, an increase in aliphatics in venous blood from 1.3 mg/kg (rest level) to 5.4 mg/kg, and an increase in aromatics from 0.2 to 2.6 mg/kg. The total uptake over a period of 30 min was measured in one subject during exposure to 1000, 1250, 1500 and 2000 mg/m³ white spirit vapour. Of the total amount of the inspired aliphatic fraction, 59% was retained at the lowest and 46% at the highest level. The uptake of the aromatics was found to be 70% at

the lowest level and 58% at the highest. (The quantitative analytical determinations were carried out on *n*-decane and 1,2,4-trimethylbenzene as markers for the aliphatic and the aromatic fractions, respectively).

Similar experiments and findings were reported by Stokholm & Cohr (1979b) in a study including 21 human volunteers. They noted rapid changes in the concentration of white spirit (17% aromatic hydrocarbons) in alveolar air if the exposure concentration or the pulmonary ventilation changed. Steady state in alveolar air was obtained after 20 min of exposure at rest and after 1 h during work. The aromatic fraction reached steady state in alveolar air earlier than the aliphatic fraction. In nine students exposed to 204, 600, 1200 and 2400 mg/m³ (34, 100, 200 and 400 ppm) (corresponding to aliphatic/aromatic levels (in mg/m³) of 172/36, 508/104, 990/203 and 1934/398), the alveolar air at steady state contained 31.6-33.6% of the aliphatic exposure levels while the alveolar contents of aromatics were 8.2-11.5% of the aromatic exposure levels. Thus, no great differences were seen in retention at the different exposure levels. After 7 h of exposure to the above-mentioned levels the concentrations in blood of aliphatics/aromatics were found to be 0.74/0.12, 2.30/0.40, 4.07/0.91 and 9.07/2.01 mg/litre, respectively. Steady state in blood was not achieved in these experiments. (The aliphatic fraction was analysed by gas chromatography as a "total aliphatic fraction", whereas the aromatic fraction was calculated on the basis of analytical determination of 1,2,4-trimethylbenzene, which was chosen to represent the aromatic fraction).

A minor accumulation of white spirit in blood was found after 5 days of exposure (6 h/day) to 600 mg/m³ (100 ppm) of white spirit (99% aliphatics). The mean concentration of white spirit in blood of seven volunteers increased from 2.00 mg/litre on day 1 to 2.54 mg/litre on day 5 (Pedersen et al., 1984).

Pedersen & Cohr (1984a) exposed 12 volunteers to a vapour concentration of 600 mg/m³ (100 ppm) of three different types of white spirit for 6 h. For two of the solvents, the concentration in blood at the end of the exposure reached mean values of 3.1 and 3.2 mg/litre. These solvents consisted of 57% aliphatics, 25% alicyclics plus 17.9% aromatics, and 52% aliphatics plus 47.9%

alicyclics, respectively. A significantly ($p < 0.001$) lower mean value of 2.3 mg/litre was obtained after exposure to the third solvent containing 98.9% aliphatic alkanes (38.7% C₁₁ isomers and 44.4% C₁₂ isomers) and 1.1% cycloalkanes.

Pedersen et al. (1987) exposed eight volunteers to 600 mg/m³ (100 ppm) of white spirit (98.9% aliphatic alkanes (83.1% C₁₁-C₁₂ isomers) and 1.09% cycloalkanes) for 3 h and seven volunteers to

600 mg/m³, 6 h/day for 5 days. The total amount of white spirit absorbed in blood was calculated to be 392 ± 38 mg after 3 h of exposure and 3464 ± 329 mg after 5 lots 6 h of exposure.

Gill et al. (1991b) reported an uptake of 55-60% in four volunteers exposed to 575 mg/m³ (100 ppm) during periods of about 4 h. The uptake for each person was determined 4-6 times throughout the exposure period and was calculated as the percentage reduction in the white spirit concentration between the inspired and the expired air. At the end of the exposure period, the level of white spirit in the blood of the four volunteers was 1.37-1.60 mg/litre. (The white spirit, Carless 100F, was reported to be a typical white spirit).

6.1.1.2 Related hydrocarbon exposure in animals

Dahl et al. (1988) examined the uptake of 19 different C₃-C₉ hydrocarbons in nose-only exposure experiments with rats. The uptake was determined by measuring the vapour concentration in the inlet and outlet airstreams. The uptakes for rats exposed to 100 ppm of each of the C₇ to C₉ hydrocarbons are listed in Table 9.

Table 9. Uptake of inhaled hydrocarbon vapour
(in nmol×kg⁻¹×min⁻¹×ppm⁻¹)

C ₇		C ₈	
n-heptane	4.5	n-octane	6.6
2,3-dimethylpentane	4.1	2,3,4-trimethylpentane	5.0
		tetramethylbutane	1.8
C ₉			
n-nonane	9.2		

1,2,4-trimethylbenzene 13.6

The animals were pre-exposed for 1 h before measurement of uptake in a 10-min period. Each value is the mean value for two sets of experiments each with two rats exposed 5 times (i.e. $2 \times (2 \times 5)$ determinations). The heptane value was only based on 2×5 determinations.

The values from Table 9 fit into the overall pattern of C_3 - C_9 hydrocarbon exposures: a) highly volatile hydrocarbons are less well absorbed than less volatile ones; b) unsaturated hydrocarbons (i.e. alkenes and aromatics) are absorbed to a greater extent than saturated ones; c) branched hydrocarbons are less well absorbed than linear ones; d) for the *n*-alkane series, uptake increases with increasing molecular size. In experiments at exposure levels in the range of

1-5000 ppm it was noted that no saturation of uptake occurred in the 1-100 ppm range for any of the substances. To achieve uptake saturation for most of the substances it was necessary to use exposure levels of 1000 or 5000 ppm (Dahl et al., 1988).

6.1.2 Dermal exposure

No quantitative data are available with respect to absorption of white spirit through human skin.

In rats dermal absorption in the tail was observed after exposure to three different kinds of white spirit (Verkkala et al., 1984). A skin area of 12 cm² was exposed for 3 h (dose not specified). Five animals were used for each experiment. The total absorbed doses of the three products were: A) 260 ± 80 mg; B) 210 ± 40 mg; and C) 240 ± 20 mg. The three kinds of white spirit consisted of: A: 60.0% aliphatics, 39.7% alicyclics and 0.3% aromatics; B: 61.0% aliphatics, 27.3% alicyclics and 11.7% aromatics; C: 83% aliphatics alicyclics (31.8% C_{11} - C_{13} isomers) and 17% aromatics.

From *in vitro* experiments performed with rat skin it was concluded that skin permeation for a variety of hydrocarbons correlates directly with the water solubility of the substances (Tsuruta, 1982). Thus it was found that the more water-soluble

aromatic compounds were absorbed through skin to a considerably greater extent than the less water-soluble aliphatic compounds. The penetration of *o*-xylene was 800 times higher than that of octane.

6.1.3 Oral exposure

There are no quantitative data available on the extent of gastrointestinal absorption following ingestion of white spirit.

6.2 Distribution

6.2.1 Human exposure

The *in vitro* $C_{\text{blood}}/C_{\text{air}}$ partition coefficient for white spirit (17% aromatics) was determined to be 23 for the aliphatic fraction and 87 for the aromatic fraction (incubation for 2 h at 37°C) (Cohr & Stockholm, 1979a).

In the study by Aastrand et al. (1975), the *in vivo* blood/air partition coefficients never exceeded 10 with respect to the aliphatic fraction or 50 with respect to the aromatic fraction (calculated by Hass & Prior, 1986). (It should be noted, however, that these *in vivo* calculations were based on data where equilibrium between the concentrations in alveolar air and in blood was not achieved).

Distribution of white spirit to adipose tissue has been demonstrated by Pedersen et al. (1984, 1987). Seven volunteers were exposed to 600 mg/m³ (100 ppm) of white spirit (99% aliphatics) 6 h/day for 5 days. The concentration of white spirit was determined in biopsies from adipose tissue, in venous blood and in alveolar air immediately after each exposure and up to 66 h after the last exposure. The level of white spirit in adipose tissue gradually rose (after the last exposure on day 5) to a value of 41 mg/kg fat, but had declined to 32 mg/kg fat 66 h later. From a mathematical fit using a three-compartment model and the data from blood and fat measurements, a fat:blood partition coefficient of 47 was calculated. The redistribution phase was estimated to be 20 h and the half-life of white spirit in adipose tissue was calculated to be 46-48 h. From these data white spirit maximum and minimum steady-state fat concentrations of 55 and 35 mg/kg, respectively, were calculated in the case of occupational exposure to 600 mg/m³ (100 ppm) (maximum

level: Friday afternoon; minimum level: Monday morning). Finally, steady-state maximum and steady-state minimum brain concentrations of 5 and 0.6 mg/kg, respectively, were estimated.

6.2.2 Animal exposure

Lam et al. (1992) exposed rats to 0, 2290 or 4580 mg/m³ (0, 400 or 800 ppm) of white spirit (20% v/v aromatics) for 6 h/day, 5 days/week, for 3 weeks. The total aromatic hydrocarbon fraction concentration in the brain at the high exposure level was about twice the concentration at 2290 mg/m³ (1.54 and 0.73 mg/kg), whereas the concentration in brain of the total aliphatic fraction at 4580 mg/m³ exceeded the 2290 mg/m³ level by more than three times (8.65 and 2.39 mg/kg). The authors concluded that accumulation may occur during long-term exposure to high levels of aliphatic hydrocarbons.

6.2.3 Exposure to related hydrocarbons

Experiments conducted with exposure to different single hydrocarbons have shed light on the differences in distribution pattern between aliphatic, alicyclic and aromatic hydrocarbons.

Zahlsen et al. (1990) exposed Sprague-Dawley rats to 1000 ppm of one of three C₉ compounds (*n*-nonane, 1,2,4-trimethylbenzene and 1,2,4-trimethylcyclohexane) for 12 h daily during 14 days. The concentrations of the three compounds in blood, brain and fat were measured during the period. From these measurements brain/blood and fat/blood partition coefficients (concentration ratios) were calculated (see Table 10). (An approximate blood/air partition coefficient is 4.3 for *n*-nonane, 3.3 for 1,2,4-trimethylcyclohexane and 14.3 for 1,2,4-trimethylbenzene, when the concentration in blood on day 1 is divided by the vapour concentration in air).

The remarkably high distribution of *n*-nonane and 1,2,4-trimethylcyclohexane to the brain is probably due to differences in biological affinity and solubility or to different metabolic rates in the tissues.

Eide (1990) exposed rats to nine different C₈-C₁₂ hydrocarbons at 100 ppm, 12 h each day for 3 days. After the last exposure, blood and brain samples were immediately taken for analysis. Table 11 shows

that while the aliphatic content in blood increased together with increasing molecular size from *n*-octane to *n*-dodecane the concentration in brain only increased from *n*-octane to *n*-decane and thereafter declined from *n*-decane to *n*-dodecane.

When the aliphatic, alicyclic and aromatic hydrocarbons were compared, it was noted that although the aromatics produced the highest concentrations in blood they were found in the lowest concentration in brain. For the alicyclic and aliphatic hydrocarbons, lower values in blood and remarkably higher values in brain were detected, especially for the alicyclic hydrocarbons.

Similar studies made by Zahlsten et al. (1992), using 15 different C₆ to C₁₀ hydrocarbons, confirmed the above findings of differences in distribution between aliphatic, alicyclic and aromatic hydrocarbons. In these studies concentrations were determined in the blood, brain, liver, kidney and fat on days 1, 2 and 3 of exposure and following 12 h of recovery after the last exposure (Table 12).

For the *n*-alkanes it was noted that accumulation in fat occurred during the 3-day exposure period. For the aromatic substances the content in fat peaked on day one and was remarkably reduced after the next two days of exposure. Overall, the alicyclics were most extensively distributed from blood to other tissues.

6.3 Metabolic transformation

Very little is known about the metabolic fate of white spirit, since metabolic studies have most frequently been conducted with single hydrocarbons and not with hydrocarbon mixtures. Consequently it is difficult to predict the extent of the metabolic conversion of single components in a mixture because several factors may influence the metabolism, e.g., substrate saturation of the metabolizing enzymes, competition phenomena and enhancement or inhibition of enzyme systems.

Table 10. Brain/blood and fat/blood partition coefficients^a

Compound	Concentration ratio	Blood concentration ^b
----------	---------------------	----------------------------------

	brain/blood	μmol/litre
n-nonane	11.4	90
1,2,4-trimethylcyclohexane	11.4	60
1,2,4-trimethylbenzene	2.0	280
	fat/blood	μmol/litre
n-nonane	113	90
1,2,4-trimethylcyclohexane	135	60
1,2,4-trimethylbenzene	63	280

^a The partition coefficients were calculated after a 12-h daily exposure to 1000 ppm on day 14 of the exposure period.

^b The blood concentrations have been read from the graphs made by Zahlse et al. (1990).

Table 11. Concentrations of C₈-C₁₂ hydrocarbons in blood and brain of rats (μmol/kg)

Substance	Brain	Blood
Aliphatics		
n-octane	25.2	3.6
n-nonane	54.5	4.1
n-decane	60.2	6.8
n-undecane	47.7	13.7
n-dodecane	12.5	17.4
Alicyclics		
1,2-dimethylcyclohexane	83.9	6.2
1,2,4-trimethylcyclohexane	84.9	6.9
Aromatics		
1,2-dimethylbenzene	28.6	10.3
1,2,4-trimethylbenzene	36.5	17.1

Concentrations were determined for each substance after the animals had been exposed to 100 ppm of the substances 12 h daily for 3 days.

Table 12. Distribution of C₈-C₁₀ hydrocarbons in rat tissue^a

	n-octane	1,2-dimethylcyclohexane	o-xylene
	n-nonane	1,2,4-trimethylcyclohexane	1,2,4-trimethylbenzene
	n-decane	tert-butylcyclohexane	tert-butylbenzene
Blood	3.6	6.2	10.3
	4.1	6.9	17.1
	6.8	12.9	15.5
Brain	25.2	83.9	28.6
	54.5	84.9	36.5
	60.2	60.2	38.7
Liver	8.4	78.0	22.4
	13.0	42.4	35.4
	45.9	21.9	47.0
Kidney	41.9	162.2 (20.8)	95.2
	45.2	349.7 (43.3)	103.6
	77.7	261.5 (84.4)	256.6 (27.9)
Fat	697 (308)	1640 (730)	1228 (71)
	1022 (577)	1476 (647)	1070 (120)
	1230 (952)	1363 (825)	1171 (320)

^a Concentration are given in µmol/kg (mean value from four animals). The animals were exposed to 100 ppm of the substances 12 h daily for 3 days. Values in parentheses are from animals that had a 12-h recovery period after the last exposure.

The aliphatic hydrocarbons are known to undergo oxidative conversion, catalysed by monooxygenases, to alcohols. The cytochrome P-450-dependent monooxygenases, located mainly in the endoplasmatic

reticulum of liver cells, are responsible for this first metabolic transition.

For *n*-alkanes with a carbon chain length of 7 or less, the predominant oxidation to alcohol occurs at the penultimate carbon (omega-1 oxidation) resulting in secondary mono- or dialcohols. For the higher *n*-alkanes, only oxidation at the terminal carbon has been observed (omega-oxidation). Branched isomers of the alkanes are mainly oxidized at the omega or omega-1 position yielding either secondary or tertiary alcohols (Scheline, 1978; Sipes & Gandolfi, 1986).

The monocyclic and polycyclic alkanes (such as cyclohexane and decalin) are mainly oxidized at the CH₂-groups in the ring structure (Longacre, 1987).

After this primary conversion, conjugation of the hydroxy group to glucuronic acid or sulfate may occur. For some substances further oxidation to aldehyde/ketone or carboxylic acid by other enzyme systems takes place. Thus 2,5-hexanedione and octanoic acids can be obtained from 2,5-hexanediol and isomers of 1-octanol. The fatty acids formed from the *n*-alkanes can be degraded by β -oxidation (Sipes & Gandolfi, 1986; Low et al., 1987; Graham et al., 1987).

The first step of alkylbenzene metabolism is generally oxidation to alcohol at the alkyl moiety in the molecule by the cytochrome P-450 enzyme system. To a lesser extent, direct hydroxylation of the aromatic structure occurs. The hydroxy group is then conjugated to glucuronic acid or sulfate, or is oxidized further to ketone/aldehyde or carboxylic acid, which may then be conjugated to glucuronic acid, sulfate or glycine (Antti-Poika et al., 1987; Riihimäki & Hänninen, 1987; Engström et al., 1987; Lee, 1987; Laham, 1987; Longacre, 1987).

During oxidation of benzene and naphthalene (or other polyaromatic hydrocarbons), intermediary arene oxides (epoxides) may be formed by cytochrome P-450. During further hydration and oxidation, the aromatic nature of the ring or the ring structure itself may be broken. In the case of benzene, the very reactive benzoquinones can be formed (Snyder, 1987; Franklin, 1987).

6.4 Elimination and excretion

Absorbed white spirit vapour is to some extent eliminated by the lungs. Stockholm & Cohr (1979b) measured the concentration of aliphatics and aromatics in the alveolar air of six volunteers during and after 7 h of exposure to either 300 or 600 mg/m³ (50 or 100 ppm) white spirit (17% aromatics). Ten minutes after exposure had ceased, the expiratory concentration levels of aliphatics and aromatics were found to be about 12% of the initial exposure level for both fractions. Sixteen hours later, the levels in expiratory air had fallen to 2% (aliphatics) and 4% (aromatics) of the initial exposure level.

Pedersen et al. (1987) measured the concentration of white spirit in blood after a single 3-h exposure and repeated daily 6-h exposures to 600 mg/m³ (100 ppm) white spirit (99% aliphatics, 1% cyclic aliphatics). After exposure had stopped there was a short phase with rapid elimination from blood resulting from distribution to other tissues. This phase was followed by a long phase with a rather slow elimination and a half-life of 46 h (see Fig. 2). The half-life of white spirit in adipose tissue was calculated to be 46-48 h (see also the description in section 6.2).

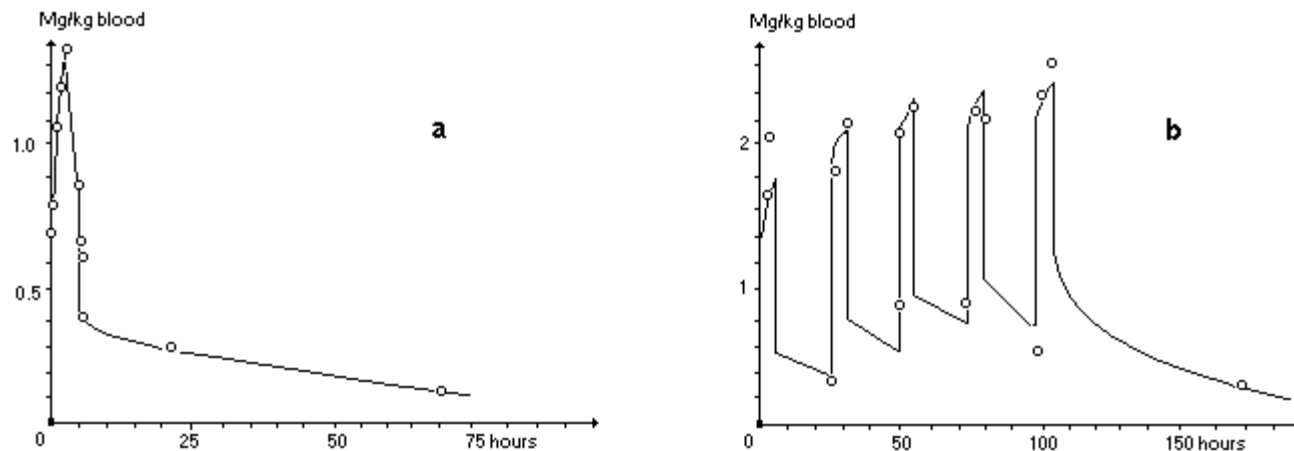


Fig. 2. Concentration of white spirit in venous blood from volunteers during and after exposure to: a) white spirit, 600 mg/m³(100 ppm) for 3 h, b) white spirit 600 mg/m³(100 ppm) 6 h daily during 5 consecutive days. (—) mathematical fit using a three-compartment model (Pedersen et al., 1987)

Gill et al. (1991b) found that white spirit was rapidly cleared from the blood stream in four volunteers. White spirit levels of 1.37-1.60 mg/litre blood were reached after 4 h exposure to 575 mg/m³ (100 ppm). Forty minutes after the exposure had stopped, the level in the blood had declined below the detection limit of 0.5 mg/litre. (The white spirit used, Carless 100F, was reported to be a typical white spirit).

Pfäffli et al. (1985) analysed urine from car washers exposed to white spirit containing 11% aromatics (the exposure levels were determined and described by Niemelä et al. (1987), see section 5.3). The authors found that the amount of dimethylbenzoic acid isomers in the urine was linearly related to the exposure. These acids are known to be formed by the oxidation of trimethylbenzenes, which in this case were present in white spirit to the extent of approximately 1%.

Most of the information concerning the elimination and excretion of aliphatic and aromatic hydrocarbons has derived from studies involving exposure to single substances. These studies indicate that the aromatics are mainly excreted in the urine as metabolites. More than 80% of the absorbed amount of toluene, xylene, ethylbenzene, 1,2,4-trimethylbenzene and tetralin has been found as metabolites in urine. Lower aromatics with high vapour pressure (and low blood/air partition coefficient) are, to a small extent, excreted unchanged in expired air. Thus about 5% of the absorbed amount of xylene was found to be expired in humans and about 9% of absorbed ethylbenzene was found to be expired in the rat. With exposure to higher aromatics, such as 1-methyl-4-isopropylbenzene, the amount excreted in expired air seems to be minute (Antti-Poika et al., 1987; Riihimäki & Hänninen, 1987; Engström et al., 1987; Laham, 1987; Longacre, 1987; Lee, 1987).

