Committee for Risk Assessment

RAC

Annex 1
Background document
to the Opinion proposing harmonised classification and labelling at Community level of
white spirit

Stoddard solvent[1]
EC number: 232-489-3; CAS number: 8052-41-3

Naphtha (petroleum), hydrodesulphurized heavy[2]
EC number: 265-185-4; CAS number: 64742-82-1

Solvent naphtha (petroleum), medium aliphatic[3]
EC number: 265-191-7; CAS number: 64742-88-7

ECHA/RAC/DOC No CLH-O-0000001193-82-03/A1
ECHA/RAC/DOC No CLH-O-0000001745-71-01/A1
ECHA/RAC/DOC No CLH-O-0000000944-70-02/A1

Adopted
10 June 2011

Please, note: the original CLH proposal presented in the ECHA Public consultation included also naphtha (petroleum), solvent-refined heavy (EC No 265-095-5; CAS No 64741-92-0, white spirit type 2) and naphtha (petroleum), hydrotreated heavy (EC No 265-150-3; CAS No 64742-48-9, white spirit type 3) which were withdrawn by the dossier submitter.

[1] *USA term for white spirit, which corresponds to white spirit type 1*
[2] *White spirit type 1*
[3] *White spirit type 0*

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TABLES

PROPOSAL FOR HARMONISED CLASSIFICATION AND LABELLING

Name:

Stoddard solvent [1]
Naphtha (petroleum), hydrodesulphurized heavy [2]
Solvent naphtha (petroleum), medium aliphatic [3]

EC Number:

232-489-3
265-185-4
265-191-7

CAS number:

8052-41-3
64742-82-1
64742-88-7

[Please, note: The original CLH proposal presented in the ECHA Public consultation included also:

- **Naphtha (petroleum), solvent-refined heavy (EC No 265-095-5; CAS No 64741-92-0, white spirit type 2) and,**
- **Naphtha (petroleum), hydrotreated heavy (EC No 265-150-3; CAS No 64742-48-9, white spirit type 3), which were withdrawn by the dossier submitter.]**

Registration number (s):

Purity:

Impurities:

RAC is in agreement with the proposal to amend the existing Annex VI entry to include the additional classification of STOT RE1 (H372). The harmonised classification would result in:

[1] *USA term for white spirit, which corresponds to white spirit type 1*
[2] *White spirit type 1*
[3] *White spirit type 0*

Classification & Labelling in accordance with the CLP Regulation

Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors	Notes
				Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictoram, Signal Word Code(s)	Hazard state-ment Code(s)	Suppl. Hazard statement Code(s)		
649-345-00-4	Stoddard solvent;[1)] Low boiling point naphtha — unspeci-fied; [A colourless, refined petro-leum distillate that is free from rancid or objectionable odors and that boils in a range of approximately 300 °F to 400 °F.]	232-489-3	8052-41-3	Carc. 1B Muta. 1B STOT RE 1 (central nervous system) Asp. Tox. 1	H350 H340 H372 H304	GHS08 Dgr	H350 H340 H372 H304			P
649-330-00-2	Naphtha (petroleum), hydrodesulphurized heavy; [2)] Low boiling point hydrogen treated naphtha; [A complex combination of hydrocarbons obtained from a catalytic hydrodesulfuriza-tion process. It consists of hydrocarbons having carbon numbers predominantly in the range of C7 through C12 and boiling in the range of approximately 90 °C to 230 °C (194 °F to 446 °F).]	265-185-4	64742-82-1	Carc. 1B Muta. 1B STOT RE 1 (central nervous system) Asp. Tox. 1	H350 H340 H372 H304	GHS08 Dgr	H350 H340 H372 H304			P

649-405-00-X	**Solvent naphtha (petroleum), medium aliph.;** [3] **Straight run kerosine;** [A complex combination of hydrocarbons obtained from the distillation of crude oil or natural gasoline. It consists predominantly of saturated hydrocarbons having carbon numbers predominantly in the range of C9 through C12 and boiling in the range of approximately 140 °C to 220 °C (284 °F to 428 °F).]	265-191-7	64742-88-7	STOT RE 1 (central nervous system) Asp. Tox. 1	H372 H304	GHS08 Dgr	H372 H304			

1) *USA term for white spirit, which corresponds to white spirit type 1*
2) *White spirit type 1*
3) *White spirit type 0*

Classification & Labelling in accordance with Directive 67/548/EEC

Index No	International Chemical Identification	EC No	CAS No	Classification	Labelling	Concentration Limits	Notes
649-345-00-4	Stoddard solvent;[1)] Low boiling point naphtha — unspecified; [A colourless, refined petroleum distillate that is free from rancid or objectionable odors and that boils in a range of approximately 300 °F to 400 °F.]	232-489-3	8052-41-3	Carc. Cat. 2; R45 Muta. Cat. 2; R46 Xn; R48/20-65	T R: 45-46-48/20-65 S: 53-45-46		P
649-330-00-2	Naphtha (petroleum), hydrodesulphurized heavy; [2)] Low boiling point hydrogen treated naphtha; [A complex combination of hydrocarbons obtained from a catalytic hydrodesulfurization process. It consists of hydrocarbons having carbon numbers predominantly in the range of C7 through C12 and boiling in the range of approximately 90 °C to 230 °C (194 °F to 446 °F).]	265-185-4	64742-82-1	Carc. Cat. 2; R45 Muta. Cat. 2; R46 Xn; R48/20-65	T R: 45-46-48/20-65 S: 53-45-46		P
649-405-00-X	Solvent naphtha (petroleum), medium aliph; [3)] Straight run kerosine; [A complex combination of hydrocarbons obtained from the distillation of crude oil or natural gasoline. It consists predominantly of saturated hydrocarbons having carbon numbers predominantly in the range of C9 through C12 and boiling in the range of approximately 140 °C to 220 °C (284 °F to 428 °F).]	265-191-7	64742-88-7	Xn; R48/20-R65	Xn R: 48/20-65 S: (2-)23-24-62		

1) *USA term for white spirit, which corresponds to white spirit type 1*
2) *White spirit type 1*
3) *White spirit type 0*

JUSTIFICATION

1 IDENTITY OF THE SUBSTANCE AND PHYSICAL AND CHEMICAL PROPERTIES

The substances covered under the category name white spirit are considered as Substances of Unknown or Variable composition, Complex reaction products or Biological materials (UVCB) substances as defined by "Guidance for identification and naming of substances under REACH, June 2007.

The substances are petroleum substances derived from crude oil. They are very complex and do consist of variable or partly undefined compositions. Terms and definition for identification of petroleum substances include in general the stream´s source, refinery processes, general composition, carbon number, boiling range or other appropriate physical characteristics, and predominant hydrocarbon type, see section 1.2,

For the group of substances included in the term white spirit the constituents are a mixture of saturated aliphatic and alicyclic C_7- C_{12} hydrocarbons with a typical maximum content of 25% of C_7- C_{12} alkyl aromatic hydrocarbons. White spirit is divided in the five types of qualities (IPCS 1996 as defined by CEFIC 1989 & 1992), see section 1.1 and 1.2 but only three of them are covered in the RAC opinion and this supporting Background Document.

1.1 Name and other identifiers of the substance

Name:	Stoddard solvent [7] Naphtha (petroleum), hydrodesulphurized heavy [8] Solvent naphtha (petroleum), medium aliphatic [9]
EC-Number:	232-489-3 265-185-4 265-191-7
EC Name:	Stoddard solvent. A colourless, refined petroleum distillate that is free from rancid or objectionable odours and that boils in a range of approximately 148.8 to 204.4°C. Naphtha (petroleum), hydrodesulphurized 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. Solvent naphtha (petroleum), medium aliphatic. A complex combination of hydrocarbons obtained from the distillation of crude oil or natural gasoline. It consists predominantly of saturated hydrocarbons having carbon numbers predominantly in the 9-12 range and boiling in the range of approximately 140 to 220°C.
CAS Number:	8052-41-3 64742-82-1 64741-92-0
CAS Name:	Stoddard solvent Naphtha (petroleum), hydrodesulphurized heavy Solvent naphtha (petroleum), medium aliphatic
IUPAC Name:	Stoddard solvent. A colourless, refined petroleum distillate that is free from rancid or objectionable odours and that boils in a range of approximately 148.8 to 204.4°C. Naphtha (petroleum), hydrodesulphurized 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. Solvent naphtha (petroleum), medium aliphatic. A complex combination of hydrocarbons obtained from the distillation of crude oil or natural gasoline. It consists predominantly of saturated hydrocarbons having carbon numbers predominantly in the 9-12 range and boiling in the range of approximately 140 to 220°C.

[7] USA term for white spirit, which corresponds to white spirit type 1
[8] White spirit type 1
[9] White spirit type 0

1.2 Composition of the substance

White spirit is a petrochemical solvent containing mainly C_7 to C_{12} aliphatic, alicyclic and aromatic hydrocarbons with a boiling range within 65-230°C. The various types of white spirit are produced as distillation fractions from naphtha and kerosene components of crude oil. The composition of the various types can vary within the specified limits, because of differences in the raw material (crude oil) and in the production processes.

In addition to the chemical definition, the various types of white spirit are further defined in EINECS according to the production process and physico-chemical properties as follows (IPCS 1996):

Stoddard solvent:

A colourless, refined petroleum distillate that is free from rancid or objectionable odours and that boils in a range of approximately 148.8 to 204.4°C.

(USA term for white spirit, which corresponds to white spirit type 1.)

White spirit type 1, Naphtha (petroleum), hydrodesulphurized 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.

White spirit type 0, Solvent naphtha (petroleum), medium aliphatic:

A complex combination of hydrocarbons obtained from the distillation of crude oil or natural gasoline. It consists predominantly of saturated hydrocarbons having carbon numbers predominantly in the 9-12 range and boiling in the range of approximately 140 to 220°C.