There are very few quantitative data for aliphatics and cyclic aliphatics concerning the different elimination routes. Because of higher vapour pressure and lower blood/air partition coefficient, the lower aliphatics and cyclic aliphatics are eliminated in expired air to a greater extent than the aromatics. Thus 25-35% of absorbed cyclohexane and 15% of absorbed methylcyclohexane has been found in expired air from rabbits. In addition, *n*-hexane and 2,2,4-trimethylpentane are reported to be eliminated by exhalation. The greater part of the absorbed amount of the aliphatic compounds is excreted as metabolites in the urine, but volatile metabolites may be expired to some extent (Longacre, 1987; Graham et al., 1987; Low et al., 1987).

7. EFFECTS ON LABORATORY ANIMALS AND IN VITRO TEST SYSTEMS

7.1 Single exposure

7.1.1 Inhalation

7.1.1.1 White spirit

The acute toxicity of white spirit in inhalation studies is summarized in Table 13.

Table 13. Acute toxicity of white spirit in inhalation studies

Species	Sex	Exposure	Effects	Reference
Rat	male/ female	> 14 000 mg/m ³ , 4 h	restlessness, no deaths	Coombs et al. (1977)
Rat	male	8200 mg/m ³ , 8 h	LC _{LOW}	Carpenter et al. (1975a)
Rat	male	10 000 mg/m ³ (aerosols), 8 h	LC _{LOW}	Carpenter et al. (1975b)
Rat	male/ female	5500 mg/m ³ , 4 h	no deaths, languid behaviour	API (1987a)
Cat		10 000 mg/m ³ , 7.5 h	LC ₁₀₀ tremor, clonic convulsions	Carpenter et al. (1975a)
Dog		8000 mg/m ³ , 8 h	tremor, clonic spasms, irritation	Carpenter et al. (1975a)

Because of low acute toxicity, LC₅₀ values for rats exposed to white spirit could not be determined (Carpenter et al., 1975a,b; API, 1987a). Groups of 15-16 male Harlan-Wistar rats (age approximately 5 weeks) were exposed for 8 h to 2400 mg/m³ (420 ppm), 4600 mg/m³ (800 ppm) and 8200 mg/m³ (1400 ppm) of white spirit (Stoddard solvent) (48% aliphatics, 38% cyclic aliphatics, 14% aromatics) and to 10 000 mg/m³, 5000 mg/m³, 2500 mg/m³, 1250 mg/m³ and 500 mg/m³ of a dearomatized white spirit (140° Flash Aliphatic Solvent: a "high flash" white spirit which has a flashpoint of 60°C (140°F) and which contains 61% aliphatics, 36% cyclic aliphatics, 3% aromatics). Out of

15 rats one died following high exposure to Stoddard solvent. Symptoms such as slight loss of coordination, eye irritation and bloody exudate from the nostrils were reported. Rats exposed to Stoddard solvent (2400 mg/m³) did not show any sign of toxicity during exposure or during the 14 days of follow-up. There were two deaths among the 16 animals exposed to 10 000 mg/m³ of 140° Flash Aliphatic Solvent (owing to condensation a vapour concentration of 2900 mg/m³ was measured). Animals exposed to this level exhibited slight loss of

coordination and irritation of the skin. At 500 mg/m³ (270 mg/m³ measured) no toxic effects were noted (Carpenter et al., 1975a,b).

In another acute inhalation study, five Sprague-Dawley rats of each sex were exposed to 5500 mg/m³ of white spirit (Stoddard solvent) vapour (boiling range, 160-199°C; 14.5% aromatics) for 4 h. All animals survived; clinical signs included languid behaviour and squinted eyes (API, 1987a).

Four cats exposed to 10 000 mg/m³ (1700 ppm) of white spirit (Stoddard solvent) died during the 7.5 h of exposure. The animals developed decreased reactivity to light, tremor and clonic convulsions. A dog exposed to 8000 mg/m³ (1400 ppm) of Stoddard solvent for 8 h suffered from eye irritation, increased salivation, tremors and clonic spasms. At 4000 mg/m³ (700 ppm) no sign of toxicity was noted (Carpenter, 1975a).

Four cats exposed to 10 000 mg/m³ (combination of vapours and aerosols) of 140° Flash Aliphatic Solvent did not show any sign of poisoning, but a dog exposed to 1700 mg/m³ for 8 h exhibited lacrimation (Carpenter et al., 1975b).

7.1.1.2 Exposure to related hydrocarbons

Ten female Harlan-Wistar rats were exposed for 8 h to an aerosol concentration (droplet size < 1 µm) of 8700 mg/m³ of High Aromatic Solvent (96% of C₉-C₁₁ aromatic hydrocarbons), which contained, in general, the same aromatic hydrocarbons as white spirit. Progressive signs of distress developed: nasal and ocular irritation, salivation, redness of extremities, loss of coordination, prostration, tremor, convulsions and anaesthesia. Two animals died but the others recovered during the following 4 days. Exposure to vapour at a calculated level of 6300 mg/m³ (2000 mg/m³ measured) did not induce any adverse effect (Carpenter et al., 1977a).

Carpenter et al. (1977b) estimated a 4-h LC₅₀ value of 5300 mg/m³ (969 ppm) as a result of studies on Harlan-Wistar rats exposed to High Naphthenic Solvent (boiling range, 157-183°C; 29% aliphatics, 70% cyclic aliphatics, 1% aromatics). The toxic signs were nasal irritation, salivation, loss of coordination, tonic convulsions, tremors and death. The lowest exposure level with lethal

outcome was 3600 mg/m³ (650 ppm).

Inhalation studies involving various fractions of hydrocarbons have been conducted by Hine & Zuidema (1970). Groups of Long-Evans male rats were exposed for 4 h to 10 different hydrocarbon test samples. Six samples contained aliphatic and alicyclic alkanes covering the range from C₆ to C₁₄, and four samples contained aromatic hydrocarbons in the C₈-C₁₄ range. Among the aliphatic and alicyclic samples, the sample containing C₉-C₁₀ alkanes was the most toxic, the LC₅₀ value being 2000-2600 ppm. The LC₅₀ for the aromatic C₈ sample was found to be 6350 ppm. LC₅₀ values for the other aromatic samples were not obtained because of the lack of lethal effect of saturated or nearly saturated vapour.

Nilsen et al. (1988) estimated a LC₅₀ value of 23 400 mg/m³ (4467 ppm) for *n*-nonane in an inhalation study with male Sprague-Dawley rats. Ataxia, general and focal seizures and spasms were observed. Pulmonary oedema and liver congestion were found in the dead animals. At an exposure level of 23 400 mg/m³ remarkable loss of Purkinje cells in the cerebellum was found in six surviving animals, in contrast to the situation in four animals dying from the exposure. No sedative or narcotic effects were observed. Eight hours of exposure to *n*-decane, *n*-undecane, *n*-dodecane and *n*-tridecane at vapour saturation level (7950 mg/m³ (1369 ppm), 2820 mg/m³ (442 ppm), 990 mg/m³ (142 ppm) and 310 mg/m³ (41 ppm)) did not cause lethal or adverse behavioural effects.

7.1.2 Oral exposure

No deaths and no toxic signs were reported following acute oral dosing of male and female rats with 1, 2, 4 or 8 mg/kg body weight of low aromatic white spirit (17% aromatics; boiling range, 157-198°C) (Coombs et al., 1977).

Five Sprague-Dawley rats of each sex were administered 5.0 g/kg of white spirit (Stoddard solvent; 14.5% aromatics) by oral gavage. No deaths occurred during the 14 days of observation. Hypoactivity and ataxia were noted in five animals (API, 1986a).

7.1.3 Dermal exposure

Four New Zealand White rabbits of each sex were exposed for 24 h with a bandage containing doses of 2.0 or 3.0 g/kg body weight of white spirit (Stoddard solvent) (14.5% aromatics). The exposed area, which measured about 10% of the body surface, was shaved before exposure and the skin of two animals in each dose group was abraded. All animals exhibited loss of appetite and hypoactivity on the first day after exposure. At the lowest dose level thickening and redness of the skin developed. One low-dose female with skin abrasion died three days after exposure (API, 1986a).

Hine & Zuidema (1970) tested rabbits with 10 different fractions of C₆-C₁₄ hydrocarbons by dermal application. Three animals per group and exposures of 2 and 5 ml/kg for 4 h were used. Exposure to 5 ml/kg of four aromatic samples covering the C₈-C₁₄ range all resulted in one death. Exposure to six solvents consisting of aliphatic and cyclic aliphatic alkanes did not cause lethal effects, except exposure to 5 ml/kg of a C₁₁-C₁₂ solvent, which caused one death.

7.1.4 Aspiration

Aspiration to the lung of non-viscous hydrocarbon solvent resulted in deaths in a series of animal experiments in which a wide range of single hydrocarbons were tested. In these tests anaesthetized male Wistar rats (2-5 animals per group) were manipulated to aspirate 0.2 ml of a solvent consisting of alkanes (C₆ to C₁₄), cycloalkanes (C₅ to C₁₂), aromatics (C₆ to C₁₈) or various mixtures of hydrocarbons (gasoline, oil of turpentine, dry cleaning solvent, kerosene, diesel oil). Rapid death (within a few seconds) due to asphyxia was produced by the most volatile hydrocarbons, whereas slower death (over a period of several hours) due to pulmonary oedema, bleeding and respiratory distress was caused by the least volatile solvents (Gerarde & Linden, 1963).

7.2 Short-term and long-term exposure

7.2.1 Inhalation

7.2.1.1 White spirit

In short- and long-term inhalation toxicity studies on white

spirits, the respiratory system, haematopoietic system, liver and kidney were generally the toxicity targets.

Rector et al. (1966) exposed Long-Evans and Sprague-Dawley rats (14-18 animals of both sexes in each group), guinea-pigs (14-59 animals per group), New Zealand albino rabbits (3-5 animals per group), squirrel monkeys (3 animals per group) and beagle dogs (2 animals per group) for 90 days to continuous levels of white spirit (boiling range, 140-190°C; 80-86% aliphatics and cyclic alkanes, 1% alkenes, 13-19% aromatics). Nine different exposure levels in the range of 114-1271 mg/m³ were used. A significant increase in mortality was seen in guinea-pigs at exposure levels of 363 mg/m³ or more. No increased mortality was found in the other animal species. No signs of toxicity during the exposure were noted, except for occasional slight diarrhoea and nasal discharge in guinea-pigs. At autopsy, irritation and congestion of the lung were commonly observed in all species. The severity of lung irritation appeared to be dose-related and congestion in general appeared in animals exposed to 1271 mg/m³. Histopathological examination of the liver revealed mild

to moderate vacuolar changes of the hepatic cells in guinea-pigs exposed to 363 mg/m³ or more. However, no clear dose-related trend was found. Occasional changes in leukocyte counts in dogs, rabbits and guinea-pigs were not judged to exceed normal variations. No significant exposure-related effects were observed with respect to weight gain, pathology, or haematological and biochemical parameters.

Jenkins et al. (1971) exposed guinea-pigs to white spirit (19-20% aromatics; 892 mg/m³) for 90 days and found similar effects in the liver to those reported by Rector et al. (1966).

Carpenter et al. (1975a) exposed groups of 25 male Harlan-Wistar rats and 4 beagle dogs to white spirit (Stoddard solvent) vapour at levels of 0 mg/m³, 480 mg/m³ (84 ppm), 1100 mg/m³ (190 ppm) and 1900 mg/m³ (330 ppm) (boiling range, 152-194°C; 47.7% aliphatics, 37.6% cyclic aliphatics, 14.7% aromatics) for a period of 13 weeks (6 h/day, 5 days/week). Histopathological lesions of the kidneys and dilated tubules were found in 6 out of 9 and 3 out of 9 rats exposed to 1900 and 1100 mg/m³, respectively. These lesions were also noted in rats killed after only 8 weeks of exposure. Significant, although not dose-related, changes in haematological values were thought to be

mainly a consequence of the deviant values found in the control group. No differences were found in weight gain. In dogs no changes were observed with respect to body and organ weights, haematological and clinical chemical values or histopathological parameters.

In a similar study with rats and dogs and with considerably lower exposure levels of dearomatized white spirit vapour (140° Flash Aliphatic Solvent; 0 mg/m³, 49 mg/m³ (7.8 ppm), 100 mg/m³ (16 ppm) and 230 mg/m³ (37 ppm)), slight tubular degeneration was noted in 14 out of 35 rats (control plus exposed animals). However, this was not considered to be due to exposure. There were no other effects on either rats or dogs, and no exposure-related changes in haematological or clinical chemical parameters were found (Carpenter et al., 1975b).

Riley et al. (1984) exposed a group of six female rats to white spirit vapour at a mean concentration level of 214 mg/m³ (boiling range, 150-195°C; 61% aliphatics, 20% cyclic aliphatics, 19% aromatics; exposure duration, 4 h/day for 4 consecutive days). Histological examination of the respiratory tract revealed the presence of inflammatory cell infiltrate in the nasal cavity, trachea and larynx, loss of cilia, hyperplasia of mucosa cells and basal cells, and squamous cell metaplasia.

Blair et al. (1979) conducted an inhalation toxicity study on Low Aromatic White Spirit (LAWS) in Wistar male and female rats. Groups of 18 males and 18 females were exposed to LAWS vapour (7500, 4000 and 2000 mg/m³) for 6 h, 5 days/week, for 13 weeks. Body weight, food and water consumption and clinical observations were recorded every week. At the end of the study, organ weight, blood chemistry and

haematology parameters and complete histopathological evaluations were performed. No clinical signs and toxicity were observed except that the high-dose groups were slightly lethargic when examined 30 min after cessation of exposure. One exposure to LAWS caused low-grade anaemia and mild degenerative changes in the kidneys of males at all exposure levels. In female rats there were dose-related increases in the liver weight of exposed animals. However, there were no histopathological lesions observed in the livers of treated animals. In the kidneys, hyaline droplets were found most frequently in the proximal tubular epithelium of the outer cortex.

Oestergaard et al. (1993) exposed groups of 30 young (3 months old) and groups of 14 old (15 months old) male rats to vapour concentrations of 0, 2290 and 4580 mg/m³ (0, 400 and 800 ppm) of white spirit (boiling range, 148-200°C; 20 v/v% aromatics). After exposure for 6 months (6 h/day, 5 days/week) and a follow-up period without exposure of 4 months, the animals were killed. The animals showed signs of discomfort during exposure, especially during the initial exposure period. Mucosal irritation, bloody discharge from the nose and lacrimation were present. Narcotic effects were gradually reduced. Although the body weights of the high-dose group were reduced, this difference disappeared during the follow-up period. At both exposure levels the rats had a significantly higher water consumption than controls (only the group of young rats were monitored). Clinical chemical parameters of the urine were unaffected, but significant increases were found for plasma urea and creatinine levels at both exposure levels. Serum alanine aminotransferase activity was significantly reduced. No macroscopic or histopathological changes were found at sacrifice, and no differences in the kidney tubules were noted between exposed and unexposed rats.

7.2.1.2 Exposure to related hydrocarbons

Nau et al. (1966) exposed groups of 18-38 rats (strain not specified) to the vapour of a C₉-C₁₀ aromatic solvent (boiling range, 155-200°C; 26 mole% aliphatics plus cyclic aliphatics, 42 mole% C₉ aromatics, 29 mole% C₁₀ aromatics, 3 mole% C₁₁ aromatics) for 18 h/day, 7 days/week for a maximum of 150 days (the C₉-C₁₀ aromatic fraction is by far the most abundant aromatic fraction in white spirit type 1, which may contain about 15% of these isomers, see section 2.1.2). The exposure levels used were 50, 200, 616 and 1000 ppm. After the first day at 1000 ppm of exposure the rats developed congestive changes in the lungs and liver, enlarged spleen and haemorrhagic kidneys. After day 8, a significant fall in white blood cell count and a shift in the polymorphonuclear-lymphocyte ratio was observed. At 616 ppm similar effects were found in connection with reduced weight gain after a total of 135 days of exposure. Fatty changes in the liver, stimulation of bone marrow activity, and haemorrhages around the nose and mouth were further reported at this level. After 2 months, 70% of a subgroup of rats was affected by

bilateral cataract. A group of rats exposed to 200 ppm for 8 h/day, 5 days/week, for 18 weeks did not show any significant changes in haematological values, weight gain, bone marrow activity or lens opacity. Groups of three rhesus monkeys exposed to the vapour at 50 ppm and 200 ppm for 7 h/day, 5 days/week, for 18 weeks developed changes in haematological parameters with a decrease in white blood cell count, increase in haematocrit readings and a shift in the polymorphonuclear-lymphocyte ratio. At 200 ppm, the animals appeared sedated and "groggy" during exposure.

7.2.2 Dermal exposure

7.2.2.1 White spirit

The shaved intact skin (15 × 20 cm) of groups of 10 New Zealand White rabbits was exposed to doses of 200, 1000, and 2000 mg/kg of white spirit (Stoddard solvent). Exposure was carried out using occlusion bandage for a duration of 6 h and was given 3 times weekly for 4 weeks. At the highest dose level, there was a significant reduction in weight gain in both sexes, whereas only the female body weight gain was reduced at 1000 mg/kg. Changes in haematological parameters noted at 2000 mg/kg were judged not to be treatment-related. At 2000 mg/kg, female rabbits developed liver lesions characterized as white streaks or foci with granular surface (API, 1986b).

7.2.2.2 Exposure to related hydrocarbons

Nau et al. (1966) exposed male C₃H mice dermally to 0.10-0.15 g of a C₉-C₁₀ aromatic solvent (for composition see section 7.2.1) 3 times a week for up to 50 weeks. The total dose per mouse was calculated to be 10.6 g. Increased incidences of histopathological findings were observed in the exposed group compared to controls. These consisted of inflammatory reactions, hyperkeratosis and ulcerations of the skin, inflammatory reactions and focal haemorrhages of the lung, amyloidosis of the spleen, necrosis of the liver, cortical scarring and sclerosis of the kidneys. Exposure to *n*-decane (total dose 16.3 g per mouse) induced increased incidences of fibrosis of dermis, pigmentation and ulceration of the skin, and haemorrhage, pigmentation and inflammation of the kidneys and lungs. However these responses were judged to be less severe than those found

after exposure to C₉-C₁₀ aromatics.

7.3 Irritation; sensitization

Appraisal

White spirit (Stoddard solvent) is judged to be a slight to severe skin irritant, depending on the duration of exposure and the animal species used.

7.3.1 Skin irritation

7.3.1.1 White spirit

Guillot et al. (1982) compared three different guidelines for the testing of irritating properties of 56 chemicals (Official French guidelines for testing cosmetics, Guidelines from the Association Française de Normalisation, and OECD guidelines). White spirit (specified as white spirit, dilutene 5) was judged to be "moderately irritant" according to the first mentioned guideline, while a "slightly irritant" score was obtained using the two other sets of guidelines. In all three tests, a quantity of 0.5 ml was used and an occlusive dressing was applied. Exposure duration was 23 h for the first method mentioned and 4 h for the other two methods.

In a test for primary dermal irritation, 0.5 ml of Stoddard solvent (14.5% aromatics) was applied to the shaved (abraded and nonabraded) skin of six male New Zealand White rabbits. The exposed area was covered with an occlusive dressing for 24 h. The exposure caused moderate to severe erythema and oedema according to the Draize test after 24 h of skin contact. After 72 h, a primary dermal irritation index of 4.5 was calculated (API, 1986a).

In a skin irritation test with New Zealand White rabbits exposed to white spirit (Stoddard solvent), Nethercott et al. (1980) found only minor signs of irritation and hence calculated an index of 1.55. The application site was covered with gauze and an elastic bandage for a duration of 24 h.

Application of 200, 1000 and 2000 mg/kg of white spirit (Stoddard solvent) to the shaved intact skin (15 × 20 cm²) of 10 New Zealand

White rabbits 3 times a week for 4 weeks resulted in a dose-related increase in irritation response (Draize testing). Following the application, the test site was occluded for 6 h with a gauze pad and a sheet of polyethylene. "Moderate irritation" was observed at the lowest dose level and "severe irritation" at the highest dose level (API, 1986b).

Semi-occluded application of undiluted 0.5 ml of Low Aromatic White Spirits (LAWS 15/20A) to the clipped dorsum (6 cm²) of six New Zealand white rabbits for 4 h caused moderate irritation and slight oedema. One inflammatory response had regressed 14 days after the application (Gardener, 1989).

Anderson et al. (1986) compared the irritating properties of 14 organic solvents in relation to the responses obtained when using 1% and 2% sodium lauryl sulfate aqueous solutions as positive reference solutions. An area of 1 cm² of shaved skin on the flanks of 10 Dunkin Hartley guinea-pigs was exposed to 10 µl of each solvent 3 times daily for 3 days. White spirit and trichloroethylene were found to be the most potent irritants among the solvents, giving similar results to the 2% sodium lauryl sulfate solution. The validation included scoring for macroscopic response, dermal thickness and the amount of affected dermal cells.

7.3.1.2 Exposure to related hydrocarbons

Hine & Zuidema (1970) tested 10 hydrocarbon solvents (covering the overall range of C₈-C₁₆ hydrocarbons), each containing a narrow range of components. They found that four aromatic solvents (covering the range C₈-C₁₄) were moderate irritants (according to the Draize test) after 24 h of skin contact in rabbits (six animals/group with both intact and abraded application sites). A similar response was found for a solvent containing C₉-C₁₀ aliphatic and alicyclic alkanes, whereas other alkane solvents containing hydrocarbons outside the C₉-C₁₀ range produced only slight responses. A C₁₃-C₁₆ solvent was a minimal irritant.

Hoekstra & Phillips (1963) conducted studies with different kinds of mineral oils and certain purified substances. Guinea-pigs were dermally exposed by spraying 0.6 ml solvent every second day for a total of four exposures. In contrast to the above-mentioned study

performed by Hine & Zuidema (1970), the authors found that maximum skin damage resulted from C₁₄ to C₁₉ alkanes. Purified *n*-dodecane and *n*-tetradecane (which may be present in high amounts in high-flash white spirits) resulted in score 5 (8 was the highest irritation score). Effects from lower hydrocarbons were thought to be caused mainly by defatting and not to be due to directly irritating properties.

Ingram et al. (1993) studied the effects of a hydrogenated white spirit/naphtha (boiling range, 134-217°C; 86.8% aliphatic and cycloaliphatic hydrocarbons; 12.9% aromatics) after application to the skin of a group of 20 mice three times per week for up to 4 weeks. From day 7 to day 14 signs of skin irritation, including skin thickening, cracking and patchy hair loss, were apparent. Microscopic observations showed epidermal necrosis after 4 days (one day after the second treatment). From day 7 epidermal necrosis, ulceration, eschar formation, vesiculation and epidermal hyperplasia were observed, indicating repeated cycles of necrosis and healing.

7.3.2 Eye irritation

No or only very slight irritation occurred after the application of 0.1 ml of white spirit (Stoddard solvent; 14.5% aromatics) to the eyes of six rabbits. One hour after application one of the rabbits showed mild injection and swelling of the conjunctiva. However, these signs of irritative response disappeared after 24 h (API, 1986a).

These findings were in agreement with studies conducted by Hine & Zuidema (1970), who tested various fractions of hydrocarbons in the C₆-C₁₆ range. They found moderate irritative responses in rabbit eyes exposed to aromatic samples (C₈-C₁₁), but minimal responses after exposure to aliphatic and alicyclic alkanes.

Dogs exposed to a vapour level of 1700 mg/m³ of 140° Flash Aliphatic Solvent developed signs of eye irritation and lacrimation (Carpenter et al., 1975b). Eye irritation was also observed in other experimental animal inhalation studies but usually at higher concentrations (see section 7.1.1).

7.3.3 Respiratory irritation

Carpenter et al. (1975a) used respiratory depression in mice as an index of irritative response in the upper respiratory tract. Three of six male Swiss-Webster mice developed a decline in respiratory rate (below 50% of the normal rate) during 1 min of exposure to 10 000 mg/m³ (1700 ppm vapour and aerosols) of white spirit (Stoddard solvent; 15% aromatics). A similar decrease in respiratory rate did not occur at 4400 mg/m³ (770 ppm).

Exposure to mice of either 350 mg/m³ (56 ppm vapour) or 1200 mg/m³ (vapour plus aerosol) of dearomatized white spirit (140° Flash Aliphatic Solvent) did not induce respiratory tract irritation or change in respiratory rate (Carpenter et al., 1975b). Exposure to an aerosol level of 3200 mg/m³ of "High Aromatic Solvent" induced a reduction in respiratory rate of more than 50% (Carpenter et al., 1977a).

7.3.4 Sensitizing properties

White spirit (Stoddard solvent containing 14.5% aromatics) was found not to be sensitizing in a Buehler test. A 75% (by volume) solution of white spirit (Stoddard solvent) in a vehicle of paraffin oil used for the three sensitizing doses was found to induce mild to moderate irritation. A 25% (by volume) solution was used as a challenge dose (API, 1986a).

7.4 Other effects

7.4.1 Nephrotoxicity

Phillips & Egan (1984) exposed groups of 35 male and 35 female Sprague-Dawley rats to the vapour of either dearomatized white spirit (boiling range, 155-193°C; 58% aliphatics, 42% cyclic aliphatics, < 0.5% aromatics) or of C₁₀-C₁₁ isoparaffinic hydrocarbon solvent (boiling range, 156-176°C; 100% isoalkanes mainly in the C₁₀-C₁₁ range). Exposure levels were measured to be 1970 and 5610 mg/m³ for dearomatized white spirit and 1910 and 5620 mg/m³ for isoparaffinic hydrocarbon solvent. The exposure period was set at 6 h/day, 5 days/week, for 12 weeks. No deaths occurred and only occasionally decreased weight gain was noted during exposure of male animals exposed at the high levels. The male rat kidney was found to be the

main target organ. After 4, 8 and 12 weeks, significant increases in absolute and relative kidney weights were found in all exposed groups, but were most striking at the high exposure levels. Histopathological examination revealed the presence of regenerative epithelium in the cortex and dilated tubules filled with proteinaceous casts in the corticomedullary areas of the kidney. The changes were focal in nature, covering 5-10% of the tubules. These observations were identical to the effects found when the authors reexamined the kidney slides from the white spirit study performed by Carpenter et al. (1975a).

Phillips & Cockrell (1984) more closely examined the renal effects of white spirit exposure. Sprague-Dawley and Fisher rats were placed in three groups of 50 animals of each sex per strain. One group of each strain was exposed to 0, 570 and 4580 mg/m³ (0, 100 and 800 ppm) of white spirit (Stoddard solvent; boiling range, 156-204°C; 55% aliphatics, 27% cyclic aliphatics and 18% aromatics) for 6 h/day, 5 days/week, for 8 weeks. Exposure affected kidney function slightly in male rats. At the end of the exposure period, dose-related increases in urine volume (and decreased osmolality) and increased urinary content of glucose and protein were found. A marked increase in the number of epithelial cells in the urine was also observed. Male Fischer rats were more significantly affected than male Sprague-Dawley rats. The structural changes in the kidneys were identical to those described in the study of Phillips & Egan (1984) and were found in animals killed after 4 weeks of exposure. In a similar study with Fischer rats exposed to C₁₀-C₁₁ isoparaaffinic solvent (boiling range, 156-176°C; mainly C₁₀-C₁₁ aliphatics) at 1830 and 5480 mg/m³ (300 and 900 ppm), electron microscopy of the kidneys disclosed electron-dense phagolysosomes corresponding to "hyalin droplets" in the epithelial cells of the proximal convoluted tubules. This was observed in male rats killed on day 5 of exposure or later. A group of rats with a recovery period of 4 weeks after exposure

regained normal kidney function, but recovery from the structural changes in the proximal convoluted tubules and at the corticomedullary junction was not complete.

Lam et al. (1994) exposed male rats to dearomatized white spirit (boiling range, 148-200°C; 20% aromatics) vapour concentrations of 0, 2290 or 4580 mg/m³ (0, 400 or 800 ppm). The kidney weights and

the relative kidney weights of the rats exposed to white spirit were increased compared to the control. In the case of the relative kidney weight, the changes were dose-dependent.

Carpenter et al. (1977b) found similar histopathological changes in kidneys of male Harlan-Wistar rats exposed 6 h/day, 5 days/week, for 13 weeks to levels of 0, 610, 2100 and 5500 mg/m³ (0, 110, 380 and 1000 ppm) of High Naphthenic Solvent (boiling range, 157-183°C; 29% aliphatics, 70% cyclic aliphatics, 1% aromatics).

In a study involving exposure to High Aromatic Solvent, (boiling range, 184-206°C; > 96% aromatics mainly C₉-C₁₁) using levels of 0, 100, 220 and 380 mg/m³ (0, 17, 38 and 66 ppm) and the above-mentioned duration, slight kidney tubule regeneration appeared in a dose-related manner (Carpenter et al., 1977a).

Viau et al. (1984) found after 9.5 months of exposure of male Sprague-Dawley rats (8 h/day, 5 days/week) to 6500 mg/m³ of a white-spirit-like solvent (99% C₁₀-C₁₂ aliphatics) a significant decrease ($p < 0.001$) in urine osmolality. After 10 months of exposure the animals were dosed with ammonium chloride 2 mmol/kg. The net acid excretion was determined and found to be significantly reduced ($p < 0.001$). Elevated activity of urinary lactate dehydrogenase was further noted as an indication of distal tubular dysfunction.

Much research effort has been devoted to elucidating the nephrotoxic effects of volatile hydrocarbons. Studies with, for instance, *n*-decalin, 2,2,4-trimethylpentane, and unleaded gasoline have revealed similar effects to those described above (Gaworski et al., 1985; Short et al., 1987; Olson et al., 1987). The effects have been found to be species- and sex-specific, since they have only been observed in male rats. More detailed examination of the development of the pathological events has been performed. In the early phase after exposure to even very low levels of hydrocarbons (e.g., 0.04 mg gasoline/kg per day or 28 mg/m³ (5 ppm) of decalin), lysosomal accumulation of crystalloid protein droplets (hyaline droplets) occurs in the epithelial cells of the renal proximal convoluted tubules. Individual cells undergo cytolysis, detach from the base membrane, and slough into the lumen of the nephron. In severe cases this may lead to granular casts at the junction of the

thin loop of Henle. Furthermore, the loss of cells at the proximal convoluted tubules leads to restorative increased cell proliferation

and hyperplasia. The male rat specific protein α_2 -microglobulin has been observed to accumulate in protein droplets, and the hindered catabolism of this protein (by coupling to specific hydrocarbons) is thought to be a crucial point in the initiation of the nephrotoxic response (Swenberg et al., 1989). However, in an assessment by the US Environmental Protection Agency (US EPA, 1991) it was concluded that if a chemical induces α_2 -microglobulin accumulation in male rats, the associated nephropathy is not used as an end-point for determining non-carcinogenic hazard.

7.4.2 Neurotoxicity

7.4.2.1 Behavioural effects

Kulig (1989) found minor behavioural changes in male Wistar rats (8 per group) exposed to white spirit vapour levels of 0, 1200, 2400 and 4800 mg/m³ (0, 200, 400 and 800 ppm) (boiling range, 158-193°C; 44% aliphatics, 36% cyclic aliphatics, 18% aromatics) 8 h/day for three consecutive days. Before the exposure the rats were trained to react to a light stimulus on either of two panels and to depress a lever at the illuminated site to get access to water. Immediately after the first day of exposure the latency time from stimulus to reaction was significantly increased in an exposure-related manner. However, on day 3 the differences in response between the exposed groups and the control group had almost disappeared. Measurement of spontaneous activity and motor coordination did not show any differences between the groups. In a similar study lasting 26 weeks, the tests were performed at least 10 h after the daily exposure had ceased. No differences in performance were seen compared to controls during the 26 weeks of exposure. In week 17, however, the test was done immediately after the end of the daily exposure and the exposed groups now had a poorer performance (increased response time) indicating that an acute effect was still demonstrable. Behavioural tests designed to measure changes in activity, coordination, grip strength and discrimination performance did not reveal significant differences compared to control rats. Measurements of tail nerve conduction velocity showed significant lower conduction velocities in rats exposed to 4800 mg/m³.

Oestergaard et al. (1993) examined the behavioural effects of 6 months of white spirit inhalation in adult and old rats. Groups of male Wistar rats were exposed to 0, 2290 and 4580 mg/m³ (0, 400 and 800 ppm) of white spirit (boiling range, 148-200°C; 80% aliphatic and cycloaliphatic hydrocarbons, 20% aromatics) 6 h/day, 5 days/week, for 6 months. Neurobehavioural tests were performed after an exposure-free period of 2 months. No changes were found compared to control groups with respect to general functional behaviour or performance in cognitive tests (passive avoidance, eight-arm radial maze, and Morris maze). The study was performed with groups (36 rats in each group) of young rats (aged 3 months at the start of exposure) and with groups

(14 rats in each group) of old rats (15 months old at the start of exposure). No differences were seen between the age groups except in the case of motor activity, young rats being more active.

Similar behavioural tests were conducted with male Wistar rats after a recovery period of two months after exposure to 0, 2339 and 4679 mg/m³ (0, 400 and 800 ppm) of white spirit type 3 (boiling range, 145-200°C; < 0.4% aromatics) 6 h/day, 5 days/weeks, for 6 months. Decreased motor activity during the dark periods was noted, compared to controls, but no exposure-related effects were noted in the other behavioural tests (Lund et al., 1996).

7.4.2.2 Neurophysiological and neuromorphological effects

In the above-mentioned study, sensory evoked potentials were recorded in 8-10 rats from each exposure group after the 2 months of recovery. The recordings of flash evoked potential, somatosensory evoked potential and auditory evoked potential all revealed exposure-related increases in the amplitudes of the early-latency peaks of the sensory evoked potentials. It was concluded that exposure to dearomatized white spirit induced long-lasting and possibly irreversible effects in the nervous system of the rat (Lund et al., 1996).

Different neurophysiological and morphological changes were found in the rat tail after percutaneous exposure to different qualities of white spirit. An area of 12 cm² on the tail of five male Wistar rats per group was treated with three different kinds of white spirit 3

h/day, 5 days/week, for 6 weeks. The solvent (dose not specified) was pipetted onto cotton wool and an occlusive dressing was made around the tail. The solvents differed mainly in aromatic content (low content of 0.3% in solvent A) and in the content of *n*-nonane (low content of 1.9% in solvent C).

	A	B	C
Boiling range (°C)	150-200	152-182	180-230
Aromatics (% by weight)	0.3	11.7	17
<i>n</i> -Nonane (% by weight)	11.3	13.3	1.9 ^a
<i>n</i> -Decane (% by weight)	7.6	10.0	9.1 ^a

^a *n*-alkane plus isomers

Motor conduction velocity in the tail was unchanged after the exposures, when compared to controls. However, the recorded electrophysiological response from exposure group A exhibited the polyphasic nature of the amplitude, the duration being significantly ($p < 0.01$) longer than that recorded from the controls. Exposure to solvent B yielded a significant ($p < 0.05$) protraction of the recorded motor response, while no significant effects were noted after exposure to solvent C. Morphological analysis of the tail nerve revealed axon swelling and widening of the nodes of Ranvier in animals exposed to solvents A and B. Demyelinated foci were found in the axons from animals exposed to solvent C (Verkkala et al., 1983, 1984).

7.4.2.3 Neurochemical effects

Savolainen & Pfäffli (1982) measured enzyme activity in the brain of male Wistar rats exposed 6 h daily, 5 days/week for 4-17 weeks to 575, 2875 and 5750 mg/m³ (100, 500 and 1000 ppm) white spirit vapour (boiling range, 152-182°C; 61% aliphatics, 27.3% cyclic aliphatics, 11.7% aromatics). After 8 weeks, a dose-dependent decrease in the cerebellar succinate dehydrogenase activity was measured and after 12 weeks creatine kinase activity had increased. The latter finding was assumed to be due to glial cell proliferation as an increase

in the specific activity in the glial cell fraction was not demonstrated. Furthermore, white spirit was suggested to affect muscle cell membranes, as sialic acid and uronic acid contents had decreased in proportion to phospholipids or total membrane protein. Exposure to 575 mg/m³ for 17 weeks was found to be a virtual no-effect level.

Edelfors & Ravn-Jensen (1985, 1992) examined calcium uptake, ATP-ase activity and membrane fluidity in rat brain synaptosomes. It was found that calcium uptake in rat brain synaptosomes was affected after short-term exposure (18 h) to white spirit at 3000 and 6000 mg/m³ (500 and 1000 ppm) (quality of the solvent not specified). Synaptosome preparations from rats exposed to 3000 mg/m³ showed an increased calcium uptake compared to control rats, while after exposure to 6000 mg/m³ the calcium uptake was reduced. Calcium uptake is known to be affected by anaesthetics altering membrane fluidity (Edelfors & Ravn-Jensen, 1985). Ca⁺⁺/Mg⁺⁺-ATPase activity in rat synaptosomes membranes was reduced after 20 min of *in vitro* exposure of the preparations to buffers containing a deaerated white spirit at 12-50% of the saturation concentration. Membrane fluidity determined by fluorescence polarization was slightly reduced due to the exposure (Edelfors & Ravn-Jensen, 1992).

Lam et al. (1992) found dose-related increases in the contents of the neurotransmitters noradrenaline, dopamine and 5-hydroxytryptamine in the whole brain after vapour exposure of male Wistar rats. Groups of five animals were exposed 6 h/day, 5 days/week, for 3 weeks to white spirit (boiling range, 148-200°C; 20% aromatics) vapour

concentrations of 0, 2290 or 4580 mg/m³ (0, 400 or 800 ppm). In a long-term exposure study with an exposure period of 6 months and a recovery period of 4 months, modified regional neurotransmitter (noradrenaline, dopamine, 5-hydroxytryptamine) concentrations were demonstrated. Furthermore, in this study whole brain dopamine and 5-hydroxytryptamine contents were increased. These results indicated that 6 months of exposure irreversibly affected neurotransmitter concentrations (Oestergaard et al., 1993).

In another 3-week study involving exposure to 0, 2339 or 4679 mg/m³ (0, 400 or 800 ppm) white spirit (boiling range, 148-200°C; 20% aromatics), the yield of synaptosomal protein per g

brain tissue was reduced (Lam et al., 1995). This finding was repeated when the exposure was extended to 6 months followed by a 4-month exposure-free period (Lam et al., 1995). It was suggested that the exposure caused a reduced number of neuronal interconnections (or a reduced nerve terminal protein content) and that this was possibly compensated for by the increased neurotransmitter contents also found in this study. The increased 5-hydroxytryptamine concentrations were maintained by increased re-uptake rate and storage capacity. The weight of the brain and the brain protein content were not affected by the exposure.

Lam et al. (1994) measured the formation of reactive oxygen species, the level of reduced glutathione, and the activity of glutamine synthetase in subcellular fractions (P2 fractions) of brain tissue taken from rats immediately after 3 weeks of *in vivo* exposure to dearomatized white spirit vapour (boiling range, 145-200°C; ≤ 0.4% aromatics). The animals (10 male Wistar rats in each group) were exposed to 0, 2339 or 4679 mg/m³ (0, 400 or 800 ppm) 6 h/day, 7 days/week, for 3 weeks. Dose-related increased levels of reduced glutathione (GSH) were found in the P2 fractions from the hemisphere, and an increased rate of generation of reactive oxygen species was found in hippocampal P2 fractions taken from rats exposed to 4679 mg/m³ (glutamine synthetase activities were not significantly affected). Both findings were interpreted as reflecting oxidative stress in the brain and were comparable to findings reported in other studies in which similar experiments were conducted with neurotoxic aromatic solvents.

Bondy et al. (1995) performed a similar study in which groups of 5- or 14-month-old male Wistar rats were exposed to 0, 2290 or 4580 mg/m³ (0, 400 or 800 ppm) of white spirit (boiling range, 150-220°C; 14-20% aromatics) 6 h/day, 7 days/week, for 3 weeks. Glutathione concentrations were unchanged in the P2 fractions isolated from the frontal cortex and hippocampus, indicating no sign of pro-oxidant events. In the hippocampus, P2 glutamine synthetase activities were elevated in young (exposed at both concentrations) and in old rats (exposure to the high dose). From this it was suggested that glial activation was taking place.

7.4.3 Biochemical effects

7.4.3.1 White spirit

In the above-mentioned study by Lam et al. (1994), dearomatized white spirit depressed liver P2 glutamine synthetase activity and the rate of generation of reactive species in the P2 fraction of kidney when rats were exposed to 4580 mg/m³. These findings suggest an induction of oxidative stress in these two organs.

Bondy et al. (1995) documented depressed levels of glutathione and depressed activity of glutamine synthetase in the P2 fraction of the kidney and liver. In the kidney the levels were only significantly affected in the groups of aged rats, indicating a higher degree of vulnerability than in the young rats. The findings were interpreted as increased pro-oxidant events occurring in both liver and kidney in rats exposed to white spirit.

7.4.3.2 Exposure to related hydrocarbons

n-Nonane (which together with *n*-decane is the most abundant chemical substance in white spirit, with approximately 10% content of each) has been found to affect liver function in rats. Female albino rats dosed intraperitoneally with *n*-octane or *n*-nonane (1.0 ml/kg) daily for 2 or 7 days developed a significant increase in relative liver weight and decreased activities of aniline hydroxylase, aminopyrine-*N*-demethylase and glucose-6-phosphatase. Phenobarbital-induced sleeping time was prolonged, indicating a decrease in the activity of metabolizing enzymes in the liver (Khan & Pandya, 1980).

In another similar study, there were increased levels of alkaline phosphatase activity in the liver, spleen and bone marrow, together with decreased levels in kidneys. No such changes were found in brain tissue. A significantly elevated level of activity in the spleen persisted for at least 42 days after one intraperitoneal dose of *n*-nonane or *n*-octane (1.0 ml/kg) (Pandya & Khan, 1982).

Pyykkö et al. (1987) observed significant increases in the activities of liver cytochrome P-450, cytochrome P-450-dependent monooxygenases and NADPH-cytochrome *c* reductase in Sprague-Dawley rats one day after intraperitoneal dosing with single isomers of C₈ and C₉ aromatics (5 mmol/kg). A more complex response was seen in the lungs, because of reduction in cytochrome P-450 activity and

increases or reductions in the activity of different monooxygenases.

7.5 Reproductive toxicity, embryotoxicity and teratogenicity

Appraisal

The studies in this section yielded essentially negative results, but details were insufficient to make a comprehensive assessment.

Female rats (26 and 27 animals per group) were exposed to 0, 600 and 2400 mg/m³ (0, 100 and 400 ppm) white spirit (Stoddard solvent; boiling range, 157-204°C; 43% aliphatics, 33% cyclic aliphatics, 24% aromatics) for 6 h a day on days 6 to 15 of gestation. No maternal toxicity was observed and there were no differences in litter size or average fetal weight between the groups. An increased incidence of pups with skeletal variations was observed in the exposed groups. The details of the skeletal variations were not reported. In each exposed group one litter contained pups with at least one unusual skeletal variation. However, these effects were considered to be expressions of retarded growth and not malformations (API, 1983).

Signs of maternal toxicity (decreased weight gain and eye irritation) were found when pregnant Wistar rats were exposed for 6 h daily to 5700 mg/m³ (950 ppm) of white spirit on day 3 to day 20 of gestation. The average fetal body weight was reduced by 14% ($p < 0.001$) and an increased incidence of delayed ossification and increased number of fetuses with extra ribs were noted. The effects were thought primarily to be a result of maternal toxicity (Jakobsen et al., 1986).

In another study in which pregnant rats were exposed to white spirit at 600 and 1800 mg/m³ (100 and 300 ppm) 6 h/day from day 6 to day 15 of gestation, no treatment-related effects were found with respect to implantation, number of live fetuses, fetal resorption, fetal size, sex distribution, or in soft tissue (Biodynamics, 1979; Phillips & Egan, 1981).

7.6 Genotoxicity

Appraisal

The overall conclusion from the tests conducted with white spirit for genotoxicity is that there is no genotoxic potential. Only one in vitro assay yielded a positive result at a cytotoxic level.

A summary of assays for determining mutagenicity and related end-points is given in Table 14.