Name:	Stoddard solvent *(USA term for white spirit, which corresponds to white spirit type 1.)* White spirit type 1 (Naphtha (petroleum), hydrodesulphurized heavy) White spirit type 0 (Solvent naphtha (petroleum), medium aliphatic)
EC Number:	232-489-3 265-185-4 265-191-7
CAS Number:	8052-41-3 64742-82-1 64742-88-7
IUPAC Name:	Stoddard solvent. A colourless, refined petroleum distillate that is free from rancid or objectionable odours and that boils in a range of approximately 148.8 to 204.4°C. Naphtha (petroleum), hydrodesulphurized 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. Solvent naphtha (petroleum), medium aliphatic. A complex combination of hydrocarbons obtained from the distillation of crude oil or natural gasoline. It consists predominantly of saturated hydrocarbons having carbon numbers predominantly in the 9-12 range and boiling in the range of approximately 140 to 220°C.
Molecular Formula:	C_nH_{2n+2} (n-alkanes and isoalkanes) C_nH_{2n} (cycloalkanes) C_nH_{2n-6} (aromatics), n>6
Structural Formula:	-
Molecular Weight:	150 (approximate average value) 92-179 (for single constituents)
Typical concentration (% w/w):	80-85% (by weight) aliphatic and alicyclic alkanes 15-20% (by weight) aromatic hydrocarbons
Concentration range (% w/w):	-
Conversion factors	1 ppm white spirit = 5.25-6.0 mg/m^3 1 mg/m^3 = 0.17-0.19 ppm

The ordinary and most widely used type of white spirit is denoted as white spirit type 1 in Europe and Stoddard solvent in the USA, and contains 80-85% (by weight) aliphatic and alicyclic alkanes and 15-20% (by weight) aromatic hydrocarbons.

There are only few detailed analytical chemical data on the different types of white spirit. Below in table 1 to 3 data are given on specific commercial available qualities.

In Table 1 and 2 data are shown from chemical analysis which illustrates the composition of specific white spirit products on the market (from IPCS 1996).

Table 1. Content of aliphatic and cyclic alkanes in white spirit (IPCS 1996)

Molecular size	North European white spirit[a]			USA white spirit (Stoddard solvent)[b]		
	Alkanes (% w/w)[c]	Monocyclic alkanes (% w/w)	Dicyclic alkanes (% w/w)	Alkanes (% v/v)	Monocyclic alkanes (% v/v)	Dicyclic 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	6.0	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: 72% specified (+ 12% unspecified)			total alkanes: 85%		

[a] Varnolene (boiling range: 162-198 °C), white spirit from the Danish market
[b] Stoddard solvent (boiling range: 152-194 °C), white spirit from the USA market
[c] The values in parentheses indicate the percentage by weight of n-alkanes

Table 2. Content of aromatics in white spirit (IPCS 1996)

Molecular size	Substance	North European white spirit [a] (% w/w)	USA white spirit (Stoddard solvent) [b] (% v/v)
C_6	Benzene	0.001	0.1
C_7	Toluene	0.005	0.4
C_8	Ethylbenzene o-xylene m-xylene p-xylene total C_8 aromatic hydrocarbons	0.2 0.34 0.49 0.22 1.3	 1.4
C_9	n-propylbenzene isopropylbenzene (cumene) 1-methyl-2-ethylbenzene	0.97 0.21 0.60	

	1-methyl-3-ethylbenzene	1.2	
	1-methyl-4-ethylbenzene	0.66	
	1,2,3-trimethylbenzene (henimellitene)	0.62	
	1,2,4-trimethylbenzene (pseudocumene)	2.1	
	1,3,5-trimethylbenzene (mesitylene)	0.83	
	trans-1-propenylbenzene	0.40	
	total C_9 aromatic hydrocarbons	7.6	7.6
C_{10}	n-butylbenzene	0.97	
	isobutylbenzene	0.37	
	sec-butylbenzene	-	
	tert-butylbenzene	-	
	1-methyl-2-isopropylbenzene (o-cymene)	0.06	
	1-methyl-3-isopropylbenzene (m-cymene)	0.47	
	1-methyl-4-isopropylbenzene (p-cymene)	0.62	
	1,2-diethylbenzene	0.13	
	1,3-diethylbenzene	0.25	
	1,4-diethylbenzene	0.13	
	1,2-dimethyl-3-ethylbenzene	0.08	
	1,2-dimethyl-4-ethylbenzene	0.25	
	1,3-dimethyl-2-ethylbenzene	-	
	1,3-dimethyl-4-ethylbenzene	0.26	
	1,3-dimethyl-5-ethylbenzene	0.38	
	1,4-dimethyl-2-ethylbenzene	0.28	
	1,2,3,4-tetramethylbenzene (prebnitene)	0.16	
	1,2,3,5-tetramethylbenzene (isodurene)	0.14	
	1,2,4,5-tetramethylbenzene (durene)	0.34	
	tetralin	0.08	
	total C_{10} aromatic hydrocarbons	5.2	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	14.7

[a] Varnolene (boiling range: 162-198 °C), white spirit from the Danish market
[b] Stoddard solvent (boiling range: 152-194 °C), white spirit from the USA market

Table 3 show data from CEFIC (1991) on typical composition of white spirit type 0 which have either been lightly treated to remove hydrogen sulphide and to turn mercaptans to disulphides, or have not been subjected to further chemical treatment.

Table 3. Composition of white spirit type 0 (CEFIC 1991)

White spirit type 0	Non-treated	Lightly treated
Mercaptan sulphur	< 10 ppm	0.1 ppm
disulphide sulphur	--	10 ppm
n – alkanes	23 % w/w	23 % w/w
Iso + cyclic alkanes	58 % w/w	58 % w/w
C8 aromatics	1 % w/w	4 % w/w

C9 aromatics	6 % w/w	8 % w/w
C10 aromatics	6 % w/w	7 % w/w
Other C9 aromatics + indane	4+1 % w/w	--

Referring to the tables above, the following classified substances have been identified as constituents in white spirit:

Benzene (CAS no. 71-43-2) approx. 0,001 %w/w, Toluene (CAS no.108-88-3) approx. 0,005 %w/w, Ethylbenzene (100-41-4) approx.1.3 %w/w, Xylenes (CAS nos.1330-20-7, 108-38-3, 95-47-6 and 106-42-3) approx. 0.22-0.49 %w/w and Cumene (Isopropylbenzene) (CAS no.98-82-8) approx. 0.21 %w/w.

However, the concentrations of all these constituents are very low, and will not by themselves imply classifications of the white spirit.

1.3 Physico-chemical properties

Table 4: Summary of physico-chemical properties

REACH ref Annex, §	Property	IUCLID section	White spirit 0	White spirit 1	Stoddard solvent
VII, 7.1	Physical state at 20°C and 101.3 KPa	3.1	liquid	liquid	liquid
VII, 7.2	Melting/freezing point	3.2	-	-	-
VII, 7.3	Boiling range (°C)	3.3	152-198[a]	130-220[a]	159-195[b]
VII, 7.4	Relative density (15°C)	3.4 density		0.75-0.8[a]	0.79[b]
VII, 7.5	Vapour pressure (kPa, 20°C)	3.6		0.8-n.i.[a]	0.285[b]
VII, 7.6	Surface tension	3.10			
VII, 7.7	Water solubility (% by weight)	3.8		"negligible"[b]	"negligible"[b]
VII, 7.8	Partition coefficient n-octanol/water (log value)	3.7 partition coefficient			
VII, 7.9	Flash point (°C)	3.11	$\geq$ 38	21-68[a]	43[b]
VII, 7.10	Flammability	3.13			
VII, 7.11	Explosive properties (limits in % by volume in air)	3.14		0.6-7.0[b]	0.8-5.6[b]
VII, 7.12	Self-ignition temperature (°C)			>200[b]	260[b]
VII, 7.13	Oxidising properties	3.15			
VII, 7.14	Granulometry	3.5			
XI, 7.15	Stability in organic solvents and identity of relevant degradation products	3.17			
XI, 7.16	Dissociation constant	3.21			
XI, 7.17	Viscosity (mm^2/sec, 25 °C)	3.22		1-1.5[a]	1.2[b]
	Auto flammability	3.12			
	Reactivity towards container material	3.18			
	Thermal stability	3.19			

a: CEFIC 1989. Data on specific commercial white spirit solvents: 70 commercial White Spirit type 1; 27. Data on 2 "typical" qualities on White Spirit type 0.
B: ExxonMobil (2009). Safety data sheets on White Spirit type 1 (Varsol 30, Varsol 40, Varsol 60);, and Stoddard solvent (Varsol 1 napthta anti-static).
n.i.: no indication

2 MANUFACTURE AND USES

White spirit does not occur naturally. However, the single chemical substances in white spirit are present in crude oil. (IPCS 1996).

2.1 Manufacture

The various types of white spirit are produced as distillation fractions from naphtha and kerosene components of crude petroleum (IPCS 1996):

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. A hydrodesulfurization process (removal of sulphur) is carried out either before or after the fractional distillation.

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.

2.2 Identified 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 (SCOEL 2007, IPCS 1996).

Approximately 700,000 tonnes (of all five types of white spirits) were used in Western Europe, with a trend towards higher consumption of de-aromatised white spirit (type 3) (SCOEL 2007).

In the ESIS (European chemical Substances Information System), a tonnage level of 100,000 – 500,000 tonnes is given for white spirit type 0, while tonnage levels above 1,000,000 tonnes are given for white spirit type 1 and type 3. White spirit type 2 is listed as a high production volume chemical with only one company as manufacturer/ importer and without further information on the tonnage level. Stoddard solvent is listed as a low production volume chemical. (http://ecb.jrc.ec.europa.eu/esis/).

The following data are from the Nordic SPIN database, 2008. SPIN is a database on the use of Substances in Products in the Nordic Countries. The database is based on data from the Product Registries of Norway, Sweden, Denmark and Finland. The database is financed by the Nordic Council of Ministers, Chemical group. (http://195.215.251.229/DotNetNuke/default.aspx):

White spirit type 0:
In 2006, white spirit type 0 was marketed in an amount of 8,000 tonnes in the Nordic countries (S, N, DK and F). The substance was identified in 179-1805 different chemical products (range of number of products for the four Nordic countries) and most widely used in products such as solvents, paint, lacquers, varnishes, cleaning/washing agents, and adhesives and binding agents.

White spirit type 1:
In 2006, white spirit type 1 was marketed in an amount of 61,000 tonnes in the Nordic countries (S, N, DK and F). The substance was identified in 758-2799 different chemical products (range of number of products for the four Nordic countries) and most widely used in products such as solvents, paint, lacquers, varnishes, cleaning/washing agents, corrosion inhibitors, degreasers, wood preservatives, biocides/pesticides, and adhesives and binding agents.