Table 14. Genotoxicity studies

System	Dose ^a	Response (+S9/-S9)	Reference
Bacterial assays			
Salmonella typhimurium strain TA98, TA100, TA1535, TA1537, TA1538; +/- rat liver S9; plate and suspension assays	0.001-5 µg/plate 3.38-25 µl/ml	negative/negative	API (1984a)
Salmonella typhimurium strain TA98, TA100, TA1500, TA1535, TA1537, TA1538	0.0001-100 µg/plate	negative/negative	Gochet et al. (1984)
Yeast			
Saccharomyces cerevisiae D4; +/- rat liver S9; plate and suspension assays	0.001-5 µg/plate 3.38-25 µl/ml	negative/negative	API (1984a)
Mammalian in vitro cell assay			
L5178Y TK+/- mouse lymphoma mutation assay; +/- rat liver S9	0.5-100 µg/ml	negative/negative	API (1984a)
L5178Y TK+/- mouse lymphoma mutation assay; +/- rat liver S9	12.5-100 µg/ml 12.5-60 µg/ml	positive ^b /positive ^b	API (1987b)

Human lymphocytes, sister-chromatid exchange	20-50 µl	negative	Gochet et al. (1984)
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Table 14. (Con't)

System	Dose ^a	Response (+S9/-S9)	Reference
Mammalian in vivo assay			
Rat bone marrow cytogenetic test (Sprague-Dawley CD rats)	0.087, 0.289 and 0.868 mg/kg per day i.p. for either a single day or 5 days	negative	API (1984a)
Micronucleus test (BALB/c mice)	0.01, 0.05, 0.1 ml i.p., or 50 g/m ³ inhalation	negative	Gochet et al. (1984)
Rodent dominant lethal test (rats)	100, 300 ppm inhalation 6 h/day, 5 days/week for 8 weeks	negative	Phillips & Egan (1981)
Rodent dominant lethal test (Swiss-Webster mice)	780 mg/kg s.c. as one single dose	negative	API (1984b)
Rodent dominant lethal test (Long-Evans rats)	780 mg/kg i.p. as one single dose	negative	API (1984b)

^a i.p. = intraperitoneal; s.c. = subcutaneous

^b more than 50% increase in mutation frequency only at cell toxic concentrations

7.6.1 Bacterial assays

Assays with *Salmonella typhimurium* TA98, TA100, TA1535, TA1537
and TA1538 elicited no mutagenic effects. Plate and suspension assays

were conducted with white spirit (Stoddard solvent; boiling range, 157-204°C; 19% aromatics), both with and without microsomal metabolic activation, at dose levels of 0.001-5 µg/plate and 3.38-25 µl/ml (API, 1984a).

Gochet et al. (1984) performed similar tests with white spirit containing 15% aromatics and obtained negative results.

7.6.2 Yeast assay

The same concentrations as used for the bacterial assays (described in section 7.6.1) elicited no mutagenic response in *Saccharomyces cerevisiae* D4 in assays with and without metabolic activation (API, 1984a).

7.6.3 In vitro mammalian cell assays

White spirit (Stoddard solvent; boiling range, 157-204°C; 19% aromatics) was found to be non-mutagenic in a L5178Y TK+/- mouse lymphoma assay, with and without metabolic activation, when used in the dose range 0.005-0.1 µl/ml (API, 1984a).

However, white spirit (Stoddard solvent; boiling range, 161-199°C; 14.5% aromatics) was judged to be positive in an assay both with and without metabolic activation (API, 1987b). In the concentration range 0.0125-0.1 µl/ml, more than a 50% increase in mutation rate was noted at 0.03-0.06 µl/ml (more than a 50% increase in mutation rate was validated as a positive mutagenic response). These levels, however, led to relative cell growth of 12-66% compared to negative controls. Most toxic responses were seen in assays without metabolic activation.

No significant increase in chromosomal abnormalities (breaks, gaps, fragments and chromosome rearrangement) were noted in the bone marrow of Sprague-Dawley rats after a single intraperitoneal exposure or after daily intraperitoneal exposure for 5 days to white spirit (Stoddard solvent; boiling range, 157-204°C; 19% aromatics). Dose levels of 0.087, 0.289 and 0.868 ml/kg were used (API, 1984a).

No induction of sister-chromatid exchange (SCE) in human lymphocytes was observed after incubation in culture medium containing

0, 20 and 50 µl white spirit (15% aromatics) (Gochet et al., 1984).

7.6.4 In vivo mammalian assays

Gochet et al. (1984) found no cytogenic damage in a micronucleus test conducted with BALB/c mice. Intraperitoneal injections of 0.1, 0.05 and 0.01 ml of white spirit (initial boiling point, 160°C; 15% aromatics) were given to 10 animals each, while inhalation of 50 g/m³ for 5 lots of 5 min (each exposure period was separated by 5 min without exposure) was performed with five mice.

In a rodent dominant lethal test, male rats were exposed to 600 and 1200 mg/m³ (100 and 300 ppm) of white spirit 6 h/day, 5 days per week, for 8 weeks. No effects on implantation rates, implantation efficiency or fetal deaths were observed (Phillips & Egan, 1981).

A similar lack of mutagenic effect on male germ cells was observed in dominant lethal tests with mice and rats dosed subcutaneously or intraperitoneally with 1 ml/kg of white spirit (Stoddard solvent) or 140 Aliphatic Solvent (API, 1984b).

7.7 Carcinogenicity

7.7.1 White spirit

No experimental animal data has been reported concerning the carcinogenic properties of white spirit.

The carcinogenic properties of petrochemical products are usually ascribed to the content of benzene or polyaromatic hydrocarbons (PAH), especially benzo[a]pyrene. In white spirit, however, these constituents are only present in very minute amounts.

7.7.2 Related refinery streams

In a series of experiments, Blackburn et al. (1986) tested a number of (undiluted) samples derived from the refining of crude oil. In each experiment, groups of 50 male C3H/HeJ mice, 6-8 weeks old, were given twice weekly applications of 50 mg of the samples on shaven interscapular skin for 80 weeks or until a papilloma larger than 1 mm³ appeared. Skin tumour incidence (histologically unspecified)

was evaluated in mice surviving at the time at which one-half of the tumour-bearing animals had developed a tumour (or at 60 weeks, whichever came first). The controls consisted of seven groups of 50 mice treated similarly with toluene and four groups of 50 mice that were only shaven. Three skin tumours were seen in the toluene-treated controls and none in the others. In the group treated with light straight-run naphtha (boiling range, 49-177°C), 11 out of 44 mice developed skin tumours, the average latent period being 85 weeks. Of two groups treated with straight-run kerosene (boiling range, 177-288°C), 9 out of 30 and 4 out of 27 mice developed skin tumours, the average latent period being 70 and 62 weeks, respectively.

8. EFFECTS ON HUMANS

8.1 Single exposure

8.1.1 Inhalation, controlled exposure

8.1.1.1 Irritation

a) White spirit

Carpenter et al. (1975a) reported eye irritation and lacrimation in six volunteers after 15 min exposure to white spirit (Stoddard solvent; 48% aliphatics, 38% cyclic aliphatics, 14% aromatics) at a vapour concentration of 2700 mg/m³. At 850 mg/m³, only one person reported slight eye irritation. No irritation was detected at 140 mg/m³.

Hastings et al. (1984) found an increase in subjective reportings of mild irritation symptoms during a 30-min exposure of 25 volunteers to a white spirit (Stoddard solvent) vapour concentration of 600 mg/m³ (35% aliphatics; 40% cyclic aliphatics; 25% aromatics). Irritation of the nose was experienced by 31% (15% in a control group) and eye irritation by 36% (24% in the control group). No changes in the rates of eye-blinking, swallowing or breathing were noted.

Stokholm & Cohr (1979a,c) exposed nine volunteers (students) to 0, 204, 600, 1200 and 2400 mg/m³ (0, 34, 100, 200 and 400 ppm) and six students and nine painters to 0, 300 and 600 mg/m³ (0, 50 and 100 ppm) for a duration of 7 h to white spirit vapour (17% aromatics).

The reporting of eye irritation was the most sensitive measure of effect. There was a significant dose-response relationship in the house painter group and in one group of students exposed up to 2400 mg/m³; there was a higher sensitivity in the house painters. Among students, a dose-related increase in irritation of the nose was noted from 600 to 2400 mg/m³.

b) Exposure to related hydrocarbons

Volunteers exposed for 15 min to vapours of "High aromatic solvent" (> 99% aromatics, comparable with the aromatic fraction in white spirit; boiling range, 184-206°C), at a concentration of 190 mg/m³, experienced mild irritation of the throat, eyes and nose. At 410 mg/m³, the ocular and nasal irritation were described as burning and stinging (Carpenter et al., 1977a).

8.1.1.2 CNS effects

In the study of Carpenter et al. (1975a) (see section 8.1.1.1), slight dizziness was reported in two out of six volunteers exposed to white spirit (Stoddard solvent) vapour at 2700 mg/m³ for 15 min.

Cohr et al. (1980), in a study using white spirit with an aromatic content of 17% (see Stockholm & Cohr (1979c) section 8.1.1.1), found dose-related increased incidences of headache, tiredness and giddiness among nine students exposed up to 2400 mg/m³ (400 ppm). There was increased reporting of headache in a group of nine painters at 600 mg/m³ (100 ppm) (original report by Stockholm & Cohr, 1979c).

8.1.1.3 Neurobehavioural effects

Gamberale et al. (1975) did not find any influence on performance in neurobehavioural tests conducted for the evaluation of perceptual speed, reaction time, short-term memory, numerical ability and manual dexterity among 14 volunteers exposed for 30 min to white spirit vapour at 0, 625, 1250, 1875 and 2500 mg/m³ (17% aromatic hydrocarbons, 83% aliphatic and cycloaliphatic hydrocarbons). However, with exposure to 4000 mg/m³ for 50 min, significantly impaired performance was seen in the tests for perceptual speed and short-term memory. At this level the white spirit concentration in alveolar air corresponded to the concentration found in exposure of

the volunteers to 2500 mg/m³ during light exercise.

Cohr et al. (1980) found altered vestibular-cerebellar reflex (in Romberg test and in a walking performance test with closed eyes) after nine students were exposed for 7 h to white spirit (17% aromatics) at exposure levels of 600, 1200 and 2400 mg/m³ (100, 200 and 400 ppm). Nine painters were not affected at 600 mg/m³ (highest level for this group). Short-term memory (verbal learning and memory test) was significantly impaired in the group of house painters at 300 mg/m³ (50 ppm) while no impairment was noticed among students at levels up to 2400 mg/m³ (also reported by Stokholm et al., 1979) (for description of neuropsychological test methods, see section 8.2.1.3).

8.1.1.4 Odour

Carpenter et al. (1975a,b) found an odour threshold level in the range of 0.5-5 mg/m³ (0.09-0.9 ppm) for white spirit (Stoddard solvent) and around 4 mg/m³ (0.6 ppm) for "140° Flash Aliphatic Solvent" (3% aromatics). The odour experiments were performed with panels of six volunteers. Olfactory fatigue (decreased sense of smell) was reported during exposure to Stoddard solvent using a panel of 50 volunteers, Hastings et al. (1984) determined the odour threshold level for Stoddard solvent to be 2 mg/m³.

A pure aromatic solvent "High Aromatic Solvent" comparable to the aromatic fraction in white spirit was found to have an odour threshold level of approximately 0.4 mg/m³ (0.07 ppm) (Carpenter et al., 1977a).

8.1.2 Inhalation, accidental exposure

Niehrenberg et al. (1991) reported a near-fatal case of poisoning involving a 42-year-old woman who after several hours of painting in a closed room developed chest pain, cyanosis, apnoea and cardiac arrest with ventricular fibrillation. During hospitalization, pulmonary oedema, haemolytic anaemia and metabolic abnormalities were observed. The exposure from the white spirit in the lacquer and paint she was using was estimated to be very high because of the lack of ventilation.

Atkinson et al. (1989) reported a case in which a 60-year-old man

developed malaise with headache, anorexia and coughing after one hour of painting in an unventilated bathroom using a white-spirit-containing paint. Because of loss of coordination he fell and was admitted to the hospital. During the following days at the hospital bone marrow suppression and liver cell damage were verified.

8.1.3 Oral exposure

Ingestion of white spirit has resulted in gastrointestinal irritation including vomiting, diarrhoea and gastrointestinal pain. Severe lesions and ulcerations in the mucous membranes of the oesophagus and the gastrointestinal tract have been reported after ingestion of about 500 ml white spirit (Paris et al., 1978).

As in the case of kerosene and other petroleum solvents with low viscosity, the severity of symptoms after ingestion of white spirit depends on whether the solvent is aspirated into the lungs. Aspiration can cause serious bronchopneumonia, which may be fatal within 24 h. A dose of 30 ml aspirated into the lung may be fatal (McDermott, 1975). Other reports describing the aspiration hazard of petroleum distillates indicate that oral doses as low as 10 ml can be fatal and aspiration of a volume of 1-2 ml may produce bronchopneumonia (Velvart, 1981; Rumack & Lovejoy, 1986).

8.1.4 Dermal exposure

From several series of patch testing with humans, it was found that petroleum solvents with boiling ranges below approximately 270°C were primary irritants (Klauder & Brill, 1947). Petroleum solvents with boiling ranges above this seemed less irritating. Increased content of cyclic aliphatics or aromatic hydrocarbons increased the irritant action of the solvent. Thus increased irritancy was assumed to be connected with the increased solvency and defatting action of the solvent.

Nethercott et al. (1980) reported five cases of ulcerative and erythematous lesions of the genitals and the buttocks in workers wearing clean coveralls which were still moist after dry-cleaning with white spirit (Stoddard solvent). In the report six further cases of cutaneous irritation (vesicle formation, crusting, erythema and

desquamation) following skin contact with Stoddard solvent were mentioned.

Tagami & Ogino (1973) reported four cases in which children developed dermatitis after wearing kerosene-soaked clothing. In a laboratory test, 0.1 g of an 85% kerosene solution applied under occlusional dressing for 24 h to 34 volunteers resulted in positive skin reactions in all subjects. The most common reactions were assessed as faint diffuse erythema and swollen clear erythema. No reactions were noted when a 40% kerosene solution was used.

8.2 Short-term and long-term exposures

This section includes human data from occupationally exposed people. The studies have been selected according to the following criteria concerning exposure:

- * studies that have actual measurements for white spirit;
- * studies with description of white spirit exposure;
- * studies where white spirit exposure is highly anticipated because of the occupation (e.g., house painters);
- * studies referring to mixed hydrocarbon exposure combined with additional data relating to white spirit exposure.

Studies with combined exposure to several chemicals have not been included if the white spirit exposure was found to be of only minor importance. Studies indicating exposure to "organic solvent" or "solvent" without further information have not been included.

8.2.1 Effects on the nervous system

White spirit belongs to the broad category of organic solvents that have created debate with respect to their neurotoxicity. In 1985, WHO and the Nordic Council of Ministers appointed a working group with the aim of setting diagnostic criteria and evaluating methods. The working group found that the symptoms and the neurological and psychological deficits occurring after long-term solvent exposure were quite non-specific (WHO/NCM, 1985). Therefore, the clinical diagnosis on an individual basis had to be based on an overall assessment of the occupational history, the clinical status, the results of some neurological and psychological tests, and the

evaluation of the role of other factors of possible etiological importance. The following criteria for identification and classification of neurological and psychological deficits were proposed:

- a) *Organic affective syndrome* in which clinical manifestations consist of depression, irritability, and loss of interest in daily activities. There is no reduced CNS function (judged from the evaluation of neuropsychological test methods).
- b) *Mild chronic toxic encephalopathy*. Clinical manifestations are fatigue, mood disturbances, and memory and concentration problems. CNS function is impaired with respect to psychomotor function (speed, attention, dexterity); short-term memory impairment and other abnormalities are commonly noted.
- c) *Severe chronic toxic encephalopathy*. This covers loss of intellectual abilities of sufficient severity to interfere with social or occupational functioning: memory impairment, impairment in abstract thinking, impaired judgement, other disturbances of cortical function, personality change. More pronounced and pervasive CNS functional deficits and some neurophysiological and neuroradiological test abnormalities.

It was emphasized that overlap exists between the different very broad categories and that they do not necessarily represent stages through which individuals have to pass to reach the most severe end-point (WHO/NCM, 1985).

At another WHO meeting in 1988 (WHO, 1989), the diagnosis of solvent-related organic brain syndrome was supplemented according to the "Diagnostic and Statistical Manual of Mental Disorders", DSM-III-R (American Psychiatric Association, 1987). Thus the organic brain syndrome was found to have features in common with the definitions of mild syndrome of dementia, mild organic affective syndrome or mild organic personality syndrome. The organic brain syndrome is characterized by a general cognitive impairment and changes in mood and personality. Symptoms and signs of these changes vary in their relative severity from case to case. Usually the changes are mild.

The above-mentioned classification of mental disorders may help

when reading literature in which many other terms such as chronic painter's syndrome, chronic organic brain syndrome, organic solvent disease, psycho-organic syndrome, psycho-organic neuropathy, pre-senile dementia, and dementia have been used to describe the neurotoxic responses^a.

The term dementia, in particular, has created some confusion, because dementia may be used in two different contexts, which must be clearly distinguished. Firstly, it is used to describe a specific

^a In the description of studies reviewed in this chapter, the terms employed in the original research reports will be used.

entity of diseases such as pre-senile and senile dementia, Alzheimer disease, or other very serious diseases characterized by progressive and widespread brain degeneration. Secondly, it is used in a broader sense to describe a clinical syndrome of impairment of intellectual capacity, memory and personality but without impairment of consciousness. The origin of this syndrome may be more benign diseases or exposure to some toxic substances. The term dementia is often used to describe a syndrome resulting from chronic organic solvent exposure, particularly in literature from the Nordic countries (CEC/DME, 1990; Arlien-Soeborg, 1992a).

8.2.1.1 Symptoms and clinical picture

Different kinds of neurotoxic effects are described in the sections 8.2.1.2 to 8.2.1.5. In this section, however, an overall and more general clinical picture from human exposure to white spirit will be presented.

In the report from the WHO/Nordic Council of Ministers meeting, Arlien-Soeborg (1985) summarized the clinical effects from long-term exposure to organic solvents. Most experience has been obtained from the monitoring of painters. This group has been very extensively studied because of high occupational exposure to organic solvent since the introduction of alkyd paint. Thus painters constitute an occupational group that to a great extent and in several countries (e.g., the Nordic countries) has been predominantly exposed to white

spirit.

The painters most often complained about the following acute symptoms: irritation of eyes, nose and throat; reduced sense of taste; nausea; loss of appetite; headache; feeling of drunkenness; dizziness; fatigue (Lajer, 1976; Elofsson et al., 1980; Hane & Hogstedt, 1980; Seppäläinen & Lindström, 1982; Lindström & Wickström, 1983; Arlien-Soeborg, 1985; Cherry, 1985; Valciukas et al., 1985; Oerbaek et al., 1985; Linz et al., 1986; Fidler et al., 1987; Askergren et al., 1988; van Vliet et al., 1989a).

Often these symptoms disappeared during exposure-free periods in weekends or holidays, but over the years these symptom-free periods got shorter and a chronic syndrome state developed. Arlien-Soeborg (1985) reported the following chronic symptoms in a group of 50 house painters: memory impairment, forgetfulness, excessive fatigue, weariness, inability to concentrate, irritability, low frustration tolerance, headache, dizziness, apathy, lack of initiative, anxiety, nervousness, depressions, low spirits, bursts of perspiration, alcohol intolerance, abdominal pains, diarrhoea, nausea, impotence, reduced libido, blurred vision.

Several of these symptoms have also been described by others, although in most cases the distinction between the acute and the chronic states has not been made.

In severe chronic cases, fatigue and impairment of learning ability, concentration, memory and initiative may change the personality of the affected person in such a way that a normal working life as well as normal family life may be impossible. In several cases it has been described how these adverse effects resulted in change of occupation or in the awarding of a disability pension (Agrell et al., 1980; Bruhn et al., 1981; Gregersen et al., 1987; Gregersen, 1988). A positive association between the awarding of disability pensions due to neuropsychological disorders and long-term solvent exposure as a painter (mainly exposure to white spirit) has been demonstrated in epidemiological studies reported by Axelson et al. (1976a), Mikkelsen (1980), Lindström et al. (1984) and Brackbill et al. (1990).

8.2.1.2 Neurological findings

This section comprises the reports from a) neurophysiological and b) clinical neurological examinations of workers exposed to white spirit. Most of the studies have been performed with few but selected subjects (often patients), and a reference group was not usually present.

a) Neurophysiological and neuroimaging examinations

The neurophysiological examinations described in this section can be divided into the following groups:

- i) electrophysiological examination of the brain
 - electroencephalography (EEG)
 - auditory evoked potentials (AEP)
 - cerebral blood flow measurement (CBF)
- ii) neuroimaging examination of the brain
 - pneumoencephalography (PEG)
 - computerized tomography (CT)
- iii) electrophysiological examination of the peripheral nerve system
 - nerve conduction velocity measurement (NCV)
 - nerve action potential amplitudes (NAP)
 - electromyography (EMG)

For further description of these methods the reader is referred to Valciukas (1991) and Arlien-Soeborg (1992b).

An overview and descriptions of the studies using these techniques with people exposed to white spirit are given in Table 15.

Table 15. Neurophysiological examination of patients with previous exposure to white spirit^a

Reference/Neurophysiological Results	Groups studied	Exposure
--------------------------------------	----------------	----------

examinations

Axelsson et al. (1976b) 6 painters were found to have Electroencephalography pathological EEG recordings	10 patients (house painters) suffering from chronic psycho-organic syndrome (POS).	aliphatic and aromatic hydrocarbons including white spirit; exposure for 20-45 years
Gregersen et al. (1978) cerebral or cortical atrophy in Computerized tomography, 17 of 18 examined painters Pneumoencephalography	35 retired house painters suffering from organic cerebral syndrome	several years (typically > 20 years) of exposure to paint solvents, mainly white spirit
Arlien-Soeborg et al. (1979) ^b EEG: slightly or moderately Electroencephalography, abnormal in 9 of 46 patients; Computerized tomography, CT: brain atrophy identified in Pneumoencephalography 19 out of 38 examined; PEG: brain atrophy identified in 12 of 12 examined	50 patients (house painters) with signs of chronic brain syndrome	exposed mainly to white spirit (paint solvent); Mexp. 27 years
Gyldensted et al. (1980) ^b 27 cases of cerebral atrophy in Computerized tomography the group of painters; atrophic patients had been exposed for longer duration than painters without atrophy	51 patients (house painters) with suspected chronic organ solvent intoxication; 38 referents	exposed mainly to white spirit; Mexp. 26.7 years
Arlien-Soeborg et al. (1981) ^b brain atrophy was judged to occur	57 out of 113 patients (house	mixed solvent exposure; house

Computerized tomography
in 28 (49%) of the patients
or Pneumoencephalography

and car painters) suffering from
suspected chronic encephalopathy

painters mainly exposed to white
spirit; Mexp. 25.3 years

Table 15. (Con't)

Reference/Neurophysiological
Results
examinations

Groups studied

Exposure

Arlien-Soeborg et al. (1982)
reduced ($p < 0.05$) CBF in the
Cerebral blood flow
group of painters (36.8 ml/100 g
per min) compared to the controls
(45.4 ml/100 g per min)

9 house painters with intellectual
impairment and suspected chronic
solvent intoxication; only subjects
with no or very slight cerebral
atrophy (observed by CT examination
were included;
11 unexposed controls

mainly exposure to white spirit
(paint solvent); Mexp. 22 years;
no recent exposure before the
CBF examination

Flodin et al. (1984)
in the neurophysiological
Electroencephalography,
examination, pathological results
Electromyography,
were found in 61% of the POS
Nerve conduction velocity
group; in 25% of the early stage
POS group, and in 32% of the
non-POS group

28 patients with POS; 20 patients
with early stages of POS;
28 patients without POS; POS was
diagnosed on the basis of neuro-
psychiatric test performance and
the occurrence of relevant
symptoms

mixed solvent exposure; Mexp.
POS group: 24 years; Mexp. early
stage POS group: 21 years;
Mexp. non-POS group: 16 years;
exposure to white spirit
occurred at frequencies of
24%, 41% and 21% (percentage of
all exposures) in the respective
groups

Gregersen et al. (1987)
slight to moderate abnormal
Electroencephalography
findings were noted in 6 out
of 16 EEG-examined patients;
Computerized tomography
Pneumoencephalography
4 out of 5 examined by PEG or
CT exhibited cerebral atrophy
to a varying degree

21 painters diagnosed with
chronic toxic encephalopathy

paint solvent exposure;
Mexp. 25.5 years

Table 15. (Con't)

Reference/Neurophysiological
Results
examinations

Groups studied

Exposure

Berstad et al. (1989)
17 patients (9 painters) were,
Computerized tomography
according to medical examination
Electroencephalography
and neuropsychological tests,
Electromyography
diagnosed with organic solvent
syndrome; EEC: abnormal findings
in 5/17 cases; CT: atrophy in
2/17 cases; EMG and other
neurological examinations revealed
5 cases (2 painters) of

26 patients referred to a neuro-
logical department with suspected
organic solvent syndrome

mixed solvent exposure;
Mexp. 23.9 years for 17 patients
with a confirmed diagnosis of
organic solvent syndrome

polyneuropathy

^a Mexp. = mean exposure period; EEG = electroencephalography; CT = computerized tomography; PEG = pneumoencephalography;

CBF = cerebral blood flow; NCV = nerve conduction velocity; POS = psycho-organic syndrome

^b These studies are made on the basis of more or less the same background population but reviewed at different times.

For most of the subjects included in the reports in Table 15, exposure has been estimated indirectly. The estimates are usually based on historical exposure data, i.e. working materials, methods, conditions, ventilation and use of protective equipment. The estimates of exposure are consequently imprecise and this makes it more difficult to establish any relationship with the chosen outcomes of the studies.

A common feature of these studies is that they were conducted in connection with other clinical examinations of workers (patients) and that the patients were highly suspected or known to suffer from toxic encephalopathy.

Although the degree of dementia in a group of painters with cerebral atrophy (n=27) was found to be more severe than the degree of dementia in a group of painters without atrophy (n=24), no significant difference in the frequency of dementia was observed between the two groups (85% and 71%, respectively) (Gyldensted et al., 1980).

In the study by Arlien-Soeborg et al. (1981), oto-neurological testing was performed but the abnormal pattern of nystagmus found in 62 of the painters could not be correlated with brain atrophy found in 28 painters.

Neurophysiological examinations have also been used in several of the epidemiological studies (Tables 16 and 17) (Elofsson et al., 1980; Seppäläinen & Lindström, 1982; Oerbaek et al., 1985; Linz et al., 1986; Askergren et al., 1988; Mikkelsen et al., 1988; Triebig et al., 1988). In these studies the neurophysiological examinations have been performed as a screening tool among active and generally healthy workers. Therefore, the extent of pathological findings would be expected to be less than in the examinations previously mentioned in

this section. However, some effects were found in these epidemiological studies. Alteration in peripheral nerve functioning was observed by Elofsson et al. (1980), Linz et al. (1986) and Askergrén et al. (1988), while some changes in cerebral parameters were observed by Oerbaek et al. (1985) and Mikkelsen et al. (1988).

b) Oto-neurological performance tests

Vestibular and vestibulo-oculomotor tests measure CNS function in connection with body balance and eye movements. These functions are vulnerable to various types of CNS intoxication and CNS disease. With respect to solvent toxicity, the monitoring of body sway in standing position (e.g., Romberg's test) and nystagmus (repetitive eye movements) from vestibular response to different challenges (change in body position or irrigation of the ear with cold or warm water) are sensitive methods for detecting abnormal function (Arlien-Soeborg, 1992b).

Arlien-Soeborg et al. (1981) performed some routine vestibular examinations as a part of the study described in Table 15. The following parameters were recorded: spontaneous nystagmus, positional nystagmus, differential-caloric nystagmus and optokinetic nystagmus. Abnormal findings occurred in 58 of the 113 patients (house and car painters) in the differential-caloric test and four further abnormal findings were detected in the other tests. However, no correlation was established between these results and findings of cerebral atrophy or intellectual impairment (evaluated in neuropsychological testing), or duration of exposure.

Ödkvist et al. (1987) studied solvent-exposed workers who had been referred to a department for occupational medicine. Of the 31 workers (mainly painters), 16 were diagnosed with confirmed psycho-organic syndrome (POS), 7 with suspected POS, and 8 without POS. The 16 plus 7 workers had been exposed for an average of 27 and 21 years, respectively, mainly to aliphatic and aromatic hydrocarbons (including white spirit). The workers were subjected to a battery of nine audiological and nine vestibular tests. All three groups showed abnormal findings in two of the audiological tests (test for interrupted speech discrimination and test for cortical response to frequency glides). In the vestibular test battery, considerable abnormal performance was observed in seven of the nine tests. The

groups with confirmed or suspected POS were most affected, especially in electronystagmography, coordination test, Romberg's test, saccade test and visual suppression test. Thus, overall performance was found to be correlated with the degree of POS. More complex and polysynaptic functions were affected to a higher degree than more simplistic functions or simple reflexes.

Ledin et al. (1989) subjected nine patients (mainly painters) diagnosed with psycho-organic syndrome to a similar audiological/vestibular test battery. Compared to 50 unexposed controls, the painters (mean exposure period 21 years) exhibited significantly increased body sway area in Romberg's test (both with eyes open and with eyes closed). In the visual suppression test, significantly impaired ability to suppress vestibular nystagmus was recorded in the exposed group. The authors found that testing for postural equilibrium control as a part of the examination of the cerebral function might be a suitable indicator for solvent-induced CNS lesions.

8.2.1.3 Neuropsychological findings

The clinical diagnostic neuropsychological examination of a person is the most comprehensive and most fully developed form of neuropsychological evaluation. The individual diagnostic examination consists of information from three sources: clinical interview, behavioural observation and psychometric testing.

a) *Clinical interview.* This interview concerns the history of subjective symptoms and their development, functioning in work, family and leisure time, prior performance level, and concurrent psychological functions and signs of brain dysfunction. In some situations the interview may be substituted by a questionnaire.

b) *Behavioural observation.* To the trained neuropsychologist, behavioural observation is a very important source of information which allows evaluation beyond the limitations of a formal testing procedure. The observation is extended to the testing situation, observing coping and compensation strategies while dealing with the tests.

c) *Psychometric testing.* These tests may be regarded as an extension

of behavioural observation, presenting intellectual tasks in a standardized way. Most neuropsychological tests are designed with the aim of studying a certain intellectual function in relative isolation and ruling out, as far as possible, other variables. Furthermore, the tests are standardized to gain a higher degree of objectivity, sensitivity, specificity, reproducibility and intra-/interpersonal comparability (Soerensen, 1992).

The individual diagnosis based on medical and psychological interviews and testing may indicate encephalopathy but not cause. It must be followed by an extensive medical and neurological work-up to exclude other causes of brain dysfunction before solvent exposure can be considered the cause.

A working group appointed by WHO and the Nordic Council of Ministers evaluated the many different neuropsychological test methods (WHO/NCM, 1985). From these tests a core test battery for clinical testing was proposed as useful for evaluating solvent-induced CNS effects:

- Cognitive verbal ability*
 - Vocabulary (power test)
- Psychomotor function*
 - Simple reaction time
 - Santa Ana dexterity test
 - Finger-tapping test
- Perceptual speed*
 - Digit symbol substitution (WAIS - Weschler Adult Intelligence Scale)
- Short-term memory*
 - Benton retention test
 - Digit span (WAIS)
- Mood*
 - Profile of mood states (POMS)

These tests were chosen because they are standardized and widely used, and they are of known empirical value in solvent neurotoxicity testing. At another WHO meeting in 1989, the test proposals were divided into obligatory and strongly recommended tests, and additional tests were included. The Trail Making A and B test and the Block Design test were put forward as obligatory tests and the Aiming test

as a strongly recommended test (WHO, 1989).

The test for cognitive verbal ability is considered to be unaffected by slight brain disruption and is therefore used for the estimation of pre-exposure ability and pre-exposure intellectual level. Testing for perceptual speed and psychomotor function, however, are judged to be rather sensitive tests for determining solvent-induced CNS effects. For further description of these tests, their performance and interpretation of test results, the reader is referred to WHO/NCM (1985), Valciukas (1991) and Soerensen (1992).

The findings from neuropsychological testing of workers and patients with known or suspected mental impairment due to white spirit or mixed solvent exposure are reported below. Findings from epidemiological studies performed mainly with healthy workers are reported in section 8.2.1.4.

Arlien-Soeborg et al. (1979) found 39 out of 50 painters to be intellectually impaired on the basis of the results from a neuropsychological test battery. More than half of the patients showed impaired performance with respect to sentence repetition (53%), paired associates (learning) (60%), digit span (62%) and visual gestalts (memory) (64%). The painters had been referred to an occupational medical clinic because of suspected chronic brain syndrome. (Data concerning exposure and neurological examinations are given in Table 15).

In the study by Arlien-Soeborg et al. (1981) (mentioned in sections 8.2.1.2 a and b and in Table 15), neuropsychological testing (using the test battery mentioned above) was performed with 81 out of a total of 113 painters. Of these, 57 were judged to be intellectually impaired. However, no correlation was found with impaired vestibular functioning, which was observed in 52 of the 113 painters.

Flodin et al. (1984) diagnosed 33 people with psycho-organic syndrome (POS), 27 with early stage POS, and 68 with non-POS on the basis of answers from a questionnaire on psychiatric symptoms and/or scorings in a Swedish neuropsychological test battery (neuropsychological testing performed with 91 persons). All were patients who were examined after they had been referred to an

occupational medical clinic because of the presence of subjective symptoms in connection with organic solvent exposure. It was concluded that POS only occurred after 9 years or more of exposure,

while early stages of POS (some subjective symptoms but not necessarily associated with reduced mental performance) may develop after only 3 years of exposure (for information on exposure see Table 15).

Gade et al. (1988) retested two groups of 10 people 2 years after a first neuropsychological testing had been performed. All were diagnosed in the first test with solvent-induced toxic encephalopathy and half of them were further diagnosed by CT scanning with cerebral atrophy. The patients were mainly occupied as house painters and had been exposed to solvents for an average period of 24 years. In the first testing no comparisons were made to appropriate controls, but, on retesting, matching was conducted with two groups of 10 patients selected from an overall control group of 120 patients recruited from different hospital wards. In the neuropsychological retest, which included nine tests evaluating intelligence, cognitive functioning and psychomotor performance, significantly lower scores were obtained by the group without atrophy. However, when regression analysis was made and differences in age, educational level, and verbal intelligence were accounted for, no clear differences in the test performances persisted compared to the controls. The authors emphasized the necessity of using proper controls to avoid misclassification with respect to toxic encephalopathy.

8.2.1.4 Epidemiological studies

The epidemiological studies on workers exposed to white spirit are listed in Tables 16 and 17. The studies are grouped in the two tables according to the exposure information. Table 16 includes those studies in which exposure was predominantly to white spirit, i.e. the exposure has been verified in the text or the study group is an occupational group known to be predominantly exposed to white spirit, e.g., house painters. Table 17 includes studies in which the white spirit exposure is not defined with the same degree of certainty or is part of a more complex exposure. It should be noted that the column labelled "results" has been mainly used to describe positive findings from the studies. Accordingly, no reporting in this column indicates

negative or inconclusive results from the testing/examinations.

8.2.1.5 Comments and uncertainties concerning the epidemiological studies

It is not possible to interpret and evaluate the studies in Tables 16 and 17 without referring to questions and problems that have been raised in connection with these studies. In sections 8.2.1.2 and 8.2.1.3, aspects concerning different views of the relevance, performance and interpretation of the neuropsychological and neurological tests have been briefly mentioned. These aspects and problems concerning sensitivity may be even more apparent when the tests and examinations are conducted with active workers, where the

Table 16. Epidemiological studies on workers exposed to white spirit^a

Reference/type of study ^b	Groups studied	Exposure ^c	Results
Blume et al. (1975); painters was significantly worse in Hane et al. (1977) classification and psychomotor Cross-sectional study Compared to a standard scale, Neuropsychological test reduced scores were further noted in battery (10 tests simple reaction-time tests. representing a range of different mental functions)	52 house painters 52 unexposed industrial workers	Paint solvents, mainly white spirit and aromatic hydrocarbons; Mexp. 14.2 years	The performance of tests for figure coordination. significantly memory tests and
Hane & Högstedt (1980) symptoms in the exposed group (in Cross-sectional study 18 out of 24 questions): Fatigue, Mailed questionnaire memory, impaired concentration, concerning symptoms and irritability, chest pain and reduced	232 solvent exposed workers (104 painters, 29 car painters, 99 metalworkers),	Mixed solvent exposure; house and car painters most heavily exposed; house painters exposed	Significantly more the answers from paraesthesia, bad depression,

daily performance most prominent symptoms; housepainters were most affected, and a positive correlation was found between increasing number of (exposure).

approximately 70% of the working hours, mainly to white spirit, toluene and xylene

libido were the and car painters correlation was symptoms and age

Mikkelsen (1980) (RR) of 3.4 ($p < 0.05$) was calculated Historical follow-up study Disability pension, presenile dementia (without specific cause information from register compared to bricklayers; a RR of 3.3 files found when using Copenhagen men

Painters mainly exposed to white spirit (about 75% of the total solvent exposure)

A relative risk for painters for because of indication) ($p < 0.05$) was as referents.

Seppäläinen & Lindström (1982) Cross-sectional study Questionnaire Neurophysiological examinations (EEG, NCV)

Mexp. 20.2 years; average exposure to white spirit was estimated to be 40 ppm during working hours

Significantly more feelings of paraesthesia, no notable group NCV measurements.

Table 16 (Con't)

Reference/type of study ^b	Groups studied	Exposure ^c	Results
Lindström & Wickström there were significantly increased	219 house painters	Mexp. 22 years with an	Among painters

(1983) Cross-sectional study 229 reinforcement
acute symptoms such as nausea, runny
Questionnaire 8 workers
Significantly poorer performance
neuropsychological tests
term visual memory and simple
determining intelligence
most affected functions. For these
and psychomotor performance
correlation between performance
exposure/exposure level was demonstrated.

Cherry et al. (1985) 1) 236 painters
significantly more often reported of
Cross-sectional study 128 non-exposed
and feet, depression, difficulties
1) Questionnaires joiners
and increased irritability.
2) Neurological examination 2) 44 painters
impaired scoring in 10 out of 14 test
(nerve conduction 44 non-exposed
rematching with other controls and
measurements); 9 joiners
lower preceding intellectual level of
neuropsychological tests
significant differences were noted.
determining intelligence
peripheral nerve function was observed.
and psychomotor function

Fidler et al. (1987) 101 construction
dose-related increase in symptoms such
Cross-sectional study painters; 31 dry wall
nausea, fatigue, feeling of drunkenness
Questionnaire tapers (the control
Impaired performance in one
Neuropsychological tests group was not used in
performance test and one short-term memory
(8 tests for intellectual the evaluation because
associated with the exposure during the

estimated average level of
white spirit of 40 ppm
during working hours;
exposure indices made for
total life-time exposure
and average exposure levels

Mixed solvent exposure;
average levels of white
spirit were under two
working conditions
measured to be 125 and
578 mg/m³; Mexp.
11.7 years (n=44)

Mixed solvent exposure.
Exposure indices were
calculated on the basis of
duration of exposure (years
as a painter), type of work,

prevalences of
nausea and malaise.
in 4 tests. Short-
reaction time were
functions a slight
and total

1) Painters
tingling in hands
in concentration
2) Significantly
parameters. After
allowance for a
the painters, no
No effect on

Among painters,
as dizziness,
and mood tensions.
psychomotor
test were

functions and psychomotor of pronounced
 Because signs of mental impairment did
 performance) differences compared
 consistent pattern the findings in the
 to the painter group)
 to be in accordance with the WHO
 mildest form of chronic solvent

frequency of exposure,
 amount of solvent used,
 exposure during the
 latest year, etc. Mexp.
 18 years.

latest year.
 not form a
 study were judged
 definition of the
 toxicity.

Table 16 (Con't)

Reference/type of study ^b	Groups studied	Exposure ^c	Results
Baker et al. (1988) as adjusted* prevalence rates of Cross-sectional study forgetfulness, lassitude, Questionnaire dysphoria and numbness of fingers and Neuropsychological test significantly with increasing LEI. battery (9 tests determining (LEI)-response relationship was also verbal ability, psychomotor mood parameters and in the symbol-digit performance and memory) stratifying according to exposure duration for the exposure intensity the parameters were affected to a	186 construction painters	Information about intensity and duration were combined and different exposure indices were calculated. Stratification to 6 subgroups according to the index of lifetime exposure intensity (LEI). Median exposure period: 12 years.	Unadjusted as well symptoms such as disorientation, toes increased Significant dose found for five test. When without accounting neuropsychological minor degree.
Mikkelsen et al. (1988) ratios (OR) for painters compared Cross-sectional study were found for the development of	85 painters 85 bricklayers	White spirit was estimated to account for about 75% of	The following odds to bricklayers

Neuropsychological test presence and degree of dementia battery (13 tests for overall performance in the test intellectual functions and exp.: OR= 5.0 (p < 0.05); medium psychomotor performance) 0.05); low exp.: OR= 1.1. Only a Neurological tests (motor was found between exposure and performance, coordination, specific neurological tests. However a reflexes, sensitivity) was found between exposure levels Neurophysiological number of abnormal scores. In CT examination (CT) and dose relationship for noted in 3 out of 11 different average no-observed-effect level of years was estimated (possible

the total solvent exposure. Mexp. 32.5 years with an average daily solvent consumption of 1.3 l/d = 41.4 (l/d)years. Solvent exposure was graded according to the cumulative solvent consumption. Low exp.: ≤ 15 (l/d) years (n=22); medium exp.: 15-30 (l/d)years (n=29); high exp.: > 30 (l/d)years

dementia (the evaluated from the battery): high exp.: OR= 3.6 (p < weak correlation performance in strong correlation and the total scanning, exposure differences were parameters. An 40 ppm for 13

* Adjustments were made by regression analysis to account for the factors age, race, education, social status and alcohol habits.

Table 16 (Con't)

Reference/type of study ^b	Groups studied	Exposure ^c	Results
identified and taken into		(n=33). Average exposure level (all painters) was estimated to be 40 ppm. 21 painters had been exposed during the latest week	confounders were account).

Gubéran et al. (1989) 1916 painters
(RR) of 1.8 (not significant) was
Historical follow-up study 1948 electricians
painters compared to the
Disability pension, Both groups were
receiving disability pension because
information from register awarded disability
neuropsychiatric diseases. files pensions

Bove et al. (1989) 93 construction
thresholds were significantly higher in
Cross-sectional study painters
than in the comparable controls.
Vibration thresholds and 105 unexposed
had a significant excess of high- controls
temperature sensitivity compared to controls.
there was a positive association
threshold and exposure level and
exposure over the past year.

Bazylewicz-Walczak et al. 226 exposed rubber
the exposed groups (as a total),
(1990) Cross-sectional study footwear industry
controls, was significantly worse with
Neuropsychological test workers; 102 non-
7 tests for intellectual exposed hosiery
battery (7 tests for plant workers
with regard to 3 of the 5 tests for
intellectual functions and performance. The affected variables were:
5 test for psychomotor
perception and reproduction of visual
performance)
projection of spatial relationships,

before examination.

Paint solvents. No further
specific data with regard
to the solvent exposure.

A relative risk
calculated for the
electricians for
of

Mixed solvent exposure.
Mexp. 18 years. Different
exposure indices were
calculated on the basis of
intensity and duration of
exposure.

The vibration
the older painters
The painter group
level temperature
Among painters,
between vibration
cumulative

Solely white spirit exposure
from gluing. Mexp. about
500 mg/m³ in the last 13
years. The two groups were
divided into three sub-
groups with respect to age.
Further the exposed subjects

The performance of
compared to the
regard to 4 of the
functioning and
psychomotor
correctness of
material,

speed of reactions to single and stimuli, and manual dexterity. Variables complex reaction time and found to deteriorate with duration

were divided according to exposure duration
I: 5-10 years (n=51);
II: 11-15 years (n=103);
III: 16-30 years (n=72).

concentration, complex light such as simple and coordination were of exposure.