Stoddard solvent:
In 2006, Stoddard solvent was marketed in an amount of 506 tonnes in the Nordic countries (S, N, DK and F). The substance was identified in 103-1961 different chemical products (range of number of products for the four Nordic countries) and most widely used in products such as paint, lacquers, varnishes, cleaning/washing agents, biocides/pesticides, corrosion inhibitors, and degreasers.

Over the years, the use of organic solvents, white spirit included, in the Nordic countries has been essentially reduced, due to a number of awareness campaigns supporting substitution from e.g., alkyd paints to water-based paints. For that reason, the use of white spirit containing products in the Nordic countries is expected to be relatively lower compared to the European countries, in general.

2.3 Uses advised against

The use of white spirit is restricted in accordance with the directive 2004/42/EC on the limitation of emissions of volatile organic compounds (VOCs) due to the use of organic solvents in certain paints and varnishes and vehicle refinishing products. VOC´s are defined as a volatile organic compound having an initial boiling point less than or equal to 250°C measured at a standard pressure of 101.3 kPa (or a vapour pressure > 0.01 kPa at 293.15 Kelvin (20°C)).

In Danish worker protection legislation, white spirit is restricted for professional use (Executive Order on the Determination of Code Numbers, No. 301 and Executive Order on Work with Code-numbered Products No. 302). Professional use of e.g. alkyd paints (mainly based on white spirit) is restricted for indoor use on ceilings and walls.

Paints based on white spirit, intended to be used by the general public, are as well restricted in Denmark for indoor use on ceilings and walls (Statutory order 830 of 30 October 1999).

3 CLASSIFICATION AND LABELLING

3.1 Classification in Annex I of Directive 67/548/EEC and in Annex VI of Regulation (EC) no. 1272/2008

Directive 67/548/EEC:

Stoddard solvent:
649-345-00-4
Carc. Cat. 2; R45, Muta Cat. 2; R46, Xn; R65 H, P
C ≥ 10 %: T; R45-65
0.1 % ≤ C < 10 %: T; R45

White spirit type 1:
649-330-00-2
Carc. Cat. 2; R45, Muta Cat. 2; R46, Xn; R65 H, P
C ≥ 10 %: T; R45-65
0.1 % ≤ C < 10 %: T; R45

White spirit type 0:
649-405-00-X
Xn; R65 H
C ≥ 10 %: Xn; R65

In Denmark, Stoddard solvent and white spirit type 0 are, since 1988 further classified with Xn; R48/20.

Note H:

The classification and label shown for this substance applies to the dangerous property(ies) indicated by the risk phrase(s) in combination with the category(ies) of danger shown. The manufacturers, distributors and importers of this substance shall be obliged to carry out an investigation to make themselves aware of the relevant and accessible data which exists for all other properties to classify and label the substance. The final label shall follow the requirements of section 7 of Annex VI of this Directive.

Note P:
The classification as a carcinogen or mutagen need not apply if it can be shown that the substance contains less than 0.1 % w/w benzene (EINECS No 200-753-7).
When the substance is classified as a carcinogen or mutagen, Note E shall also apply.
When the substance is not classified as a carcinogen or mutagen, at least the S-phrases (2-)23-24-62 shall apply.
This note applies only to certain complex oil-derived substances in Annex I.

Regulation (EC) no. 1272/2008:

Stoddard solvent:
649-345-00-4
Carc. 1B H350, Muta 1B H340, Asp. Tox. 1 H304 H, P

White spirit type 1:
649-330-00-2
Carc. 1B H350, Muta 1B H340, Asp. Tox. 1 H304 H, P

White spirit type 0:
649-405-00-X
Asp. Tox. 1 H304 H

Note H:
The classification and labelling shown for this substance applies to the hazardous property(ies) indicated by the hazard statement(s) in combination with the hazard class(es) and category(ies) shown. The requirements of Article 4 for manufacturers, importers or downstream users of this substance apply to all other hazard classes and categories. For hazard classes where the route of exposure or the nature of the effects leads to a differentiation of the classification of the hazard class, the manufacturer, importer or downstream user is required to consider the routes of exposure or the nature of the effects not already considered.
The final label shall follow the requirements of Article 17 and of section 1.2 of Annex I.

Note P:
The classification as a carcinogen or mutagen need not apply if it can be shown that the substance contains less than 0,1 % w/w benzene (EINECS No 200-753-7). When the substance is not classified as a carcinogen at least the precautionary statements (P102-)P260-P262-P301 + P310-P331 (Table 3.1) or the S-phrases (2-)23-24-62 (Table 3.2) shall apply.
This note applies only to certain complex oil-derived substances in Part 3.

3.2 Self classification(s)

4 ENVIRONMENTAL FATE PROPERTIES

4.1 Degradation

4.1.1 Stability

Corresponds to IUCLID 4.1

4.1.2 Biodegradation

4.1.2.1 Biodegradation estimation

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4.1.3 Summary and discussion of persistence

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4.3.1 Aquatic bioaccumulation

4.3.1.1 Bioaccumulation estimation

4.3.1.2 Measured bioaccumulation data

4.3.2 Terrestrial bioaccumulation

4.3.3 Summary and discussion of bioaccumulation

4.4 Secondary poisoning

No CLH proposal for environment.

5 HUMAN HEALTH HAZARD ASSESSMENT

This dossier specifically covers classification in relation to repeated dose toxicity; thus, only data for section 5.1 regarding toxicokinetics and section 5.6 repeated dose toxicity are considered relevant.

The documentation for the classification proposal in this CLH-report is based on the expert group evaluation of SCOEL (2007): ´Recommendation of the Scientific Committee on Occupational Exposure Limits for white spirit´ and the IPCS (1996) expert group evaluation in connection with the Environmental Health Criteria document 187 on ´white spirit´. Thus the experimental animal data, and the human data, as well as the conclusions are cited from these sources.

NOTE: It should be noted that for transparency, and for facilitating the comparison with the IPCS and SCOEL assessments, the information submitted by Denmark covering the five white spirits types has been maintained in some parts of this section. However, as the proposals for two types were withdrawn by the dossier submitter, only three types are covered in the RAC assessment and proposal for harmonised classification and labelling.

Category approach and grouping of white spirit substances:

In the assessment of the repeated dose toxicity, a category approach was used by grouping the five different types of white spirit, however, as the proposals for two types were withdrawn by the dossier submitter, the category approach and grouping discussed by RAC covers only the three types assessed in this proposal for harmonised classification and labelling. The justification for this is the very large overlap in the composition of these very comparable UVCB substances.

The various types of white spirit consist of a complex mixture of hydrocarbons in the C_7-C_{12} range (predominantly in the C_9-C_{11} range, see section 1.2). Although differences exist in the complex hydrocarbon mixture, especially in regard to the content of aromatic hydrocarbons, this difference may be less clearly expressed in the actual vapour exposure under normal conditions of use, as the vapours will be dominated by the most volatile hydrocarbon components in the solvents, i.e., aliphatic and alicyclic components as well as the lower aromatic components.

Due to the large overlap of constituents between the various types of white spirit and also due to the difficulties to identify differences in the toxic responses from the various types, the Danish evaluation covered all types of white spirit. This was in accordance with the approach used and conclusions from the evaluations performed by IPCS (1996) and SCOEL (2007) that also covers these various types of white spirit.

In 1989 and 1991 CEFIC provided the TC C&L group with data on the five types of white spirit. These were due to their very comparable composition and physical chemical properties handled together and thus identical classifications were proposed by CEFIC. The concluded classifications were included in 21 ATP (1994).

A somewhat broader grouping approach in relation to classification is used by CONCAWE (2005) where the petroleum substances are allocated to a number of distinct groups according to their refinery processing and similarities in their physico-chemical, toxicity and eco-toxicity properties. Using this approach CONCAWE classifies groups such as *'Low boiling point naphthas (gasolines)'*, which cover saturated and aromatic hydrocarbons in the C_4-C_{12} range (white spirit type

1, 2, 3 and Stoddard solvent are included in this group), and '*Kerosines*, which cover saturated and aromatic hydrocarbons in the C_7-C_{16} range (white spirit type 0 is included in this group). Thus, read-across on data within each of these rather broad groups leads to the overall classification of the groups. Thus, the two groups used by CONCAWE cover a much wider range in hydrocarbon size compared to the group of white spirits used here and still read-across is considered appropriate by CONCAWE.

CONCAWE assessed the relevance for classification for all toxicity end-points for each group. The evaluation of classification for R48/20 for the groups containing the various types of white spirit was based on the content of toluene only (classified as R48/20) and classification was not considered warranted due to toluene levels lower than the trigger value of 10 w/w%.

5.1 Toxicokinetics (absorption, metabolism, distribution and elimination)

Exposure to white spirit

The data on toxicokinetics following inhalation of white spirit in this section are compiled from the recent evaluation by the EU Scientific Committee on Occupational Exposure Limits (SCOEL 2007) as well as the WHO/IPCS Environmental Health Criteria 187 (IPCS 1996). The data on toxicokinetics is considered relevant in relation to classification for neurotoxic effects following repeated inhalation exposure as the data indicate that all types of hydrocarbons contained in white spirit are absorbed, distributed and accumulated in the brain after repeated inhalation exposure.

Since white spirit is a mixture of numerous hydrocarbons with very different chemical properties, the study of toxicokinetics is complex. The relative percentage of the single compounds and their different physical and chemical properties greatly affect the toxicokinetics of white spirit. The absorption of white spirit after inhalation depends on several factors including concentration in the inspired air, blood partition coefficient, pulmonary ventilation and pulmonary blood flow. (SCOEL 2007).

Volunteers exposed to 0, 300, 600, 1200 mg/m^3 (0, 50, 100 and 200 ppm) for 6 hours showed a dose-dependent increase in the concentration of white spirit (17% aromatics) in venous blood: 0, 1.5, 3.0 and 7.2 mg/l respectively. During strenuous exercise the concentration can be 2 to 4 times higher. (Aastrand et al. 1975, from SCOEL 2007).

In a single dose 6 hour exposure study by Pedersen et al. (1984, from SCOEL 2007), 12 volunteers were exposed by inhalation to 610 mg/m^3 (approximately 100 ppm) white spirit (17.8% aromatics), exercise being restricted to normal physical activity. The mean venous concentration of white spirit was 3.1 mg/l (SD = 0.7).