Table 16 (Con't)

Reference/type of study ^b	Groups studied	Exposure ^c	Results
Bolla et al. (1990); related response in test for Bleecker et al. (1991) threshold and in 5 test parameters for Cross-sectional study attention and concentration. The effects Questionnaires subclinical. No differences between Neuropsychiatric evaluation groups were observed regarding symptoms Vibration threshold test to the "painter's syndrome". Neuropsychological test battery (13 tests for intellectual functions and psychomotor performance)	187 workers selected from two paint manufacturing plants	Mainly exposure from aromatic hydrocarbons (toluene, xylene) and aliphatic hydrocarbons. Average lifetime exposures estimated to be 2, 7, 12 and 18 ppm (as total hydrocarbons) for 4 sub- groups of workers (n = 44 in each group). Mexp. 15-16 years for the four groups.	Significant dose- vibration sustained were judged to be the exposure typically related
Brackbill et al. (1990) 0.05) for painters for getting Cross-sectional study because of chronic	3565 people receiving disability pensions	Painters was selected as a group highly	OR = 1.42 (p < disability pension

Disability pension
diseases compared to unexposed
information from register
files

because of chronic
neuropsychiatric
conditions;
83 245 people receiving
disability pensions
because of other
reasons not mental
4291 painters and
1641 bricklayers were
included in the
two groups

exposed to solvents.

neuropsychiatric
bricklayers.

Table 16 (Con't)

Reference/type of study ^b	Groups studied	Exposure ^c	Results
Demers et al. (1991) experienced by 82% and syncopal episodes Cross-sectional study of the painters. Vibration tests Subjective symptoms with a "Vibrometer" on the index Vibration perception big toes to assess peripheral nerve threshold test tests demonstrated significantly perception thresholds compared to	28 solvent-exposed painters 20 nonexposed boilermakers	Mixed solvent exposure. 76% of the painters reported white spirit exposure. 42% of the painters were solvent exposed more than 50% of the working time. Mexp. 30 years.	Dizziness during work by 11% were performed fingers and the functioning. The reduced vibration the control group.
Spurgeon et al. (1990, significantly impaired performance was 1992); Cross-sectional study symbol-digit substitution test for the Questionnaire concerning study 2, the performance of workers	Study group 1: 90 brush painters 90 unexposed age-	Study 1: Mainly exposed to white spirit. Estimated average level of 50 ppm	In both studies observed in the exposed groups. In

symptomatology and than 10 years was worse in paired psychiatric state test. After accounting for other Neuropsychological test influences on performance, significant effect battery for intellectual functions and perceptual speed remained only for the subgroups exposed that the investigation provided some effects on cognitive functioning after exposure.	matched controls Study group 2: 144 solvent-exposed brush painters, spray painters, printers and others 144 unexposed age-matched controls	for 2 days a week. Study 2: Exposure more diverse because of the inclusion of several different occupations. Both groups divided into four subgroups of exposure duration: < 10 years; 10-20 years; 21-30 years; > 30 years.	exposed for more associate learning possible from exposure for more than 30 It was concluded evidence for long-term solvent
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Table 16 (Con't)

Reference/type of study ^b	Groups studied	Exposure ^c	Results
Hooisma et al. (1993a) Cross-sectional study Neuropsychological test the test scores for immediate battery (8 WHO core tests and 14 computerized tests) related to nonprotected spray painting in and the time spent in painting during For the older painters the test motor performance and memory were	47 young painters (30-40 years old) 45 older painters (55-72 years old) 53 young controls (30-40 years old) 43 older controls	Cumulative solvent consumptions of young and older painters were 11.5 (l/d)years and 23.1 (l/d) years, respectively, with daily average consumptions of 0.8 and 0.7 l/d.	No consistent young and old For young painters memory were the last 5 years the last 5 years. scores for visuo-

(55-72 years old)
time spent in painting during the last
total number of prenarcotic episodes,
However, these isolated findings were
inconsistent.

related to the
5 years and the
respectively.
found to be

Hooisma et al. (1993b) 120 young painters
painters experienced significantly
Cross-sectional study (30-40 years old)
21/43 and 18/43 questions
Questionnaire containing 169 young controls
symptoms. In no cases did the controls
43 questions regarding (30-40 years old)
significantly more complaints. The two
subjective symptoms and 127 older painters
more complaints concerning core
9 questions regarding (55-72 years old)
relation to solvent exposure such as
personality 157 older controls
memory and impaired concentration.
(55-72 years old)
appeared to be related to periods of
rather than to other exposure
significant differences were observed in
concerning personality.

Paint solvent exposure.
Individual data collected
on: total hours of painting
or spray-painting, hours
of non-protected spray-
painting, numbers of
prenarcotic episodes.

Younger and older
more complaints in
concerning
experience
exposed groups had
symptoms in
fatigability, bad
The symptoms
heavy exposure
measures. No
questions

Table 16 (Con't)

Reference/type of study ^b	Groups studied	Exposure ^c	Results
Bolla et al. (1995); the exposed group was worse in 14	144 workers from two	At both plants aliphatic	The performance of

Ford et al. (1991)	paint manufacturing	hydrocarbon mixtures	out of 15 test
parameters. Significantly impaired			
Cross-sectional study	plants (from same	(white spirits), toluene	performance was
noted in 5 tests for motor function			
Neuropsychological	exposure group as	and xylene were the three	and manual
dexterity. In 10 out of the 15 tests there			
test battery	Bolla et al. (1990)	most widely used solvents.	was a positive
trend between impaired performance and	and Bleecker et al.	Cumulative hydrocarbon	duration of
exposure (for 3 tests $p < 0.05$). The	(1991))	exposure: 180 ppm x years	scorings were
adjusted for the cofactors age,		and 97 ppm x years at the	vocabulary and
race.			
	52 unexposed	two plants. Lifetime-	
	workers	weighted average exposure	
		were 11.7 ppm and 7.6 ppm,	
		respectively.	

^a This table includes those studies in which exposure was predominantly to white spirit, i.e. the exposure has been verified in the text

or the study group is an occupational group known to be predominantly exposed to white spirit.

^b AEP = auditory evoked potential; CBF = cerebral blood flow; CT = computerized tomography; EEG: electroencephalography;

EMG = electromyography; ENG = electroneurography; NCV = nerve conduction velocity; VER = visual evoked responses

^c Mexp.: mean exposure period

Table 17. Epidemiological studies on workers exposed to white spirit^a

Reference/type of study ^b	Groups studied	Exposure ^c	Results
Lindström (1973)	42 solvent exposed	Mixed solvent exposure,	The performance of
the exposed groups was			
Cross-sectional study	workers (including 11	including paint solvents.	significantly
worse in all of 5 psychomotor			
Neuropsychological testing	spray-painters) with	Mexp. 6 years for both	functioning tests,
in 3 out of 4 tests for vigilance			

for intelligence, dexterity, and in 1 out of 3 intelligence personality, psychomotor performance of the subgroup of workers function, vigilance and poisoning was significantly worse than dexterity exposed workers.	symptoms of suspected solvent poisoning, 126 solvent exposed workers (including 40 spraypainters) 50 unexposed controls	groups.	and manual tests. The with suspected that of the other
Axelsson et al. (1976a) 1.8 (p < 0.05) was calculated Case-control study exposed workers for being awarded Data collected from because of chronic neuropsychiatric disability pension to workers without solvent register files	151 persons awarded pensions because of chronic nonspecific neuropsychiatric disorders 248 persons awarded pensions because of other, non-mental causes	Selected occupations with solvent exposure: painters, varnishers and carpet-layers. Main exposure: white spirit and other aliphatic and aromatic solvents. Mexp. 14.2 years.	A relative risk of for solvent-disability pension disorders compared exposure.
Lajer (1976) increased number of painters with Cross-sectional study suffered from 4.1 symptoms per Questionnaire electricians 0.9. The painters more often concerning symptoms irritation, reduced sense of taste headache, nausea, vertigo, fatigue, of intoxication.	44 solvent exposed painters 38 unexposed electricians	Paint solvents, including white spirit. Exposed for 1-45 years. Exposed on the day of questioning.	Significantly symptoms. Painters person, complained of eye and appetite, and of sensations

Table 17. (Con't)

Reference/type of study ^b	Groups studied	Exposure ^c	Results
Elofsson et al. (1980) of neurological and psychiatric Cross-sectional study complaints in the group of painters. Medical and psychiatric significantly impaired performance in tests examinations reaction time, manual dexterity, Neurological examinations and memory. Reduced nerve conduction (EEG, VER, NCV, CT) lowered nerve action potentials were Neuropsychological test between degree of exposure and battery (18 tests - was not demonstrated (exposure was representing a range of to age, and age to some degree to different mental functioning)	80 spray painters 2 × 80 referents from electronic industry	Mixed solvent exposure. Levels of about 100 mg/m ³ were measured. Exposure ranked according to years and intensity of exposure. (Exposure-free period of 18-24 h before the examinations).	Higher frequency symptoms and Further concerning simple perceptual speed velocity and found. Correlation extent of effects highly correlated performance).
Lindström (1980) reduced scoring of the exposed group in Cross-sectional study parameters. Most pronounced was Neuropsychological testing visuomotor performances (symmetry drawing, (11 tests for intelligence decreased freedom from distractibility and psychomotor tests significant correlation was functioning) reduced score and exposure duration. exposure level was found.	56 solvent exposed workers (26 painters) diagnosed with solvent induced occupational disease 43 unexposed construction workers	Mixed solvent exposure. Main exposures: paint solvent (n=21), aromatic and aliphatic hydrocarbons (n=13), halogenated hydrocarbons (n=21). Exposure graded roughly into low (n=3), intermediate (n=26) and high (n=27)	Significantly 6 out of 14 test decline in Mira test) and (digit span). In 2 found between the No correlation to

Olson (1982) impaired performance of the exposed Cross-sectional study determining simple reaction time and Questionnaire The performance of the exposed Neuropsychological tests in the afternoon compared to the (4 tests performed before performance of the most heavily and after a working day) than that of long-term exposed that symptoms were mainly due to exposure.	47 solvent exposed workers from the paint industry 47 unexposed workers	exposure levels. Mexp. 9.1 years	
		Mixed solvent exposure. Mexp. 24.1 years (n=38). Mexp. 4.3 years (n=9, but more heavily exposed). 18 definitely exposed to white spirit at a mean level of 44 mg/m ³ .	Significantly workers in tests perceptual speed. workers was worse morning test. The exposed was worse workers, indicating acute solvent

Table 17. (Con't)

Reference/type of study ^b	Groups studied	Exposure ^c	Results
Lindström et al. (1984) 5.5 (p < 0.05) was calculated for Case-control study workers for being awarded disability Disability pension, data neurosis (a diagnostic group from register file neurosis, persona pathologica, psychosomatic nervositas) compared to workers not exposed	374 construction workers awarded pensions because of neuropsychiatric disorders 374 construction workers awarded pension because of other reasons	Painters and carpet- layers were chosen as selected occupations with solvent exposure. No specific exposure information.	An odds ratio of solvent-exposed pension because of including disease, to solvents.

Valciukas et al. (1985) 55 shipyard
 significantly impaired in 2 out of
 Cross-sectional study painters
 neuropsychological tests. Significantly
 Questionnaire 55 non-exposed
 prevalence of acute symptoms in painters.
 3 neuropsychological tests controls
 were found in chronic symptoms.
 for perceptual functions
 found between duration of exposure
 symptoms.

Oerbaek et al. (1985) 50 solvent exposed
 higher scores in the solvent-exposed
 Cross-sectional study workers from the
 60 questioned symptoms. Subjects
 Clinical examination painting industry
 exposure indices were the most
 Questionnaire of 60 50 unexposed sugar
 Significant changes in EEG measurements and
 symptoms refinery workers
 regional cerebral bloodflow was observed
 Neuropsychological test
 group. Further, an overall tendency
 battery (9 tests for
 performance in the neuropsychological
 intellectual functions and
 in the exposed group. Analysis of
 psychomotor performance)
 scores recalled that 7 of the exposed
 Neurophysiological
 pathological brain dysfunction.
 examination (EEG, CBF, NCV)

Wide variety of solvents
 including white spirit. 95%
 of the painters exposed
 > 10 years. The painters
 divided into 5 subgroups
 according to exposure
 duration.

Mixed solvent exposure.
 Exposure indices were
 calculated on the basis of
 intensity and duration of
 exposure. Mexp. 18 years.
 One group of 4 subjects
 had only been exposed
 to white spirit.

The painters were
 the 3
 increased
 No differences
 No correlation was
 and test scores or
 duration.
 Significantly
 group in 15 of the
 with the higher
 affected.
 decrease in
 in the exposed
 towards impaired
 testing was noted
 individual test
 workers had

Table 17. (Con't)

Reference/type of study ^b	Groups studied	Exposure ^c	Results
Linz et al. (1986) Cross-sectional study Questionnaire Neuropsychological test Neurophysiological NCV)	15 solvent exposed industrial painters referred to an occupational health clinic. 30 workers with no or minor exposure to solvents.	Mixed solvent exposure from paint solvent. Mexp. 8.8 years. No-one exposed during the last 2 months before examination.	The group of neurasthenic and personality poor short-term an array of 30 test parameters normal average (EMG + NCV) 7 painters.
Askergren et al. (1988) Cross-sectional study Questionnaire Neurophysiological examinations (ENG, AEP, vibration threshold) proteinuria and altered haematological found in both painter groups. effects of mixed exposure from water-based paints were found.	39 house painters (group I) 40 house painters (group II) 44 bricklayers (group III)	Group I and II exposed to solvent-based paint for 22% and 42% of the total painting time in the latest year, and to water-based paint for 72% and 57% of the time. Mexp: 22.3 years (group I) and 21.2 years (group II). Very low exposure levels were measured.	Groups II and III as impaired problems (group consumption than signs of ENG measures). Furthermore, parameters were Overall, only mild solvent-based and

Triebig et al. (1988) higher degree of "change in Cross-sectional study registered in one test in the painter Questionnaire short-term memory was found in a Neurophysiological painter subgroup. No other noteworthy examinations (CT, EEG, NCV) made in other tests or examinations. Neuropsychological test battery assessing intellectual functions	86 house painters 39 matched controls	Mixed solvent exposures from paint solvents. Measurements of daily exposure level on different paint solvents (white spirit not included in the measurements). Exposure indices were calculated on the basis of time spent	A significantly personality" was group. Impaired highly exposed observations were
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Table 17. (Con't)

Reference/type of study ^b	Groups studied	Exposure ^c	Results
van Vliet et al. (1989a) 0.05) for the exposed group with Cross-sectional study prenarcotic symptoms such as nausea, Questionnaire (questions breath and loss of appetite. The about solvent exposure, symptoms was correlated to the prenarcotic (acute) and exposure but not to exposure duration. neurasthenic (chronic) association between the occurrence of symptoms) symptoms and solvent exposure.	379 solvent-exposed workers (painters, carpet-layers and road-markers) 443 workers not exposed to solvents	each day by painting with solvent-based paints. Mexp. 24 years. Mixed solvent exposure. Exposure indices were calculated on the basis of either exposure intensity or duration.	RR = 1.7-3.5 (p < respect to shortness of of the prenarcotic intensity of Only weak neurasthenic

van Vliet et al. (1989b); for relevant confounders) of 2.3 van Vliet et al. (1990) found for association between solvent Case-control study pension due to neurotic disorders (based Questionnaire concerning cases). The OR was not significantly solvent exposure association between exposure and disturbances, single or combined. painters a significant dose-response found (disability pension vs. exposure intensity). Only a weak found with exposure duration. 1.7 and 2.6 were found for painters with paint rolling or spraying for more week.	252 persons awarded disability pensions because of mental disorder 822 workers chosen randomly as control All subjects were members of either the painter or the construction worker organization	Approximately 46% in each group exposed to solvents (painters, carpet-layers, and road-markers). Painters exposed to C8-C11 alkanes and C7-C10 aromatics. Exposure indices were calculated on the basis of exposure intensity or duration. Mexp. (cases) 20.6 years. Mexp. (controls) 15.6 years.	An OR (corrected (P < 0.05) was exposure and on 76 exposed increased for the other mental However, among association was increasing association was Increased OR of who had worked than one day each
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Table 17. (Con't)

Reference/type of study ^b	Groups studied	Exposure ^c	Results
Spurgeon et al. (1994) cognitive functions or mental health Glass et al. (1994) group of paint-makers. Cross-sectional study	110 paint-makers from two paint production plants	Many different paint solvents used. White spirit use largely reduced since	No effects on were found in the

Neuropsychological test battery	110 age-matched controls	1976 and 1982 at the two plants. Exposure individually described in relation to mean ppm level and to the cumulative dose ppm x year. 26 workers exposed to mean levels above 40 ppm and 25 workers exposed to more than 600 ppm x years.
Questionnaire concerning mental health status		

^a This table includes studies in which the white spirit exposure is not defined with the same degree of certainty as in

Table 16 or is part of a more complex exposure.

^b AEP = auditory evoked potential; CBF = cerebral blood flow; CT = computerized tomography; EEG = electroencephalography;

EMG = electromyography; ENG = electroneurography; NCV = nerve conduction velocity; VER = visual evoked responses

^c Mexp.: mean exposure period

so-called "healthy worker effect" may be expected to dilute effects from exposure and thus tend to bias the results towards a no-observable effect. On the other hand, an overestimation of the neurotoxicity of white spirit may result from case-studies if a primary connection between adverse effects and exposure to white spirit is made without consideration being given to other potential causal factors.

In a report from the Commission of the European Communities on long-term neurotoxic effects in painters, one of the major limitations was found to be the lack of exact knowledge about exposure levels and the nature of exposure (CEC, 1990). Although white spirit is the most frequently used paint solvent, additional solvents such as other aliphatic or aromatic hydrocarbon thinners, glycol ethers, secondary and tertiary alcohols, esters and ketones are also used in considerable amounts. Furthermore, painters may be exposed to various kinds of dust. Dust from old paint layers may contain lead because of the previous use of lead-containing colour pigments.

However, some of the studies mentioned in Table 16 contain more specific exposure information (duration and exposure levels) with

respect to white spirit (Seppäläinen & Lindström, 1982; Lindström & Wickström, 1983; Mikkelsen et al., 1988; Spurgeon et al., 1990, 1992; Bazylewicz-Walczak et al., 1990). In these studies, together with the studies by Blume et al. (1975) and Hane et al. (1977), the most predominant solvent exposure is to white spirit.

Mikkelsen et al. (1988) critically reviewed the literature and presented several items that could bias the studies. The "healthy worker effect" may be present in all cross-sectional studies conducted with active workers. Recent solvent exposure, which has occurred to a varying degree in most of the studies, makes it impossible to determine whether impaired performance in neuropsychological testing was caused by acute or chronic effects on the CNS. Thus, acute effects caused by recent solvent exposure may lead to an overestimation of the chronic effects on the one hand, or alternatively they may mask an underlying chronic dose-response relationship.

In several studies, the absence of any observed toxicity resulting from chronic exposure may be due to the relatively low exposure levels in the study groups. Further attention should be paid to the fact that the occupational level of solvent vapour has been reduced in the past decade. Another factor is a short exposure period, since an exposure period of 10 years or more is, according to some authors, considered to be a minimum for induction of chronic CNS effects. To overcome some of these problems, it was concluded that the likelihood of observing positive findings would increase if the workers were consistently divided into different graded exposure groups.

Another crucial point mentioned by Mikkelsen et al. (1988) is the selection of a proper control group. The intellectual level in this group should ideally match the pre-exposure intellectual level in the group of interest, e.g., painters. Although very careful selection and matching have been made according to possible cofactors such as age and educational, cultural and social backgrounds, and no overt differences exist in life-style or in use of drugs or alcohol, this still does not guarantee that the individuals from the control group and the group of interest were comparable with respect to the pre-exposure intellectual level. However, if some of the above-mentioned covariates can be identified, it may be possible to

compensate for the influence from them by the use of statistical methods such as multiple regression analysis. Pre-exposure intellectual level could also be validated if previous military intelligence tests were made available or by the use of "hold tests", which are intelligence tests for abilities that are thought not to be influenced by solvent toxicity or minor brain dysfunctions (e.g., tests for cognitive verbal ability, see section 8.2.1.3).

Thus, Mikkelsen et al. (1988) concluded that hidden differences may very well occur between unexposed and exposed groups due to the difficulties in overcoming these problems. However, false dose-response relationships are very unlikely to occur when the workers have been stratified according to different exposure groups, and therefore a positive dose-response association should be taken as very strong evidence for real differences between groups.

Dose-response relationships for different end-points have been demonstrated in some of the studies shown in Tables 16 and 17. In these studies, exposure was graded into different subgroups (Mikkelsen et al., 1988; Bazylewicz-Walczak et al., 1990; Bleecker et al., 1991; Bolla et al., 1995) or individual exposure indices were estimated (Fidler et al., 1987; van Vliet et al., 1989a,b).

8.2.1.6 Prognosis and follow-up

Agrell et al. (1980) made a 5-year follow-up on the population (52 house painters and 52 unexposed controls) described by Blume et al. (1975) and Hane et al. (1977) (Table 16). Of the 52 age-matched pairs, 42 answered a mailed questionnaire concerning subjective symptoms. After the 5-year period there was a significant increase in the symptoms reported by the painters with respect to irritability, impaired memory and depression, whereas the symptoms reported by the controls had not changed. Four of the painters had changed occupation to non-exposed jobs and 11 painters were receiving disability pension.

Bruhn et al. (1981) performed a 2-year follow-up study on 26 of the 50 patients (previously occupied as house painters) who were initially examined by Arlien-Soeborg et al. (1979) (Table 15). After the 2-year follow-up period, most of the subjective symptoms were

present to a similar degree. However, considerable improvements were

noted with respect to headache, dizziness, and irritability. On a group basis, no significant changes were noted after re-examination for neurological status, neuropsychological impairment (a battery of seven tests) and cerebral atrophy (CT scanning). At the individual level, the performance of two patients was significantly worse in the neuropsychological tests, and in two patients cerebral atrophy had progressed. At the time of the follow-up, 16 patients received disability pensions and two patients were recommended for this.

Lauritsen et al. (1985) re-examined 69 out of 77 solvent-exposed workers (41 of these were painters) after a 3-year follow-up period. In exposed workers without encephalopathy, the number of symptoms was found to have diminished while patients with diagnosed toxic encephalopathy showed unchanged conditions or slight deterioration (all workers were questioned about 12 different symptoms). No significant difference was found in intellectual functioning following neuropsychological retesting (battery of five tests). Of the 69 workers, 29 were still occupationally active (type of work not specified), but 42 received disability pension and/or other compensation because of work-related sequelae.