Distribution of white spirit to adipose tissue has been demonstrated by Pedersen et al. (1987, from SCOEL 2007 and IPCS 1996). In a single exposure study, 8 male subjects were exposed to 600 mg/m^3 (approximately 100 ppm) white spirit (< 1% aromatics) in an experimental exposure chamber for 3 hours. After an interval of 6 to 8 weeks, seven of the volunteers were then exposed in a multiple exposure study to 600 mg/m^3 of the same white spirit, 6 hours per day for 5 consecutive days, and the concentrations of white spirit in adipose tissue, venous blood and alveolar air were measured during and up to 66 hours after exposure. The redistribution phase of white spirit in adipose tissue was estimated to be approximately 20 hours and the half-life of white spirit in adipose tissue was calculated to be 46-48 hours. The total body clearance was estimated to be 263 ml/minute. After 5 consecutive days of 6 hours exposure per day, the maximum steady state concentration was approximately 55 mg/kg fat and the minimum steady state concentration

approximately 35 mg/kg fat. This is due to the poor blood flow in this tissue and the high solubility of white spirit. The overall half-life of white spirit in the body is 46-48 hours, meaning that steady state in adipose tissue and in the brain will first be reached after approximately 3 weeks (SCOEL 2007).

In male rats exposed to 2320 and 4680 mg/m^3 (400, 800 ppm) of white spirit (20% aromatics) for 3 weeks, 6 hours/day, 5 days/week, concentrations of the solvent in the brain were 3.4 and 10.2 mg/kg wet weight, respectively. The concentrations of aromatic components doubled from 0.7 to 1.5 mg/kg wet weight, but those of aliphatic components tripled (from 2.4 to 8.7 mg/kg wet weight) (Lam et al. 1992, from SCOEL 2007).

The concentration of white spirit (11.7% aromatics) in adipose tissue was measured in rats exposed for 17 weeks (5 days/week, 6 hours/day) to air concentrations of 575, 2875 and 5750 mg/m^3 (100, 500 and 1000 ppm). Concentrations measured in fat were 180 mg/kg and 440 mg/kg at the two higher exposure levels, respectively, with only a trace at the low exposure level (Savolainen and Pfäffli 1982, from SCOEL 2007).

In a study on acute central nervous system (CNS) effects of white spirit (aromatics: 21.3%) in rats and humans, effects were compared with CNS concentrations. The CNS concentration was measured in rats, where exposures were for 9 hours/day for three consecutive days at 0, 600, 2400 or 4800 mg/m^3; and predicted in humans, where the exposure was to 583 mg/m^3 (about 100 ppm) for four hours, by means of a physiologically based pharmacokinetic model, using the two marker compounds, 1,2,4-trimethyl benzene (TMB) and n-decane (NDEC). TMB and NDEC could be detected in alveolar air 24 and 72 hours post exposure, respectively. From the CNS concentrations, it was shown that the no effect level of acute CNS effects (about 100 ppm) was at a similar CNS concentration in the two species. This suggests that animal studies can directly predict the acute CNS depression in humans. (Hissink et al. 2007, from SCOEL 2007).

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.
The aliphatic hydrocarbons are known to undergo oxidative conversion to alcohols. For *n*-alkanes with a carbon chain length of 7 or less, the predominant oxidation results in secondary mono- or dialcohols. For the higher *n*-alkanes, only oxidation at the terminal carbon has been observed. Branched isomers of the alkanes are mainly oxidised to yield either secondary or tertiary alcohols.
The monocyclic and polycyclic alkanes (such as cyclohexane and decalin) are mainly oxidised at the CH_2-groups in the ring structure. The first step of alkylbenzene metabolism is generally oxidation to alcohol at the alkyl moiety in the molecule. After this primary conversion, the hydroxy group is then conjugated to glucuronic acid or sulphate, or is oxidised further to ketone/aldehyde or carboxylic acid, which may then be conjugated to glucuronic acid, sulphate or glycine. (IPCS 1996).

Excretion of metabolites in the urine and elimination of parent compounds through expiration have been demonstrated in humans. (IPCS 1996).

Exposure to single hydrocarbons contained in white spirit

The description of the kinetics in IPCS (1996) in relation to some of the single components contained in white spirit gives the general view that, although the aliphatic and alicyclic hydrocarbons by inhalation are taken up in the bloodstream to a lesser extent compared to the aromatic hydrocarbons, they are to a higher degree distributed to and accumulating in the brain:

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, from IPCS 1996) exposed Sprague-Dawley rats to 1000 ppm of one of three C_9 compounds (*n*-nonane, 1,2,4-trimethylbenzene and 1,2,4-trimethylcyclohexane) for 12 hours 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 5). (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-tri-methylcyclohexane to the brain is probably due to differences in biological affinity and solubility or to different metabolic rates in the tissues.

Table 5. Brain/blood and fat/blood partition coefficients [a] (from IPCS 1996)

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-hour daily exposure to 1000 ppm on day 14 of the exposure period.

[b] The blood concentrations have been read from the graphs made by Zahlsen et al. (1990).

Eide (1990, from IPCS 1996) exposed rats to nine different C_8-C_{12} hydrocarbons at 100 ppm, 12 hours each day for 3 days. After the last exposure, blood and brain samples were immediately taken for analysis. Table 7 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 Zahlsen et al. (1992, from IPCS 1996), using 15 different C_6 to C_{10} hydrocarbons, confirmed the above findings of differences in distribution between aliphatic, alicyclic and aromatic hydro-carbons. 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 hours of recovery after the last exposure (Table 7).

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.

Table 6. Concentrations of C_8-C_{12} hydrocarbons in blood and brain of rats (µmol/kg) (from IPCS 1996)

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 hours daily for 3 days.

Table 7. Distribution of C_8-C_{10} hydrocarbons in rat tissue [a] (from IPCS 1996)

	n-octane *n*-nonane *n*-decane	1,2-dimethylcyclohexane 1,2,4-trimethylcyclohexane *tert*-butylcyclohexane	o-xylene 1,2,4-trimethylbenzene *tert*-butylbenzene
Blood	3.6 4.1 6.8	6.2 6.9 12.9	10.3 17.1 15.5
Brain	25.2 54.5 60.2	83.9 84.9 60.2	28.6 36.5 38.7
Liver	8.4 13.0 45.9	78.0 42.4 21.9	22.4 35.4 47.0
Kidney	41.9 45.2 77.7	162.2 (20.8) 349.7 (43.3) 261.5 (84.4)	95.2 103.6 256.6 (27.9)
Fat	697 (308) 1022 (577) 1230 (952)	1640 (730) 1476 (647) 1363 (825)	1228 (71) 1070 (120) 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 hours daily for 3 days. Values in parentheses are from animals that had a 12-hour recovery period after the last exposure.

Overall MSCA conclusion, toxicokinetics

White spirit is readily absorbed into the blood stream following inhalation of the vapour. Aromatic components are generally more soluble in blood than aliphatic and alicyclic hydrocarbon components. White spirit is widely distributed throughout the body of humans (brain, kidney, liver and fat), preferentially partitioning into fat; the half-life in adipose tissue has been estimated to be 46-48 hours. Although the aliphatic and alicyclic hydrocarbons are absorbed to a lesser extent than the aromatic hydrocarbons, higher levels of the aliphatic and alicyclic hydrocarbons are detected in the brain. This may be due to differences in biological affinity and solubility or different metabolic rate in the tissues. The main metabolic pathway for both aliphatic and aromatic compounds is by oxidation to alcohol, ketone/aldehyde or carboxylic acid, which may then be conjugated prior to excretion. The excretion is mainly via the urine, with a minor proportion via exhaled air.

5.2 Acute toxicity

5.2.1 Acute toxicity: oral

5.2.2 Acute toxicity: inhalation

5.2.3 Acute toxicity: dermal

5.2.4 Acute toxicity: other routes

5.2.5 Summary and discussion of acute toxicity

No CLH proposal for acute toxicity.

5.3 Irritation

5.3.1 Skin

5.3.2 Eye

5.3.3 Respiratory tract

5.3.4 Summary and discussion of irritation

No CLH proposal for irritation.

5.4 Corrosivity

5.5 Sensitisation

5.5.1 Skin

5.5.2 Respiratory system

5.5.3 Summary and discussion of sensitisation

No CLH proposal for sensitisation.

5.6 Repeated dose toxicity

There is a large amount of information from human studies with occupational inhalational exposure to white spirit. These data comprise neurophysiological and neuropsychological examinations of solvent exposed patients with encephalopathy, as well as a large body of epidemiological studies.

The repeated dose toxicity following inhalation of white spirit has been extensively investigated in experimental animals. Several of the available studies have focused on neurotoxicity, especially effects on the central nervous system (CNS) using neurobehavioural, neurophysiological and/or neurochemical methods for investigations. The findings in the experimental animal studies are considered to be supportive to the human data on adverse CNS effects from inhalational exposure to white spirit.

5.6.1 Repeated dose toxicity: oral

5.6.2 Repeated dose toxicity: inhalation

The critical effects following repeated inhalation exposure to white spirit are the neurotoxic effects, which in humans after prolonged exposure may develop to chronic toxic encephalopathy.

In mild cases of chronic toxic encephalopathy, the clinical manifestations are fatigue, mood disturbances, and memory and concentration problems. The CNS function is impaired with respect to psychomotor function (speed, attention, dexterity), and short-term memory impairment and other abnormalities are commonly noted. The term *'Severe chronic toxic encephalopathy'* covers loss of intellectual abilities of sufficient severity to interfere with social or occupational functioning including memory impairment, impairment in abstract thinking, impaired judgement, other disturbances of cortical function, and personality change. Also more pronounced and pervasive CNS functional deficits and some neurophysiological and neuroradiological test abnormalities may be observed. (IPCS 1996).

The following sections give a summary of the relevant data that justifies a classification for white spirit with Xn; R48/20 (67/548/EEC) or STOT RE 1, H372 (Regulation (EC) no. 1272/2008).