In a 5-year follow-up study, Gregersen et al. (1987) described the social consequences for 21 painters who had been diagnosed with chronic toxic encephalopathy. The diagnosis was based on detailed clinical examinations, including interviews about exposure (levels and duration) and subjective symptoms, neuropsychological testing, and neurological and neurophysiological examinations. At the time of diagnosis all the painters had given up their job and five years later 11 worked in other jobs while 10 were receiving the highest disability pension. Clear differences were noted between those who were still working and those who were awarded a pension. The former group were considerably younger, had a history of lower exposure and were less impaired in their intellectual functioning.

Edling et al. (1990) examined 102 out of 111 solvent-exposed workers after a follow-up period of 6.7 years. All the workers (of whom 71 were painters) were at the time of the initial examination referred to a medical clinic. Forty-six were at that time diagnosed as having mild toxic encephalopathy (MTE, defined as neuropsychiatric symptoms plus mental impairment as shown by neuropsychological testing) while 65 subjects exhibited the neuropsychiatric symptoms but

without additional mental impairment. The two groups were comparable with respect to age (mean age 56 and 53 years, respectively) and exposure duration (26 and 23 years, respectively). At the time of follow-up, more people in the MTE group had stopped working (74 compared with 35%) and were receiving disability or early retirement pensions. At re-examination the MTE group had deteriorated with respect to depression, concentration difficulties and lack of initiative, while improvements were seen in the non-MTE group. In a

neuropsychological test battery, the differences in performance between the two groups persisted from the initial to the follow-up examination. The only deterioration noted was poorer performance of the MTE group in two hold-tests (tests in which performance is not supposed to be affected by solvent exposure). In a reclassification of these workers, 12 from the MTE group were diagnosed as belonging to the non-MTE group, while three from the non-MTE group were diagnosed as having MTE. As an explanation for this, the authors suggested that acute effects from exposure just prior to the initial examination could have led to some workers being incorrectly assigned to the MTE group. It was concluded that solvent-induced effects on the CNS persist even after exposure had ceased. However, people with neuropsychiatric symptoms but without impairment of mental function may in many cases recover after removal from exposure. (The authors found that some bias was possible because of the lower frequency of employment in the MTE group).

Oerbaek et al. (1986) and Oerbaek & Lindgren (1988) conducted a follow-up study with 32 workers (25 painters) previously diagnosed with solvent-induced chronic toxic encephalopathy. After 21-88 months without exposure, the workers were retested with the neuropsychological tests conducted at the time of the diagnosis. Significant improvement was seen in a test for visual perception whereas impairment was found in tests for verbal memory and simple reaction time. Improvement was reported in subjective symptoms, especially with respect to irritability, headache and dizziness, whereas impairment was noted with respect to short-term memory, peripheral sensory perception and anxiety. In conclusion, impaired intellectual function was judged to be permanently affected, since no firm conclusion could be drawn with respect to overall improvement/impairment in the exposure-free period.

The overall picture of the follow-up studies is that symptoms improve, particularly in younger subjects having normal test results, but are still partially present after cessation of exposure. The abnormal neuropsychological findings remain unchanged, thus suggesting that the brain disorder is neither fully nor partially reversible.

8.2.2 Effects on skin

From a questionnaire study it appears that white spirit (18% aromatics) may give rise to skin disorders of the hands consisting of dry and rough skin surface with small fissures. This was reported by 11% in a group of 148 people with dermal exposure to white spirit, compared to 4% in an unexposed group of 71 people. A dose-response relationship was observed, since heavily exposed workers (exposure > 4 h/day) more often reported these effects (Björn et al., 1983).

Among 98 American railroad workers suffering from occupational dermatitis, a connection between the disease and the use of kerosene and white spirit was found in 10 cases. Six of these cases were identified by the use of patch testing in combination with exposure data, while four cases were identified solely on the basis of the history of exposure (Kaplan & Zeligman, 1962).

8.2.3 Effects on kidneys

There have been few human studies on the nephrotoxicity of white spirit. However, there have been several studies and case reports on renal disease and dysfunction among workers exposed to paints and mixed solvents.

Table 18 shows a series of case reports of glomerulonephritis with exposure to white spirits and paint solvents.

Ravnskov (1978) reported eight cases in which exposure to organic paint solvent was apparently involved in the development of post-streptococcal glomerulonephritis. In three of the cases the exposure had lasted for a long time (occupational exposure), whereas for the remaining five patients it was of shorter duration (exposure from home painting). In all cases the subjects had suffered from respiratory tract infections around the time of the exposure. The

glomerulonephritis and the nephrotic syndrome developed within one day to a few weeks after exposure/infection.

In an evaluation of case-studies concerning the development of glomerulonephritis after solvent exposure, Churchill et al. (1983) reported one case in which white spirit was involved. In an additional 16 cases the exposures were from other related hydrocarbon mixtures. The actual case described in more detail by D'Apice et al. (1978) involved a pair of 16-year-old identical twin sisters who within a period of 6 weeks developed Goodpasture's Syndrome (syndrome with acute antibody-mediated glomerulonephritis). One sister developed the syndrome after 5 days at a job in which she sprayed ball-bearings with white spirit. The other sister developed this very serious syndrome after selling petrol (gasoline) for 2 weeks. The author assumed that hydrocarbon exposure may in some cases be a cofactor in the development of the syndrome.

Daniell et al. (1988) reported the case of a 29-year-old man who developed renal failure after one year of floor cleaning with white spirit (Stoddard solvent) (often for 6 h each day without using any kind of protective equipment). Renal biopsy revealed diffuse glomerulonephritis and focal necrosis. Findings from radioimmunoassay for antibodies towards anti-glomerular basement membrane (anti-BGM) were strongly positive. The patient often experienced a feeling of getting "high" during the working day.

Table 18. Case series of glomerulonephritis and exposure to white spirit and paint solvent

Exposure Reference	Subjects			Ages	Diagnosis ^a
	Males	Females	Total		
Paint solvents	5	0	5	19, 21, 22	Goodpasture's syndrome
Beirne & Brennan (1972)					
jet fuel	1	0	1	28, 32, 44	Rapidly progressive GN
Stoddard solvent	1	0	1	29	Anti-GBM nephritis
Daniell et al. (1988)					

Paint solvent von Scheele et al. (1976)	1	0	1	59	Subacute GN
Paint solvent Ravnskov (1978)	7	1	8	10, 10, 15, 36, 41, 45, 51, 55	Post-streptococcal GN Nephrotic syndrome
White spirit D'Apice et al. (1978)	0	1	1	16	Goodpasture's syndrome

^a GN = glomerulonephritis

Harrington et al. (1989) studied 50 cases of biopsy-proven glomerulonephritis and 50 community-based healthy referents matched for age, sex, place of residence and socio-economic and ethnic groupings. Fifteen of the cases had a history of workplace exposure to paints and varnishes compared to 11 of the controls (OR:1.4).

Yaqoob et al. (1992) assessed the exposure history of 55 patients with end-stage renal failure due to biopsy-proven primary glomerulonephritis. The 55 patients were divided into two groups based on duration and intensity of exposure. The intensity of exposure was divided as follows:

1. heavy intensity (factor of 2): e.g., occupational house painting indoors; industrial spray painting without protection; carpet cleaning and floor-covering agents; production of paint and glue;
2. moderate intensity (factor of 1): e.g., non-occupational house painting indoors; spray-painting with protection devices; industrial degreasing of metal; printing work, dry cleaning;
3. low intensity (factor of 0.5): e.g., outdoor painting, motor repairs (Bell et al., 1985).

Those with heavy exposure were shown to have higher serum creatinine despite similar degrees of proteinuria and proportion of hypertensives. This suggests that those with greater hydrocarbon exposure had more advanced disease. The authors further compared the hydrocarbon exposure score of the 55 patients with 55 normal controls

matched for age, sex, social class and residential status. The hydrocarbon exposure score was significantly higher among the patients. When compared to a third control group of 45 patients with end-stage renal failure secondary to other diseases, the hydrocarbon exposure scores were again significantly higher in the patients with primary glomerulonephritis.

In another case-referent study (Porro et al., 1992), 60 patients with primary glomerulonephritis were compared with 120 controls matched by sex and age. Intensity of solvent exposure was evaluated using criteria similar to those of Yaqoob et al. (1992). The OR was 5.42 (95% CI 2.01-14.59) in the high exposure group and 2.12 (95% CI 0.81-5.57) in the lower exposure group. A test for linear trend was statistically significant.

While the evidence for solvent-induced glomerulonephritis in humans is at best circumstantial, the hypothesis remains credible and consistent with current concepts of immunologically mediated glomerular diseases. Alterations in the glomerular basement membrane by solvents may render them antigenic. Alternatively, impairment of the immune system by solvents may suppress self-recognition and permit antibody production against unaltered tissue components (Wilson & Dixon, 1986; Yamamoto & Wilson, 1987).

Most of the studies using biomarkers of nephrotoxicity involved mixed solvent exposure. In only one study (Lauwerys et al., 1985) was white spirit specifically mentioned. However, studies on painters and paint manufacturing workers will be of relevance in this report.

In a review article Lauwerys et al. (1985) reported the results of an unpublished study on 33 workers in the metallurgical industry. The workers had been exposed to an estimated mean white spirit vapour concentration of 93.6 mg/m³ (15.6 ppm) for an average of 8.5 years. However, no indication of altered kidney function was found from measurements of urinary β_2 -microglobulin, retinol-binding protein and albumin. Similar examinations performed on 43 car painters mainly exposed to white spirit and toluene (exposure duration, 6-36 years; average levels of 43.8 mg/m³ (7.3 ppm) white spirit and 7.9 mg/m³ (2.1 ppm) toluene) yielded negative results as well.

The most extensive study on paint manufacturing workers was

conducted by Normand et al. (1990); 420 workers were studied. The exposure consisted of a complex mixture with 124 mg/m³ (33 ppm) of toluene and concentrations of other organic solvents less than 10% of the threshold limit value (time-weighted average). The potential influence of lead and cadmium pigments was assessed through biological monitoring. Exposed groups had higher mean microalbuminuria as well as higher prevalence of elevated microalbuminuria. Similar results were found in 40 paint manufacturing workers by Askergren et al. (1981).

In studies by Ng et al. (1990) and Franchini et al. (1983) on 45 paint manufacturing workers and 118 painters, respectively, no difference in the albumin excretion was found but the range was higher in the exposed groups.

Hotz et al. (1989) used a similar hydrocarbon exposure score to Yaqoob et al. (1992) on a group of 148 workers. The results suggest that *N*-acetyl-glucosaminidase activity and erythrocyturia is associated with hydrocarbon exposure.

Yaqoob et al. (1993a,b) evaluated the glomerular and tubular markers of 112 paint sprayers with exposure to paint-based mixtures of hydrocarbons. They had significantly higher prevalence of elevated serum creatinine, abnormal urinary total protein, and *N*-acetyl-glucosaminidase, gamma-glutamyl transferase and leucine-aminopeptidase excretion.

Stevenson et al. (1995) found higher levels of serum laminin and soluble E-selectin in a group of 111 workers exposed to paint-based hydrocarbons. Serum laminin is a basement membrane turnover marker and E-selectin an endothelial activation marker. These elevations suggest alterations to the basement membranes and overlying vascular endothelial cells resulting in auto-antibody production.

The long-term significance of these early markers of nephrotoxicity has often been questioned. However, the elevation of these markers lends support to the hypothesis that painters are at higher risk of developing nephropathy, presumably from hydrocarbon exposure.

8.2.4 Effects on liver, blood and bone marrow

Braunstein & Schenectady (1940) reported a case in which a previously healthy 26-year-old man developed swelling of the liver and jaundice. The man worked at a dry cleaning factory and had been exposed to white spirit (Stoddard solvent) for a period of 3 months (heavy skin and inhalation exposure). In addition to the liver effects, symptoms and diseases, such as muscular weakness, dermatitis of the hands, anaemia, gastrointestinal disorders, blood in the stools, albuminuria and glucosuria, were described. After hospitalization and removal from exposure, complete recovery took place.

In another case a 41-year-old man working as a heavy equipment mechanic was exposed frequently for 16 years to white spirit (Stoddard solvent). He developed diffuse petechia, anaemia and depression of all cellular components of the bone marrow. The patient died 11 months later, the diagnosis being aplastic anaemia (Prager & Peters, 1970). Other cases in which white spirit (Stoddard solvent) was considered the cause of lethal or non-lethal aplastic anaemia have been described (Kegels, 1958; Scott et al., 1959).

Liver damage, revealed by histological findings (steatosis and fibrosis) and by elevated serum transferase activity, was recorded in 13 out of 156 patients who were admitted to hospital because of suspected long-term solvent intoxication. No other factors (e.g., alcohol abuse, exposure to known hepatotoxic agents such as pesticides, drugs) could explain the findings. Ten of the 13 patients were house painters and had for a period of 6-39 years been exposed to vapour from paint solvents. Liver biopsies were repeated after 4-37 months in three of the workers. The histological findings were unchanged, although the workers had stopped working with solvents (Doessing et al., 1983).

8.2.5 Haematological and biochemical effects

Appraisal

There have been few reports on the haematological and biochemical effects of white spirit. However, clinical studies have revealed decreased erythrocyte, leukocyte and platelet counts, and increased mean corpuscular volume in exposed workers. Similar

haematological changes have been observed in animal studies. There are no consistent serum biochemical changes; reduced aspartate

aminotransferase and lactate dehydrogenase activities and elevated creatinine kinase activity have been observed.

Hane et al. (1977) determined a significantly lower mean concentration of haemoglobin in a solvent-exposed group (n=52) compared to controls (n=52) (Table 16). Sedimentation rate and serum transaminase activities were unaffected.

In a cross-sectional study, Elofsson et al. (1980) determined haematological parameters in 80 spray painters (Table 17). The group mean values were all within normal limits. Compared to two reference groups, however, significantly higher values were found in the exposed group with respect to haemoglobin, haematocrit, erythrocyte numbers and alkaline phosphatase activities.

Oerbaek et al. (1985) carried out measurements of haematological and biochemical parameters in a group of 50 solvent-exposed workers from the painting industry and in a reference group (Table 17). Significant differences were found for several parameters (lowered platelet counts, altered leukocyte differential counts, reduced lactate dehydrogenase activity and increased aspartate aminotransferase activity). However, no consistency was found in these differences as an exposure-effect relationship could not be demonstrated. The authors concluded that significant alterations in haematological and biochemical parameters may only occur with exposure to very high levels of organic solvents.

Pedersen & Rasmussen (1982) analysed 21 haematological and biochemical parameters in 122 male patients referred to a medical clinic because of a suspected solvent poisoning syndrome. From a detailed description of exposure, white spirit turned out to be one of the dominant agents for 55 construction painters and 18 printers. The only significantly affected parameters were lowered leukocyte counts, lowered serum creatinine level and, in recently exposed workers, increased serum creatine kinase activity. These findings were not considered to be substantial enough to provide evidence for some solvent-induced effects, basically due to the limitations of the comparison of exposed hospital out-patients with a control group of

non-exposed hospital in-patients. In an earlier study, Pedersen et al. (1980) found an increase in the serum creatine kinase activity in a group of 69 solvent-exposed workers. This increase was assumed to be an early sign of solvent-induced myopathy.

In a clinical study, seven volunteers (students) were exposed to 600 mg/m³ (100 ppm) of white spirit (99% aliphatic alkanes), 6 h/day for 5 days. After the exposures the serum creatine kinase activity had increased to 76% above the pre-exposure level, and serum follicle stimulating hormone (FSH) had significantly decreased to 9% below the initial level. No changes were found in plasma immunoglobulins (Pedersen & Cohr, 1984b).

Beving et al. (1983) determined the level of platelets in the blood from 12 car painters exposed to solvents (mainly white spirit and methyl- *n*-butyl-ketone) and organic isocyanates. The mean level of platelets was significantly reduced compared to that of 50 unexposed subjects (150×10^9 and 220×10^9 platelets/litre, respectively), while the serotonin uptake rate in the platelets was significantly increased.

Beving et al. (1988) examined the fatty acid composition in platelets from 12 workers exposed to paint solvents (consisting of 70% white spirit and 30% aromatic hydrocarbons and various acid esters). A minor but significant shift towards a higher proportion of saturated fatty acids and a lower proportion of unsaturated fatty acids in the phospholipid fraction of the platelets was found in the exposed group, compared to a group of 12 subjects. The authors suggested that this may reflect similar changes in other membranes, e.g., in the CNS neurons.

Significantly decreased erythrocyte count and increased erythrocyte volume, compared to controls, were observed in a group of 17 car repair painters (as well as in a group of 28 car mechanics) frequently exposed to white spirit and other paint solvents (Beving et al., 1991).

8.3 Reproductive toxicity

Appraisal

There have been several reports on the effect of solvents on reproductive function. However, no distinction has generally been made between the types of solvent, as to whether they are chlorinated hydrocarbons or oxygenated solvents. It should be noted that low molecular weight glycol ethers have been used in solvents which are developmental and reproductive toxins. It is not always clear which solvents are used or the extent of exposure.

Using questionnaires Holmberg & Nurminen (1980) examined occupational exposure of 120 case mothers who had given birth to children with congenital CNS defects (anencephaly, hydrocephaly, spina bifida, microcephaly and other anomalies) and of 120 referent mothers who had normal children. Case mothers were found to be more frequently exposed to organic solvents during the first trimester of the pregnancy than referent mothers (rate ratio estimate $RR = 5.5$, $p < 0.025$). A total of 12 case mothers had been exposed to solvents and four of these to white spirit (two in combination with other solvents).

In a study by Peters et al. (1981), 92 cases of brain tumour in children less than 10 years old were compared with 92 matched controls for parental occupational history. A relative risk of 2.8 ($p=0.02$)

was calculated for fathers being exposed to solvents and a relative risk of 7.0 ($p=0.04$) was found for exposure to paint solvents in particular (seven case fathers and one referent father).

In a similar study concerning 948 children with cancer (282 cases of tumours), an increased odds ratio of 5.00 ($p < 0.05$) was calculated for the connection between brain tumour of the child and the father's occupation as a painter (based on seven cases with the father employed as a painter) (Hemminki et al., 1981). Similar findings were also reported in a study by Olsen (1983), who emphasized that until further data were available the relationship between childhood brain tumour and paternal occupation as a painter should be considered purely hypothetical.

In another case-control study, 388 mothers of children born with oral clefts were matched to 388 mothers of children without anomalies. By interviewing the mothers about their occupational and domestic work and chemical exposure during the pregnancy it was found that 14 of the

cases, as opposed to 4 of the controls ($p < 0.05$), had been exposed to organic solvents in the first trimester. Ten of the cases had been exposed to hydrocarbon products of the white spirit type (six of these as the only exposure). Two of the referents had been exposed to this kind of solvent. The women were only considered as exposed if their average exposure level was estimated to exceed one third of the current threshold limit value (TLV) for the solvent, or if the exposure data indicated peak levels reaching or exceeding the TLV (Holmberg et al., 1982).

Mikkelsen et al. (1983) collected reproduction data by combining data registers from trade unions and public register files concerning birth, death and cancer. The study included 11 543 men from the painters union and 21 421 men from the electrician union. No differences were found between the groups with respect to reproductive parameters such as the risk of having children with congenital malformations, the female/male sex-ratio and infant mortality. Minor (not significant) differences were observed with respect to slightly reduced birth weight and size of the children of the painters, and a slightly increased frequency of childhood cancer. However no firm conclusions could be drawn from these findings.

Similar trends towards lowered birth weight and/or birth body length of children whose fathers worked as spray-painters/construction painters were reported by Daniell & Vaughan (1988) and Höglund et al. (1992).

A questionnaire study concerning the rate of infertility included 3251 male painters and 1397 male construction workers in the Copenhagen district. Infertility was defined as having been involuntarily childless for a period of at least 2 years. A significantly increased infertility rate was detected among the

painters aged 21-40 years compared to the group of construction workers. No such differences were found in the older groups (age: 41-60 years). The authors noted that for the group of painters with increased infertility the period in which they desired to have children coincided with the period in which organic solvents were most intensively used in alkyd paints (Bjerrehuus & Detlefsen, 1986).

Heidam (1984) observed an increased odds ratio (OR: 2.9; 95%

CI: 1.0-8.8) of spontaneous abortion among 76 women occupied as painters compared to controls (women working as shop assistants or packers within the same county). The study was performed with mailed questionnaires and covered all women working as painters and women in nine other selected occupations in a population of 430 000. The questionnaire included the entire reproductive history of the women before May 1980. At the calculation of the odds ratios the values were adjusted with respect to the number of pregnancies in the group, with respect to the pregnancy order, and to the woman's age using a logistic regression model. The elevated OR for painters (and for factory workers as well) could not be associated to any single agent.

The association between solvent exposure and spontaneous abortion was examined in an interview study with 1926 women of whom approximately one-third had experienced spontaneous abortion during the first 20 weeks of gestation. The women were questioned about solvent exposure (different types of solvents, exposure duration during pregnancy and exposure intensity). From 15 cases and 12 controls exposed to paint thinner a crude odds ratio (OR) of 2.3 (95% CI: 1.0-5.1) was calculated. An adjusted OR of 1.8 (CI: 1.1-3.0) was calculated from a total of 75 cases and controls exposed to aliphatic solvents (mainly from paints and paint thinner). In the latter OR, allowance (by logistic regression) was made for different confounding factors (maternal age, race, education, previous fetal loss, smoking, working hours per week). No positive relationship was found between duration of exposure and the OR (Windham et al., 1991).

Overall, there is a suggestion that parental exposure to solvents may have an untoward effect on the offspring.

8.4 Carcinogenicity

Appraisal

Several epidemiological studies of cancer in workers with potential exposure to white spirit, e.g., painters, metal machinists, construction workers and dry cleaners, are available. Increased relative risks for certain cancers (e.g., lung, kidney, prostate, Hodgkin's lymphoma) have been observed, but the studies are insufficient to demonstrate causal association with exposure to white spirits.