The Danish classification with R48/20 for Stoddard solvent and white spirit type 0 goes back to 1988 and basically refers to the data on neurotoxic / neurobehavioural effects described in a series of Nordic studies in the 1970-ies and 1980-ies. These are studies, which also form a significant part of the data used in the expert assessments made by a WHO/IPCS expert group and published in the WHO/IPCS Environmental Health Criteria 187 (IPCS 1996) as well as by the EU Scientific Committee on Occupational Exposure Limits (SCOEL 2007). The IPCS (1996) documentation is based on numerous studies (>30) overall suggesting that long-term occupational exposure to white spirit (all types) cause chronic toxic encephalopathy. The SCOEL (2007) recommendation for an OEL value is based on data on eye and respiratory tract irritation as well as the chronic neurotoxic and neurobehavioral effects of white spirit. The studies referred to by SCOEL are to a major extent the same studies, which also are covered in the IPCS review (IPCS 1996); however, some additional recent studies are also included in the SCOEL evaluation. The OEL by SCOEL covers white spirit with the varying content of aromatic and aliphatic hydrocarbons including the de-aromatised white spirit. SCOEL concludes in relation to the neurotoxic and neurobehavioral effects that there is no basis for differentiating between the different types of white spirit.

5.6.2.1 Studies in experimental animals

Introductory remarks

Numerous studies investigating the neurotoxic potential of white spirit in experimental animals following inhalation are available. The animal data in this section are compiled from the recent evaluation by the EU Scientific Committee on Occupational Exposure Limits (SCOEL 2007) as

well as the recent review by Nielsen et al. (2006). The WHO/IPCS Environmental Health Criteria 187 (IPCS 1996) has also been consulted when considered relevant.

Neurobehavioural studies, short-term repeated exposure

The following information from a recent short-term study with repeated exposure is considered of relevance in support of a classification for white spirit as Xn; R48/20 according to the current EU classification criteria (STOT RE 1, H372 according to the CLP classification criteria):

In male rats exposed to white spirit type 1 (0, 600, 2400 or 4800 mg/m³ (approximately 0, 100, 400 and 800 ppm, respectively), 8 hours/day for three consecutive days), the spontaneous motor activity was decreased at the highest exposure level and the psychomotor speed was affected exposure-dependently at the two highest levels. Overall, the NOAEC was 600 mg/m^3 (approximately 100 ppm). Neurobehavioural effects were also evaluated in humans. According to the authors, these studies demonstrated a qualitative similarity in response between rats and humans, adding support to the view that the rodent tests can be used to predict levels of response in humans and to assist in setting occupational exposure levels for hydrocarbon solvents. (Lammers et al. 2007).

Neurobehavioural studies, long-term repeated exposure

Four studies on behavioural effects in rats following inhalation for 13-26 weeks of white spirit with high and low content of aromatics are briefly summarised:

Adult male rats were exposed to white spirit type 3 (CAS No.: 64742-48-9, <0.4% w/w aromatics) at 400 or 800 ppm (2339 or 4670 mg/m^3), 6 hours/day, 5 days/week for 6 months followed by an exposure free period of 70-80 days. Decreased motor activity was observed in the dark period at 800 ppm, which the authors themselves suggested could be due to long term disturbance, but evaluated as "*changes in activity, thus requires further testing to evaluate the significance of the differences observed*". Nevertheless, this study suggests an effect on the CNS using electrophysiological endpoints (see Section 'Neurophysiological studies'). There was no significant exposure-related effect in the other behavioural tests (Functional Observational Battery, passive avoidance test, Morris water maze tests, and radial arm maze). Overall, the NOAEC was 400 ppm (2339 mg/m^3). (Lund et al. 1996, from Nielsen et al. 2006 and SCOEL 2007).

In an abstract, Kulig (1990) reported the results from exposures of rats to white spirit (type not specified) at 200, 400 or 800 ppm (1200, 2400 or 4800 mg/m^3), 8 hours/day, 5 days/week for 26 weeks. Psychomotor slowing was observed, but there was no carry over of effect into the post-exposure period. (Kulig 1990, from SCOEL 2007).

Three month old male rats were exposed to white spirit (type not specified – probably type 0, aromatics 20% v/v) at 400 or 800 ppm (2290 or 4580 mg/m^3) 6 hours/day, 5 days/week for 6 months followed by a 2-month exposure free period. There were no exposure-related effects on motor activity, in a Functional Observational Battery, on passive avoidance test, or in eight-arm radial maze and Morris water maze testing at any of the exposure levels. (Østergaard et al. 1993, from SCOEL 2007, IPCS 1996, Nielsen et al. 2006).

Rats were exposed to high flash aromatic naphtha (CAS No.: 64742-95-6, 100% w/w aromatics) at 101, 432 or 1320 ppm (497, 2125 or 6494 mg/m^3), 6 hours/day, 5 days/week for 13 weeks. No biological relevant effects on total motor activity or functional tests (grip strength, auditory startle

response, hot plate test, and hind limb foot splay) were observed at any of the exposure levels. (Douglas et al. 1993, from SCOEL 2007).

Neurobehavioural studies, pre-natal repeated exposure

In a study using prenatal exposure, rats were exposed (6 hours/day on gestational days 7-20) to 800 ppm (4679 mg/m^3) de-aromatised white spirit type 3 (aromatic content of <0.4% (w/w), Exxsol D 40, CAS No. 64742-48-9) and the offspring were followed for 5 months. The offspring were studied for reflex ontogeny, motor ability (Rotarod), motor activity, and learning and memory abilities by means of Morris water maze testing. The learning and memory functions were significantly impaired. The body weight of exposed dams was decreased by 26%, but the weight of their offspring was increased by 7%. (Hass et al. 2001, from Nielsen et al. 2006).

Neurobehavioural studies, summary

In summary, one study with de-aromatised white spirit type 3 showed decreased activity of rats in the dark period at 800 ppm (Lund et al. 1996) and another study with prenatal exposure to white spirit type 3 showed memory and learning deficit in offspring also at 800 ppm (Hass et al. 2001). However, neurobehavioural effects were not observed in rats after inhalation of white spirit with a high content of aromatics at concentrations up to 800 ppm (Østergaard et al. 1993, Kulig 1990).

The recent short-term study with repeated exposure (for 3 days) showed a NOAEC of 100 ppm for neurobehavioural effects in rats and demonstrated a qualitative similarity in response between rats and humans (Lammers et al. 2007).

Neurophysiological studies

Central nervous system effects of white spirit type 3 (Exxsol D 40, CAS No. 64742-48-9) with an aromatic content of <0.4% (w/w) were studied in rats. Exposures were 6 hours/day, 5 days/week for 6 months, followed by an exposure-free period of 70-80 days before the neurophysiological studies were performed. Exposure concentrations were 0, 400 and 800 ppm (0, 2339 and 4679 mg/m^3). Central nervous system effects were investigated by means of sensory evoked potentials. Thus, effects of stimulation by light were obtained from recording electrodes above the visual cortex (flash evoked potential, FEP), effects of electrical stimulation of the tail were collected from electrodes above the somatosensory cortex (somatosensory evoked potential, SEP), and auditory effects of sound were obtained from electrodes above the cerebellum and brain stem (auditory brain stem responses, ABR). Both concentrations changed FEP, SEP and ABR in an exposure-dependent manner. The FEP suggested that the retino-geniculate pathway was affected. The similarity between the exposure-dependent effects on SEP and FEP might suggest that the first neurons of the somatosensory system may be involved and that in addition cortical-subcortical networks were involved with the higher concentration. The changes in ABR suggested that changes may have occurred in excitability of either the cochlear apparatus or the first neurons of the auditory pathway. Overall, this indicates that de-aromatised white spirit can induce long-lasting and possibly irreversible effects at 400 and 800 ppm. (Lund et al. 1996, from SCOEL 2007).

In a study lasting 26 weeks with male Wistar rats exposed to white spirit vapour levels of 0, 1200, 2400 and 4800 mg/m^3 (0, 200, 400 and 800 ppm) (boiling range, 158-193°C; 44% aliphatics, 36% cyclic aliphatics, 18% aromatics), measurements of tail nerve conduction velocity showed

significant lower conduction velocities in the rats exposed to 4800 mg/m^3. (Kulig 1989, from IPCS 1996).

Neurochemical studies

Transmitter related neurochemical effects and neurochemical endpoints related to neuronal injury and oxidative stress in rats following inhalation of white spirit with high and low content of aromatics have been reported, see Table 8 and 9, respectively.

Comparison of effects of high aromatic versus low aromatic white spirit (Lam et al. 2001) showed less effect of the low aromatic product on a limited number of endpoints. Persistent changes were apparent in important neurotransmitters at exposure for six months to white spirit with a high content of aromatics (Østergaard et al. 1993, Lam et al. 1995). (SCOEL 2007).

The up-regulation of glial fibrillary acidic protein at exposures to white spirit with a high content of aromatics compared to white spirit with a low content of aromatics indicates that the high aromatic-containing product may cause more neuronal injury than the product with low content. In general, the high aromatic white spirit had little effect on glutathione (GSH) levels, except for a decrease at a very high exposure level. In contrast, low aromatic white spirit increased the GSH level, but at the same time, at the very high exposure level, it increased formation of reactive oxygen species. Glutamine synthetase was up-regulated by high aromatic white spirit, but unaffected by a low aromatic product. As no down-regulation occurred, excessive formation of reactive oxygen species is not apparent, which is in agreement with the findings from the GSH content in the CNS. (SCOEL 2007).

The persistent increase in cerebellar creatinine kinase activity, almost exclusively associated with astroglial cells, might suggest proliferation of the glial cells (Savolainen & Pfäffli 1982). As no effect was observed on the 2',3'-cyclic nucleotide 3'-phosphohydrolase, this suggests that no demyelination had occurred (Savolainen and Pfäffli 1982), which is in agreement with the lack of findings in the histopathology. A decrease in succinate dehydrogenase was observed; the enzyme is involved in the Krebs cycle in the mitochondria. The result apparently has not been confirmed in other studies. (SCOEL 2007).

Table 8. Comparison of central nervous system effects in rats at exposures to white spirit with high and low content of aromatics, transmitter related neurochemical effects (from SCOEL 2007)

I: Product II: CAS No. III: Boiling range in °C	**Aromatics (%) [a)]**	**Exposure Period [b)]**	**Concentration ppm (mg/m^3) and group size (N)**	**CNS effect [c)]**	**Reference**
I: Shell K-30 II: 64742-88-7 III: 148-200	20 (v/v)	6 h/day 7 days/week for 3 weeks	400 (2290) N=8-10 800 (4581) N=8-10	No change in 5-HT$_{2A}$ R, 5-HT$_4$ R, NCAM and SNAP-25 In the forebrain, ↓ 5-HT$_{2A}$ R while the affinity ↑ and also the affinity ↑ by the 5-HT$_4$ R. NCAM ↑ in the hippocampus. NCAM/SNAP-25 ↓ in the entorchinal cortex	Lam et al. 2001
I: Exxsol D 40, De-aromatised white spirit II: 64742-48-9 III: 145-200	0.4 (w/w)	6 hrs/day 7 days/week for 3 weeks	400 (2339) N=8 800 4679) N=8	No change in 5-HT$_{2A}$ R, 5-HT$_4$ R, NCAM and SNAP-25 In the forebrain, ↓ 5-HT$_{2A}$ R. No effect was seen in any brain region on NCAM, SNAP-25 or NCAM/SNAP-25	Lam et al. 2001
I: Shell K-30 II: 64742-88-7 III: 148-200	20 (v/v)	6 hrs/day 5 days/week for 6 months followed by a 4-month exposure free period	400 (2290) N=7 800 (4580) N=7	↑ NA, ↑ DA, ↑ 5-HT synaptosomal content. ↑ Synaptosomal 5-HT uptake rate ↑ NA, ↑ DA, ↑ 5-HT synaptosomal content. ↑ Synaptosomal 5-HT uptake rate. ↓ Synaptosomal protein content – a possibly marker of the number of synapses	Lam et al. 1995
I: Shell K-30 II: - III: 148-200	20 (v/v)	6 hrs/day 5 days/week for 6 months followed by a 4-month exposure free period	400 (2290) N=36 800 (4580) N=36	Three month old rats at start of exposures. ↑ NA in cerebellum and hemisphere, ↑ DA in hemisphere, and ↑ 5-HT in cerebellum Three month old rats at start of exposures. ↑ NA in cerebellum and hippocampus, ↑ DA in hemisphere, hippocampus and thalamus, and ↑ 5-HT in cerebellum, hemisphere, hippocampus, hypothalamus, pons, thalamus and medulla oblongata	Østergaard et al. 1993

a) Percent weight/weight is indicated by "w/w" and volume/volume % by "v/v".
b) All studies had an unexposed control group, which was used for evaluation of exposure effects. For simplicity, the control groups are not mentioned in the table.
c) Abbreviations: 5-hydroxytryptamine (5-HT); 5-HT2A receptor (5-HT2A R); 5-HT4 receptor (5-HT4 R); neural cell adhesion molecule (NCAM), which is involved in interneuronal adhesion and intraneuronal signal transduction; the (presynaptic) 25-kDa synaptosomal associated protein (SNAP-25), which is involved in the fusion of synaptic vesicles with the presynaptic membranes; noradrenaline (NA), dopamine (DA). An increase is indicated by ↑ and a decrease is indicated by ↓.

Table 9. Comparison of central nervous system (CNS) exposure-effects of white spirit with high and low content of aromatics in rats, neurochemical endpoints related to neuronal injury and oxidative stress (from SCOEL 2007)

I: Product **II: CAS No.** **III: Boiling range in °C**	**Aromatics (%)** [a)]	**Exposure Period** [b)]	**Concentration ppm (mg/m^3) and group size (N)**	**CNS effect** [c)]	**Reference**
I: Shell K-30 II: 64742-88-7 III: 148-200	20 (v/v)	6 h/day 7 d/week for 3 weeks	400 (2290) N=10 800 (4581) N=10	↑ GFAP in cerebellum and medulla oblongata ↑ GFAP in cerebellum, thalamus and medulla oblongata	Lam et al. 2000
I: Exxsol D 40 De-aromatised white spirit II: 64742-48-9 III: 145-200	0.4 (w/w)	6 h/day 7 d/week for 4 weeks	400 (2339) N=10 800 (4679) N=10	No consistent, dose-dependent effect on GFAP Dito	Lam et al. 2000
I: Shell K-30 II: - III: 150-220	14-21	6 h/day 7 d/week for 3 weeks	400 (2290) N=? 800 (4580) N=?	Five month old rats: ↑Gln synthetase in hippocampus. No effect on GSH in cerebral cortex or hippocampus Dito	Bondy et al. 1995
I: Exxsol D 40 De-aromatised white spirit II: - III: 145-200	0.4 (w/w)	6 h/day 7 d/week for 3 weeks	400 (2339) N=8-10 800 (4679) N=8-10	Three month old rats: ↑ GSH in synaptosomal fractions from hemispheres. No effect on Gln synthetase, neither in hemispheres nor in hippocampus Three month old rats: ↑ GSH in synaptosomal fractions from hemispheres. No effect on Gln synthetase neither in the hemispheres nor in the hippocampus. Increased formation of ROS in hippocampus	Lam et al. 1994
I: White spirit II: - III: 152-182	11.7 (w/w)	6 h/day 5 d/week for 17 weeks	100 (575) N=5 500 (2875) N=5 1000 (5750) N=5	Cerebellar effects: No effect on GSH,↓ succinate dehydrogenase (overall: dose-dependent), no effect on creatine kinase, but ↓ glial cellcreatine kinase Cerebellar glial cells: No effect on GSH, ↓ succinate dehydrogenase, ↑ creatine kinase (overall: dosedependent). Normal glialcell creatine kinase activity [d] Cerebellar glial cells: ↓ GSH, ↓ succinate dehydrogenase, ↑ creatine kinase. Normal glial cell creatine kinase activity [d]	Savolainen and Pfäffli 1982

a) Percent weight/weight is indicated by "w/w" and volume/volume % by "v/v".
b) All studies had an unexposed control group, which was used for evaluation of exposure effects. For simplicity, the control groups are not mentioned in the table.
c) Abbreviations: glial fibrillary acidic protein (GFAP), which is a marker of neuronal injury; glutamine synthetase (gln synthetase), which is expected to be inactivated (decrease) by reactive oxygen species; glutathione (GSH); reactive oxygen species (ROS). An increase is indicated by ↑ and a decrease is indicated by ↓.
d) The dose-dependent decrease was only observed at 8 weeks of exposure.

Conclusion, neurotoxic effects in experimental animals (SCOEL 2007, Nielsen et al. 2006)

The majority of long-term studies showed no adverse effect in most behavioural testing, using white spirit concentrations in the range of 101 to 1320 ppm. However, in the Lund et al. (1996) study, decreased activity in the dark period was observed with exposures to de-aromatised white spirit at 800 ppm. Furthermore, this study also indicates an effect on the CNS using electrophysiological endpoints. Additional support for an exposure-related CNS effect of de-aromatised white spirit is available from a study with prenatal exposures (Hass et al. 2001) where the offspring showed memory and learning deficit at 800 ppm. (SCOEL 2007, Nielsen et al. 2006).

It is remarkable that behavioural effects of white spirit were noted in the two recent studies with white spirit with a low content of aromatics (Lund et al. 1996, Hass et al. 2001), whereas products with a high content (20-100%) of aromatics showed no adverse behavioural effect. This either suggests that the two types of white spirit have different toxicity or that the more recent toxicological testing of the de-aromatised products may have used more efficient toxicological methods. (Nielsen et al. 2006).

Persistent or irreversible induced neurochemical changes are indicative of neurotoxicity. An overall comparison of the studies on neurochemical effects of the white spirit with a high or a low content of aromatics is difficult as several end-points were not identical. However, the increased glial fibrillary acidic protein fulfils the requirement being a directly interpretable end-point (US-EPA 1998) and, thus white spirit with a high content of aromatics can be considered neurotoxic at 400 ppm. The interpretation of the changes in enzyme activity at 100 ppm is more difficult, but the changes are considered as supporting evidence. A product with a low content of aromatics increased glutathione in the synaptosomal fraction at 400 ppm. When generalising, fewer neurochemical parameters were affected with white spirit with a low content of aromatics compared to white spirit with a high content of aromatics, but as several different end-points were studied, no definite conclusion can be drawn about the relative toxicity of the two types of white spirit from these studies. (Nielsen et al. 2006).

Taking all end-points into account, there are no major differences in neurotoxicity when comparing aromatised and de-aromatised white spirit (SCOEL 2007, Nielsen et al. 2006).

5.6.2.2 Studies in humans

Introductory remarks

Numerous studies investigating the neurotoxic potential of white spirit in humans following inhalation are available. The human data in this section are compiled from the recent evaluation by the EU Scientific Committee on Occupational Exposure Limits (SCOEL 2007) as well as the evaluation by WHO/IPCS in the Environmental Health Criteria 187 (IPCS 1996).

Most of the human data originate from exposure to ‘white spirit’, i.e., the type of white spirit in use was generally not characterised or not specified in the reports. However, the white spirit in use when most of the human studies were performed was generally high in aromatics, and less human information is thus available on de-aromatised white spirit.

A general clinical picture of the neurotoxic effects observed in humans exposed to white spirit will briefly be presented here (from IPCS (1996):

Most experience has been obtained from the monitoring of painters. This group has been very extensively studied because of high occupational exposure to organic solvents 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, and fatigue. 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.

The following chronic symptoms have been reported among 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.

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. 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.

5.6.2.2.1 Human studies as described by SCOEL (2007)

In a cross-sectional study by Seppäläinen and Lindström (1982), 72 maintenance house painters were examined by a questionnaire and by neurophysiological examinations. The exposed group was matched by a control group of 77 reinforcement workers. The mean exposure was 20.2 years with an average exposure to white spirit estimated to be 232 mg/m³ (40 ppm) during working hours. This estimation of exposure was based on information collected about the paints used and about work experience from the painters themselves, as well as from hygienic measurements of workplaces during the study, but the type of white spirit was not specified. Significantly more painters reported acute symptoms (nausea, mucous membrane irritation, impaired sense of smell and vertigo). No notable group differences were found in EEG and nerve conduction velocity measurements.

Lindström and Wickström (1983) extended the study with neurophysiological and behavioural tests (questionnaire and 8 neuropsychological tests) determining intelligence and psychomotor performance; 219 housepainters, mean age 42 years, and 229 reinforcement workers were included in the cross-sectional based study. The groups had similar consumption of alcohol and drugs; the study design used matched groups. Among painters, there were significantly increased prevalence of acute symptoms such as nausea, runny noses and malaise. The chronic symptoms, forgetfulness, sensitisation, weakened sense of smell and dizziness, were significantly more common among the painters, whereas paresthesia of the hands and feet were significantly more common among reinforcement workers. The exposed group was significantly poorer in the performance in the Block Design, Digit Symbol, Visual Reproduction and the Symmetry Drawing test. In a subgroup (N=43) matched for pre-exposure intellectual level, the painters performed worse only in the Visual Reproduction test. The painters performed less well in the simple reaction time tests, which did not correlate with intellectual levels. Thus, simple reaction time and short-time visual memory were most affected. For these functional tests, a slight correlation between performance and total

exposure or exposure level was demonstrated at a mean exposure of 22 years to an estimated average level of white spirit of 232 mg/m³ (40 ppm). The aromatic content was not specified. The shortest period between the exposure and the examination was 20 hours, suggesting that acute effects might have played a role.