Twenty-five patients suffering from Hodgkin disease were matched with 50 reference workers and interviewed about occupation and chemical exposure. Exposure was defined as handling organic solvents every working day for at least 1 year within the preceding 10-year period. Twelve (48%) patients with Hodgkin disease and six referents (12%) were occupationally exposed with a relative risk of 6.6 ($p = 0.0005$). These 18 subjects had been exposed for a median period of 8 years. Two of the patients had been exposed to white spirit (together with other solvents) while another three (painters) had been exposed to paint solvents (not further specified) (Olsson & Brandt, 1980).

Hardell et al. (1984) performed a matched case-control study including 102 cases of primary liver carcinoma (83 hepatocellular carcinomas, 15 cholangiocellular carcinomas, 3 haemangiosarcomas, and one unspecified liver sarcoma) and 204 controls. Exposure data was obtained from questionnaires sent to close relatives of the cases and controls. The exposure to organic solvent of 22.4% of the cases and 13.5% of the controls was "high-grade" (more than one week of continuous exposure or more than one month of repeated brief exposures). In the exposed group a risk ratio of 2.1 ($p < 0.05$) was calculated for hepatocellular carcinoma. The most common exposures were to solvents such as thinners, turpentine and white spirit. (The ratio was calculated without accounting for alcohol consumption, which in itself gave rise to an increased relative risk for hepatocellular carcinoma of 4.2).

In a case-control study, Siemiatycki et al. (1987) examined the association between cancer of many sites and exposure to 12 petroleum-derived liquids including white spirit. In all, 3726 cancer patients were interviewed about occupation and exposure history. Of these, 739 had been exposed to white spirit primarily in their work as construction painters (20.8%), mechanics and repairmen (19.6%), or working with metal machining equipment (5.4%). Among these, 92 cases of squamous-cell lung cancer and 100 cases of prostate cancer were identified. A grading of exposure into four groups, according to intensity and duration of exposure, was made, and relative risks were calculated, allowing for any possible cofactor (factors which were calculated to affect the risk estimate by more than 10% in a confounder analysis). With respect to squamous-cell lung cancer and

prostate cancer, the relative risk increased with increasing exposure, and for the highest exposure group relative risks of 1.7 (90% CI: 1.2-3.3) and 1.8 (90% CI: 1.3-2.6) were calculated for the two cancer forms. For Hodgkin's lymphoma a relative risk of 2.0 (90% CI: 1.0-4.1) was calculated on the basis of 12 cases with long-term (≥ 20 years) exposure. There was no increased risk for cancers of the bladder, kidney, stomach, colon, rectosigmoid colon or rectum, or for non-Hodgkin's lymphoma. Analysis of the association between job titles and cancer only revealed positive associations for metal machinists (relative risk = 2) and for construction workers

(relative risk = 1.4), occupations in which white spirit was found to be used extensively. (Relative risk for a specific cancer was calculated using the patients having cancers at other sites as controls).

Several studies have been performed with laundry and dry cleaning workers exposed to perchloroethylene and/or white spirit (Stoddard solvent). These studies reported increased risk of cancer of the kidney, lung and pancreas (Duh & Asal, 1984; Brown & Kaplan, 1987; Petrone et al., 1987). Stoddard solvent was extensively used as the cleaning solvent ($> 50\%$ of the solvent consumption), especially in the Oklahoma studies (Duh & Asal, 1984; Petrone et al., 1987).

In the study by Duh & Asal (1984) an elevated standardized mortality odds ratio of 1.7 (37 deaths, $p < 0.05$) was found for lung cancer and a ratio of 3.8 (7 deaths, $p < 0.05$) for kidney cancer. Petrone et al. (1987) conducted a cohort-mortality study with 4000 dry-cleaning workers and found an increased proportionate mortality ratio for respiratory cancer of 1.42 (44 deaths, $p < 0.05$) and for pancreatic cancer of 1.96 (12 deaths, $p < 0.05$). Similar results were obtained for the subset of workers (about 60% of the cohort) solely exposed to white spirit (Stoddard solvent).

Nakamura (1985) studied causes of death among 1711 laundry and dry-cleaning workers in Japan and found non-significantly elevated standardized proportional mortality ratios (SPMR) of 1.4 (16 deaths) for respiratory cancer and 2.5 (2 deaths) for kidney cancer in women (but not for these sites in men). Significantly elevated ratios were seen for cancer of the bone in women (SPMR 10; 5 deaths) and for cancer of the small intestine in men (SPMR 1.7; 18 deaths). Petroleum

solvents such as white spirit (Stoddard solvent) and naphtha were the most widely used (in about 65% of cases) of the cleaning solvents.

In an aircraft maintenance facility, no statistically significant risks of non-Hodgkin's lymphoma or multiple myeloma were seen among small groups of workers exposed to white spirit (Stoddard solvent) (Spirtas et al., 1991).

8.4.1 Epidemiological studies with painters

The International Agency for Research on Cancer has evaluated in detail epidemiological cancer studies on painters or workers in the paint manufacturing industry (IARC, 1989b). No further description of these studies will therefore be given in this monograph. In the overall IARC evaluation, it was found that the larger cohort studies, in particular, indicated a consistent excess of all cancers (about 20% above the respective national averages) and a consistent excess of lung cancers (about 40% above the national averages). Less consistent but increased risks were noted for cancers of the oesophagus, stomach and bladder. Some studies reported excess leukaemia and cancers of the buccal cavity and larynx.

Gubéran et al. (1989) (not included in the IARC evaluation, see Table 16) found higher incidences of cancer among 1916 painters than those expected for the region of Geneva. Significantly increased incidences were observed with respect to lung cancer (n = 40; SIR = 147; 90% CI: 111-191), cancer of the gall bladder (n = 3; SIR = 375; 90% CI: 102-969), testis cancer (n = 5, SIR = 313; 90% CI: 123-657) and bladder cancer (n = 13; SIR = 171; 90% CI: 101-272).

In a case-control study based on 19 904 male patients in the New Zealand Cancer Registry, Bethwaite et al. (1990) identified three cancer sites associated with occupation as a painter. Increased odds ratios were calculated for bladder tumours (OR: 1.52; 95% CI: 1.00-2.31), kidney and other urothelial tumours (OR: 1.45; 95% CI: 0.85-2.50) and multiple myeloma (OR: 1.95; 95% CI: 1.05-3.65). In the calculation of the OR values for each cancer site, the remaining registrants for the other cancer sites served as controls.

8.5 Genotoxicity

Sixteen tank cleaners exposed to the vapours of white spirit, xylene and petrol (gasoline) were examined for chromosomal aberrations in bone marrow cells and in peripheral lymphocytes and for micronuclei in erythropoietic bone marrow cells. Significantly elevated values compared to unexposed controls were found with respect to chromosome aberration in peripheral blood lymphocytes and with respect to micronuclei in polychromatic erythrocytes and erythroblasts. A dose-response relationship was noted between a high and a low exposure group, but the high exposure group (n = 9) contained eight smokers. Differences were still present when all the smokers from the group of tank cleaners (n = 10) were compared with smokers from the referent group. The cleaners had a median exposure period of 7 years and the hydrocarbon exposure level had in some cases been measured as 100-300 ppm. There was a high degree of dermal contact with the hydrocarbon solvents, as well as exposure to liquids containing heavy metals (Högstedt et al., 1981).

Kelsey et al. (1988, 1989) did not find any correlation between sister chromatid exchange (SCE) frequency in peripheral blood lymphocytes and cumulative lifetime (chronic) solvent exposure in a group of 106 painters. Elevated SCE frequency was noted in recently (acutely) exposed and currently smoking painters, whereas the SCE frequencies in recently exposed not currently smoking painters were comparable to non-smoking controls.

Nylander & Berg (1991) tested the mutagenicity of urine from 32 road tanker drivers handling petrol, diesel, paraffin and white spirit. No difference in mutagenicity was found compared to 33 office workers serving as referents. Mutagenicity was tested in the *Salmonella*/microsome system using strain TA98 and TA100.

9. EFFECTS ON OTHER ORGANISMS IN THE LABORATORY AND FIELD

Appraisal

There have been very few studies on the toxicity of white spirit to organisms in the environment. LC₅₀ values in the order of 0.5 to 5 mg/litre have been reported for aquatic organisms either for white spirit or for related hydrocarbon mixtures. There are difficulties in obtaining meaningful results from such tests with volatile materials. It is likely that exposure in the general

environment will be low, given the volatility of many of the components of white spirit and sorption to soil/sediment. Since information on general environmental concentrations of white spirit is unavailable, it is not possible to assess the risk of white spirit exposure to organisms.

9.1 Laboratory experiments

9.1.1 Microorganisms

Persidsky & Wilde (1956) studied the effect of white spirit (Stoddard solvent) (1123 litres/ha, 100 gallons/acre) on the growth of *Aspergillus niger*. The exposure reduced the number of colonies per membrane by 49%. The nitrification capacity and carbon dioxide evolution were reduced by 88% and 79%, respectively. The growth of *Aspergillus*, over a 5-day incubation period, as measured by the average weight of the mycelium, was reduced by 30 to 40%. The effect of Stoddard solvent on the growth and development of symbiotic mycorrhizal fungi was studied in sand cultures using *Pinus radiata*. The application did not significantly affect the weights of total seedlings, tops or roots.

9.1.2 Aquatic organisms

Dennis et al. (1979) exposed the water flea (*Daphnia magna*) and two species of fish, the fathead minnow (*Pimephales promelas*) and bluegill (*Lepomis macrochirus*), to heavy aromatic naphtha (boiling point, 168-274°C; hydrocarbons C₈-C₁₁) under static conditions at 20°C. On the basis of preliminary bioassays, the 48-h LC₅₀ for the daphnids was estimated to fall within the range of 0.42-2.3 mg/litre, and the 96-h LC₅₀ values were estimated to fall within the ranges of 4.2-20.8 and 2.1-4.2 mg/litre for the two fish species, respectively.

Adema (1985) tested the toxicity of white spirit (C₇-C₁₁; alkanes 53%; ratio of *iso* to *normal* alkanes, 1.3; cycloalkanes 27%; aromatics 20%) to two marine crustaceans, the brown shrimp (*Crangon crangon*) and the gammarid *Chaetogammarius marinus*. Three different test methods were used in closed or open systems to give a total of five tests (two closed, three open) for the gammarid and three tests (one closed, two open) for the shrimp. The different

methodologies for the preparation and extraction of the test medium and different chamber design meant that, in some cases, surface films or droplets of undissolved white spirit components were present. As expected, test methods providing opportunity for evaporation of white spirit and those with lower extraction efficiency for chemical analysis produced 96-h LC₅₀ estimates higher than those for other methods. The 96-h LC₅₀ values for closed systems with high efficiency extraction ranged from 2.5 to 4.5 mg/litre, whereas those for open systems ranged from 10 to 40 mg/litre (both based on dosed amounts). The average LC₅₀ for closed systems based on measured amounts was 0.53 mg/litre. In open containers without renewal of test solutions, the concentrations of all components of the white spirit fell to undetectable levels within 96 h. Comparison of tests with and without renewal in open systems showed that the majority of animals killed were affected at an early stage of exposure. Results were the same regardless of the presence or absence of surface film or droplets, suggesting that the dissolved component was responsible for the toxicity. The authors suggested C₉-C₁₁ aromatics and alkanes as the most likely white spirit components to contribute to toxicity.

9.1.3 Terrestrial organisms

Voigt (1953) studied the effect of white spirit (Stoddard solvent; 1123 litres/ha, 100 gallons/acre) on the oxygen uptake of excised root tips of the plant seedlings of jack pine, red pine, white pine and black locust. Oxygen uptake (µl/h per mg dry weight) was increased by 38.5, 7.6, 18.8 and 19% for the four plant species, respectively.

10. EVALUATION OF HUMAN HEALTH RISKS AND EFFECTS ON THE ENVIRONMENT

10.1 Evaluation of human health risks

All the constituents of white spirit are readily absorbed into the blood stream following inhalation of the vapour. White spirit is also dermally absorbed. Absorbed white spirit is widely distributed throughout the body. It passes through the blood-brain barrier. Quantitative distribution figures are available for some constituents showing preferential partitioning into fat for both aliphatics and aromatics. However, residues of white spirit constituents remaining in the body following short- or long-term exposure are likely to

concentrate in fat.

There is no information on the brain concentration of white spirit constituents in humans. In rats, the ratio of aliphatic to aromatic concentrations in the brain following 3 weeks of exposure increased with dose. Insufficient information is currently available to enable extrapolation from animal studies to humans on distribution of components.

Adequate information is not available on the metabolic breakdown of white spirit. However, metabolism studies have been reported for some of the single constituents. The main metabolic pathway for both aliphatic and aromatic compounds is by oxidation. Some metabolites are then conjugated prior to excretion. The half-life for white spirit elimination from fat has been estimated to be 46 h. The majority of excretion is via the urine, with a minor proportion through exhaled air.

Residual white spirit from the high acute exposure of amateur painters will be lost within a few days. Regular occupational exposure will lead to accumulation in fat.

White spirit has low acute toxicity by the inhalation, dermal and oral routes. Central nervous system depression following acute exposure may lead to lack of coordination and extended response time. Dizziness and tiredness were reported following a 7-h exposure to 600 mg/m³ (100 ppm). Exposure to very high concentrations of white spirit in enclosed spaces can lead to narcotic effects and loss of consciousness. Chest pain, cyanosis, apnoea and cardiac arrest have been reported. White spirit may cause serious lung damage after oral ingestion because of aspiration of the solvent into the lungs.

White spirit is a slight to moderate irritant to skin in humans. Prolonged or repeated exposure can lead to severe irritant dermatitis due to defatting. Slight irritation of the eye, nose and throat has been reported in humans at a white spirit vapour concentration of 600 mg/m³ (100 ppm).

Nervous system effects have been reported following repeated exposure of rats by inhalation; these include slight neurobehavioural effects, increased levels of brain dopamine, noradrenaline and

serotonin, and changes in sensory evoked brain potentials. Other reported effects include mild anaemia, change in liver weight, and "alpha₂-microglobulin nephropathy". The interpretation of neurobehavioural effects after acute exposure to white spirit is difficult and only one study is available; a lowest-observed-effect level (LOEL) of 1200 mg/m³ was indicated for an acute narcotic effect in rats. No-observed-adverse-effect level (NOAEL) and lowest-observed-adverse-effect level (LOAEL) values in laboratory animals are given in Table 19.

Table 19. No-observed-adverse-effect levels and lowest-observed-adverse-effect levels from animal studies

Route	Effects	Exposure	NOAEL/LOAEL
Dermal	systemic (weight gain, haematological)	200 mg/kg occlusion 6 h 3 times weekly for 4 weeks	NOAEL
Inhalation	kidney function/structure	600 mg/m ³ 8-13 weeks	LOAEL
Inhalation	liver weight	2000 mg/m ³ 13 weeks	LOAEL
Inhalation	biochemical effects in brain, glial cell proliferation	575 mg/m ³ 17 weeks	LOAEL
Inhalation	neurotransmitters	2290 mg/m ³ 26 weeks	LOAEL
Inhalation	motor activity, evoked potentials	2339 mg/m ³ 26 weeks	LOAEL

There have been no reproduction studies, and the developmental toxicity studies in animals are inadequate to evaluate these end-points.

The weight of evidence indicates that white spirit is not genotoxic.

There have been no white spirit carcinogenicity studies on laboratory animals.

Many epidemiological studies on occupationally exposed humans have identified symptoms of central nervous system effects of solvent exposure, predominantly to white spirit. These have ranged from dizziness and headache to impaired capability in performing neuropsychological tests. In severe cases, chronic toxic encephalopathy has been diagnosed. The prevalence of impaired functioning increased with increasing exposure duration in studies comparing painters with control groups from other building trades. Details of symptoms and case studies are given in chapter 8 and the summary in section 1.7.

Estimates of occupational exposure in epidemiological studies have been based on historical exposure indications, i.e. working materials, methods, conditions, ventilation and use of protective equipment. Such imprecise estimates of exposure make it difficult to establish exposure-effect relationships for the subjects studied.

There are few reported measurements of occupational exposure concentrations of white spirit for painters in epidemiological studies. Therefore, estimates have been made from measurements in other studies. There is general agreement that brush and roller application of alkyd paints leads to an average white spirit concentration of around 600 mg/m^3 (100 ppm). Given that painters are estimated to spend around 40% of their time applying alkyd paints (as opposed to applying water-based paints or preparing surfaces), an estimated average daily 8-h exposure to 240 mg/m^3 (40 ppm) has been used in studies. Without ventilation, exposure can peak at much higher levels of between 1800 and 6000 mg/m^3 (300 and 1000 ppm). Similar average and peak exposures have been reported in other industries, such as dry cleaning, where Stoddard solvent is used.

On the basis of these average exposure levels and results of neuropsychological tests (see section 8 for details), an attempt has been made to model exposure/effect of white spirit on house painters. This leads to the suggestion that exposure to an average of 240 mg/m³ (40 ppm) white spirit for more than 13 years could lead to chronic central nervous system effects. However, considerable reservations apply to this estimate. The Task Group could not estimate a no-observed-adverse-effect level for occupational exposure to white spirit based on the studies available. The frequent occurrence of neuropsychological signs among workers in house painting implicates white spirit in the development of "chronic toxic encephalopathy".

Case-control studies and studies on early markers of nephrotoxicity are conflicting and the long-term significance of these markers has been questioned. However, they suggest that painters have a higher risk of primary glomerulonephritis and renal dysfunction.

It is not possible to evaluate reproductive toxicity and carcinogenicity end-points for humans, since there are no adequate studies directly relating to white spirit exposure.

10.2 Evaluation of effects on the environment

There are no measurable concentrations of white spirit in the environment except following spills. However, the constituent compounds would be expected to partition largely to the atmosphere. Less volatile constituents partition to soil and sediment, where lowered bioavailability reduces uptake by organisms. White spirit is readily biodegradable under aerobic conditions. Octanol/water partition coefficients ranging from 3.5 to 6.4 indicate moderate potential for bioaccumulation. No studies have measured bioconcentration factors; however, because of the reported fate studies, these would be expected to be low in the field. The few toxicity studies available show moderate toxicity to aquatic organisms.

11. RECOMMENDATIONS FOR PROTECTION OF HUMAN HEALTH

- a) In order to reduce exposure concentrations for the general public and the occupationally exposed, paints based on white spirit should not be used in inadequately ventilated areas.

- b) All practicable methods should be used to minimize exposure of indoor painters to white spirit. Greater use should be made of water-based and other paints.

12. FURTHER RESEARCH

- a) Comparative studies should be made of different types of white spirit to elucidate differences in the toxicity of components (aliphatics, aromatics, etc).
- b) Reproductive and developmental toxicity studies need to be carried out on animals.
- c) Assessment of dermal absorption needs further research.
- d) Further study is needed to model the kinetics and metabolism of white spirit.
- e) Clarification is needed on the relationship between acute and long-term neurotoxicological effects in humans.
- f) Research is needed on neurotoxicological mechanisms in order to evaluate animal-to-human extrapolation.
- g) Rodent carcinogenicity studies are needed.
- h) If a suitable population exposed to white spirit could be identified, longitudinal studies should be conducted.
- i) Further studies are needed to establish a no-observed-adverse-effect level for occupationally exposed humans. Validation of modelling studies is recommended.

13. PREVIOUS EVALUATIONS BY INTERNATIONAL BODIES

IPCS (1982) made an evaluation of petroleum solvents (special-boiling-point solvents, white spirit and high-boiling-point aromatic solvents). In this evaluation attention was drawn to acute CNS effects (narcosis) from accidental inhalation of very high vapour concentrations and to general non-specific symptoms (feelings of

ill-health) from excessive chronic exposure. In addition it was noted that solvents containing benzene or *n*-hexane may have specific chronic effects.

In 1986 the Nordic Expert Group for Documentation of Occupational Exposure Limits concluded in its evaluation that the critical effects of white spirit are irritation of the eyes and mucous membranes and acute and chronic CNS effects. It was also noted that the risk of developing chronic toxic encephalopathy following long-term exposure should be taken into consideration (Hass & Prior, 1986).

The International Agency for Research on Cancer evaluated some petroleum solvents, including white spirit, in 1989 and found these solvents not classifiable with respect to their carcinogenicity to humans (IARC group 3). There was inadequate evidence for carcinogenicity in humans and no experimental animal data on white spirit were available (IARC, 1989a).

In their report "Organic Solvents and the Central Nervous System", the World Health Organization and Nordic Council of Ministers (WHO/NCM, 1985) concluded: "Clinical, epidemiological and experimental data indicate that long-term exposure to organic solvents may cause adverse effects in the central and peripheral nervous system." ... "The principal central nervous system disorders caused by long-term solvent exposure can be classified in two categories: the organic affective syndrome, consisting mainly of different psychiatric symptoms, and chronic toxic encephalopathy." ... "In view of the potential severity of the disorder and the uncertainty regarding the reversibility of some neurological and psychological deficits and their impact on social life, adequate preventive action should be taken to reduce solvent exposure whether at the workplace or in relation to leisure use."

The Commission of the European Communities and the Danish Ministry of the Environment in 1990 organized an international conference on organic solvents and the nervous system. In the conference report it was concluded: "Occupational exposure to organic solvents in concentration levels at workplaces in the last 30 years imply a risk of central nervous system deficits." ... "All longitudinal studies show a uniform indication of increased risk of being awarded an early disability pension due to neuropsychiatric disorders,

although the individual diagnosis might vary from registry to

registry. Thus, a marked association between occupational exposure and neuropsychiatric disorders is established." (CEC/DME, 1990; Arlien-Soeborg et al., 1992).

In 1994 the European Union agreed to classify a large number of petroleum-derived substances with regard to carcinogenicity and risk from lung aspiration (other toxicological effects were not evaluated). The five EINECS numbers for white spirit were included in different petrochemical groups, owing to differences in refinery treatment. They were (with the exception of white spirit type 0) classified as carcinogenic category 2, with the risk phrase R45 (may cause cancer) attached. However, this classification need not apply if it can be shown that the substances contain less than 0.1% (by weight) benzene. In addition, all the white spirit solvents were, owing to the aspiration risk, classified as harmful (Xn), with the risk phrase R22 (harmful if swallowed) attached (European Commission, 1994). This risk phrase may, in the near future, be replaced by a new phrase R65 (harmful: may cause lung damage if swallowed) (European Commission, 1995).

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