In a cross-sectional study in a large dockyard in England (Cherry et al. 1985), 44 painters were matched to 44 joiners based on age, alcohol consumption and if possible on the highest levels of school examination passed. The paints contained white spirit, trichloroethylene, dichloromethane, methyl n-butyl ketone and n-butanol; exposures to white spirit may have been from low levels to levels exceeding 500 mg/m^3 at some tasks (the average levels of white spirit were under two working conditions measured to be 125 and 578 mg/m^3), but an exposure estimate was not possible. Mean duration of painting in the dockyard was 11.7 years. In the nine behavioural tests, painters performed less well in the trail making test, visual search test, block design, grooved pegboard, simple reaction time, memory test and the reading tests. As the reading test is considered resistant to an effect of recent central nervous system damage, adjustment for this parameter was performed by multiple regression analysis. The painters still performed less well in the block design, pegboard, reaction time, and memory tests. However, the difference was only significant in reaction time in a subgroup of 34 painters and controls when the matching was for age and reading score. The mixed solvent exposure and the white spirit exposure were not well defined and thus the study is not useful for an evaluation of neurotoxic effects of white spirit.

In a more extended cross-sectional study, Mikkelsen et al. (1988) examined a random sample of 85 painters, using 85 bricklayers as a non-exposed group. The predominant type of painting was house painting, but 27 out of the 85 painters had also been involved in other types of painting. The solvents used in house painting were mainly white spirit containing approximately 15-20% aromatic hydrocarbons, and 80-85 % aliphatic hydrocarbons. The median of years occupied as a painter was 31 years, the median of the solvent exposure index was 25 (l/d) years, the mean 41.4 (l/d) years. The authors stated that the risk of developing any degree of dementia was associated with solvent exposure. The estimated odds ratio for painters with medium solvent exposure (15-30 (l/d) years) was 3.6 and for painters with high solvent exposure (>30 (l/d) years) 5.0. The prevalence for painters with a low exposure level (<15 (l/d) years) was the same as for bricklayers. In psychometric tests, painters with high and medium solvent exposure performed poorer than painters with low solvent exposure and poorer than bricklayers in almost all of the tests. This measure of acquired mental impairment decreased with increasing solvent exposure level, but a test for trend was not significant ($p = 0.066$). The estimated odds ratios for abnormal coordination tests were 2.4 for painters with a medium and 5.5 for painters with a high solvent exposure level. For computer tomography (CT) 46 painters and 34 bricklayers were selected by scoring the degree of dementia with questionnaire and clinical examinations. All CT variables increased with increasing solvent exposure level. The difference between solvent exposure levels was significant for the maximum cortical sulcus size, the interhemispheric fissure and the cerebral atrophy index. In this study, painters with low solvent exposure level did not seem to differ significantly from bricklayers with respect to the risk of abnormal coordination. These results indicate, as the authors mentioned, that painters with low solvent exposure index 15 (l/d) years have no or little extra risk of an organic brain damage, possible confounders (e.g. age, alcohol intake, education) were identified and taken into account. Following evaluation and comparison of other cross-sectional studies, the risk of an organic brain damage seems to be increased for accumulated exposure levels above 15 (l/d) years, corresponding to approximately 6 years with daily time-weighted average exposure to 100 ppm of white spirit. An average level of 40 ppm white spirit was calculated as a NOAEL for 13 years of exposure.

In a paper by Spurgeon et al (1992), two comparable cross-sectional studies were carried out employing the same methodology, but involving two separate solvent-exposed populations (n= 90 (brush painters) and n= 144 (brush painters, paint sprayers, printers, coat trimmers, boat builders and degreasers)). Solvent exposed workers were compared with age-matched controls. Participants were 21-65 years old males. Standardized questionnaire outcome measures were done by the General Hospital Questionnaire (GHQ), the cognitive failure questionnaire (CFQ) and the Orebro 16-item questionnaire. Further tests were selected from the Neurobehavioural Evaluation System (NES). A similar pattern of results was obtained in the two studies, indicating a significantly decreased performance in the Symbol-Digit Substitution test in those with more than 30 years of exposure. In the group with 144 subjects, a decrease was observed in the Paired Associate Learning test in those with more than 10 years of exposure. In both exposed groups, there was no difference in the scores in the GHQ and CFQ questionnaires. Concerning exposure assessment, industrial hygiene data were unavailable for most of the period covering the working lives of the participants and no type of solvent exposure was specified.

In a cross sectional study in a large paint manufacturing company, Spurgeon et al. (1994) found no effects on cognitive functions or mental health in the group of paint makers (110 paint makers in two paint making sites, matched to 110 controls). The paint makers were predominantly exposed to white spirit (aromatic content not specified), toluene, xylene, methyl ethyl ketone, and methyl isobutyl ketone, but other solvents were also present. The exposure assessment was done on the basis of past and current exposure monitoring data. Three sub-groups were formed on the basis of cumulative exposure: low = < 100 ppm year (n= 42), medium = 300-600 ppm year (n= 37), high = > 600 ppm year (n= 23); range 12-1800 ppm year and by individual exposure intensities: low = < 20 ppm (n= 31), medium = 20-40 ppm (n= 47), high > 40 ppm (n= 26); range 2.6-60 ppm. The performance of the exposed subjects was not inferior to that of the controls, based on any neurobehavioural outcomes, either in the highest (> 40 ppm, n=26) or longest duration (> 30 years, n=11) exposure groups. These results strongly suggest that workers with moderate levels of exposure to a mixture of solvents do not experience effects on the nervous system even when such exposure takes place over many years. The authors noted the low response rate (about 43%), which leads to over or underestimation of the results.

In a cohort study (Lundberg et al. 1995), neuropsychiatric effects were studied in 135 house painters and 71 house carpenters, affiliated with their respective trade unions for at least 10 years before 1970; in the latter part of the 1950s and in the 1960s, white spirit was the dominating solvent in alkyd-based paints. Their lifetime organic solvent exposure was evaluated through the aid of an interview. Neuropsychiatric symptoms compatible with chronic toxic encephalopathy were more common among the painters than among the carpenters, and these symptoms became increasingly prevalent with increasing cumulative solvent exposure. Nevertheless, Profile of Mood State was not different. In the block design test, one of the 12 used psychometric tests, the painters performed worse than the carpenters and the painters' performance decreased with increasing cumulative exposure. In the majority of the psychometric tests, the painters with low exposure tended to show better and heavily exposed painters worse results than the carpenters. The 52 painters with the heaviest cumulative exposures and 45 carpenters were examined for psychiatric diagnosis, with electroencephalography and auditory evoked potential. These three investigations showed no difference between the painters and the carpenters. The authors considered that the symptoms were causally related to the solvent exposures and that the cumulative exposure to solvents below 130 exposure-limit months does not lead to functionally lasting disturbance of the nervous system. An exposure of about 130 to 250 exposure-limit months was related to an elevated risk of symptoms associated with chronic toxic encephalopathy and showed an indication of effects on one psychometric test, which, however, may have been confounded by recent exposure. The 130

exposure-month can roughly be estimated to no higher than 540 mg/m^3 (approximately 90 ppm), assuming the shortest exposure period of 10 years (120 exposure-months).

The performance of 226 rubber workers in a number of neurobehavioural tests was compared with that of 102 controls (Bazylewicz-Walczak et al. 1990). The workers were gluing footwear elements using glue containing white spirit (not specified) as a solvent. Company records indicated that white spirit concentrations in the atmosphere have been close to or somewhat higher than 500 mg/m³ (approximately 85 ppm) for the past 13 years. It was not clear whether confounding factors such as having (had) a neurological disease, alcohol consumption, and pre-morbid intelligence were adequately taken into account. Exposure data did not report exposure patterns. [Note: The results of this study are not included in the SCOEL (2007) evaluation. According to IPCS (1996) *"The performance of the exposed groups (as a total), compared to the controls, was significantly worse with regard to 4 of the 7 tests for intellectual functioning and with regard to 3 of the 5 tests for psychomotor performance."*, see section 5.6.2.2.2.2)].

In a cross-sectional study (Triebig et al. 1992a, 1992b), 83 spray painters and 42 controls were compared; subjects were matched for age, pre-exposure intelligence level, occupation and socioeconomic status. The spray painters had median exposure duration of 26 years and a minimum exposure of 10 years. Large amounts of paints based on nitrocellulose and alkyd resins, and acrylic paints were used up to 1975. Since 1975, the use of polyurethane coating has increased. The air concentration was dominated by aromatic hydrocarbons (mainly xylene, ethylbenzene, ethyltoluene, and trimethylbenzene), aliphatic hydrocarbons (mainly iso-octane, nonane and decane) and ethyl and butyl acetate. The concentrations varied from far below the OEL and up to three times the OEL taken as the sum of the concentration of each compound divided by its OEL value. About 92% of the spray painters used personal respiratory protection at least some of the time. Solvent exposures were estimated from exposure indices, including the SEI3, which was the product of the years of exposure, proportion of spray painting, protection factor (1-3), and frequency of symptoms (factor 1-3). There was no statistical difference between painters and controls regarding questionnaire reported symptoms. Neurological (e.g. reflex status, polyneuropathy, paresthesia, nerve conduction velocities, vibration thresholds, hand tremor, gait and ataxia) examinations did not show any exposure-dependent effect. The psychiatric examinations showed that "special feature of depression", a syndrome comprising self-depreciation, guilty ideas of reference, guilt, dulled perception and loss of affect was more common among the painters (14.7 versus 3% in controls). Similar findings were reported for "loss of interest and concentration", which were found in 16% of the painters and 2.5% of the controls. The "poor concentration syndrome" occurred among 18 painters. However, this symptom may also be related to mood since it is based on complaint, which does not correspond to the psychometric performance. The psychological tests, based on a test battery similar to that recommended by the World Health Organization, showed no exposure-dependent difference between painters and controls. In the computerised axial tomography of the brain, the only significant change was a higher mean value (higher atrophy index) in the cella media index, the quotient of the smallest cross-sectional diameter of the lateral ventricles and the maximal transverse diameter of the cranial fossa in the same section. The index quantifies alterations in the region of the corpus ventriculi. Nevertheless, the index did not correlate with the exposure index. Overall, this study is difficult to evaluate in relation to neurotoxic effects of white spirit. First, it is not clear whether the solvent exposures can be used as proxy for white spirit. Secondly, the inhaled concentration is not clearly related to the exposure or the exposure index. Finally, half of the worksites had low exposures (<OEL/10).

Conclusion, human data from SCOEL (2007):

Many epidemiological studies on occupationally exposed humans have identified central nervous system effects following solvent exposure. In severe cases, chronic toxic encephalopathy (CTE) has been diagnosed, but the diagnostic procedures are still far from uniform. Nevertheless, most international experts agree that a diagnostic procedure for CTE should contain an interview and neurological, physical and neuropsychological examinations. However, criteria for referral, diagnostic procedures, and classification and diagnosis are highly variable (van der Hoek et al., 2001). This makes it difficult to compare results from different studies and to establish generally agreed exposure-effect relationships.

However, on the basis of these average exposure levels and results of neuropsychological tests, an attempt has been made to model exposure/effects of white spirit on house painters (Mikkelsen et al. 1988). 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 (IPCS 1996). But considerable uncertainty still surrounds this estimate.

Triebig and Hallermann (2001) summarised the results of a European survey on solvent-related chronic encephalopathy (SRCE), that a single solvent cannot be identified as the main cause in most cases. SRCE is predominantly found in association with solvent mixtures.

From a cohort study (Lundberg et al. 1995), a LOAEL for long-term effects can be estimated to be no higher than about 540 mg/m^3 (90 ppm).

SCOEL departed from the narrow range of NOAELs and LOAELs between 40 to 90 ppm in human studies applying a safety factor of 2 for the recommended Occupational Exposure Level (OEL) of 116 mg/m^3 (20 ppm) in order to prevent subtle chronic nervous system effects and organic brain damage. The OEL covers white spirit with the different content of aromatic, de-aromatised white spirit and various aliphatics.

5.6.2.2.2 Human studies as described by IPCS (1996)

This section comprises information from case studies involving neurophysiological examination of patients and neuropsychological testing of workers and patients (section 5.6.2.2.2.1) and epidemiological studies performed mainly with healthy workers (section 5.6.2.2.2.2).

The neurophysiological examinations described can be divided into 1) electrophysiological examination of the brain comprising electroencephalography (EEG), auditory evoked potentials (AEP) and cerebral blood flow measurement (CBF); 2) neuroimaging examination of the brain comprising pneumoencephalography (PEG) and computerised tomography (CT); and 3) electrophysiological examination of the peripheral nerve system comprising nerve conduction velocity measurement (NCV), nerve action potential amplitudes (NAP) and electromyography (EMG).

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.

5.6.2.2.2.1 Case studies

5.6.2.2.2.1.1 Neurophysiological studies, patients

The findings from neurophysiological examination of patients with previous exposure to white spirit are summarised below (from Table 15 in IPCS 1996).

For most of the subjects included in the reports, 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.

Ten patients (house painters) suffering from chronic psycho-organic syndrome (POS) were examined by electroencephalography (EEG) (Axelson et al. 1976). The painters had been exposed to aliphatic and aromatic hydrocarbons including white spirit for 20-45 years. Six painters were found to have pathological EEG recordings.

Thirty-five retired house painters suffering from organic cerebral syndrome were examined by computerised tomography and pneumoencephalography (Gregersen et al. 1978). The group had been exposed several years (typically > 20 years) to paint solvents, mainly white spirit. Cerebral or cortical atrophy was noted in 17 of 18 examined painters.

Fifty patients (house painters) with signs of chronic brain syndrome were examined by electroencephalography, computerised tomography (CT) and pneumoencephalography (PEG) (Arlien-Soeborg et al. 1979). The group had mainly been exposed to white spirit (paint solvent) with a mean exposure period of 27 years. The EEG was slightly or moderately abnormal in 9 of 46 patients. The CT identified brain atrophy in 19 out of 38 examined. The PEG identified brain atrophy in 12 of 12 examined.

Fifty-one patients (house painters) with suspected chronic organ solvent intoxication and 38 referents were examined by computerised tomography (Gyldensted et al. 1980). The house painters had mainly been exposed to white spirit with a mean exposure period of 26.7 years. Twenty-seven cases of cerebral atrophy were noted in the group of painters. The atrophic patients had been exposed for longer duration than painters without atrophy. 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).

Fifty-seven out of 113 patients (house and car painters) suffering from suspected chronic encephalopathy were examined by computerised tomography or pneumoencephalography (Arlien-Soeborg et al. 1981). The exposure had been to mixed solvents; house painters had mainly been exposed to white spirit. The mean exposure period was 25.3 years. Brain atrophy was judged to occur in 28 (49%) of the patients. 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.

The studies by Arlien-Soeborg et al. (1979, 1981 and Gyldensted et al. 1980) were performed on the basis of more or less the same background population but reviewed at different times.

The cerebral blood flow (CBF) was examined in nine house painters with intellectual impairment and suspected chronic solvent intoxication (Arlien-Soeborg et al. 1982). Only subjects with no or very slight cerebral atrophy (observed by CT examination) were included. Eleven unexposed subjects served as controls. The painters had mainly been exposed to white spirit (paint solvent) with a mean exposure period of 22 years. There was no recent exposure before the CBF examination. The CBF in the group of painters (36.8 ml/100 g/min) were reduced ($p < 0.05$) compared to the controls (45.4 ml/100 g/min).

Twenty-eight patients with psycho-organic syndrome (POS), 20 patients with early stages of POS and 28 patients without POS were examined by electroencephalography, electromyography and nerve conduction velocity (Flodin et al. 1984). The psycho-organic syndrome was diagnosed on the basis of neuro-psychiatric test performance and the occurrence of relevant symptoms. The exposure had been to mixed solvents. The mean exposure period was 24 years in the POS group, 21 years in the early stage POS group, and 16 years in the non-POS group. The exposure to white spirit occurred at frequencies of 24%, 41% and 21% (percentage of all exposures) in the respective groups. In the neurophysiological examination, pathological results were found in 61% of the POS group, in 25% of the early stage POS group and in 32% of the non-POS group.

Twenty-one painters diagnosed with chronic toxic encephalopathy were examined by electroencephalography (EEG), computerised tomography (CT) and pneumoencephalography (PEG) (Gregersen et al. 1987). The group had been exposed to paint solvents with a mean exposure period of 25.5 years. Slight to moderate abnormal findings were noted in 6 out of 16 EEG-examined patients. Four out of 5 examined by PEG or CT exhibited cerebral atrophy to a varying degree.

Twenty-six patients, referred to a neurological department with suspected organic solvent syndrome, were examined by computerized tomography (CT), electroencephalography (EEG) and electromyography (EMG) (Berstad et al. 1989). The group had been exposed to mixed solvents. The mean exposure period was 23.9 years for 17 patients with a confirmed diagnosis of organic solvent syndrome. Seventeen patients (9 painters) were, according to medical examination and neuropsychological tests, diagnosed with organic solvent syndrome. The EEC showed abnormal findings in 5/17 cases and the CT found atrophy in 2/17 cases. The EMG and other neurological examinations revealed 5 cases (2 painters) of polyneuropathy.

5.6.2.2.2.1.2 Neuropsychological findings, patients

The findings from neuropsychological testing of workers and patients with known or suspected mental impairment due to white spirit or mixed solvent exposure are summarised below (IPCS 1996). Findings from epidemiological studies performed mainly with healthy workers are summarised in section 5.6.2.2.2.

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 the previous section.

In the study by Arlien-Soeborg et al. (1981, summarised in the previous section), 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 the previous section.

Gade et al. (1988) re-tested 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 re-testing, 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 re-test, 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 emphasised the necessity of using proper controls to avoid misclassification with respect to toxic encephalopathy.

5.6.2.2.2.2 Epidemiological studies

The findings from 19 epidemiological 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, are summarised below (from Table 16 in IPCS 1996). The studies are presented in chronological order.

In a cross-sectional study (Blume et al. 1975, Hane et al. 1977), 52 house painters and 52 unexposed industrial workers were examined by a neuropsychological test battery (10 tests representing a range of different mental functions). The painters were exposed to paint solvents, mainly white spirit and aromatic hydrocarbons. The mean exposure period was 14.2 years. The performance of painters was significantly worse in tests for figure classification and psychomotor coordination. Compared to a standard scale, significantly reduced scores were further noted in memory tests and simple reaction-time tests.

In a cross-sectional study (Hane and Högstedt 1980), 232 solvent exposed workers (104 painters, 29 car painters, 99 metalworkers) and 173 unexposed electricians and postmen were examined by a mailed questionnaire concerning symptoms and daily performance. The exposure was to mixed solvents. The house and car painters were most heavily exposed; house painters were exposed approximately 70% of the working hours mainly to white spirit, toluene and xylene. Significantly more symptoms were noted in the exposed group (in the answers from 18 out of 24 questions):

Fatigue, paraesthesia, bad memory, impaired concentration, depression, irritability, chest pain and reduced libido were the most prominent symptoms. Housepainters and car painters were most affected, and a positive correlation was found between increasing number of symptoms and age (exposure).

A historical follow-up study (Mikkelsen 1980) used information from register files of 2601 painters and 1790 bricklayers who were awarded disability pensions. The painters were mainly exposed to white spirit (about 75% of the total solvent exposure). A relative risk (RR) of 3.4 ($p < 0.05$) was calculated for painters for being awarded disability pensions because of *pre-senile dementia* (without specific cause indication) compared to bricklayers; a RR of 3.3 ($p < 0.05$) was found when using Copenhagen men as referents.

In a cross-sectional study (Seppäläinen and Lindström 1982), 72 maintenance house painters and 77 reinforcement workers were examined by using a questionnaire and by neurophysiological examinations (electroencephalography (EEG) and nerve conduction velocity (NCV)). The mean exposure period was 20.2 years. The average exposure to white spirit was estimated to be 40 ppm (232 mg/m³) during working hours. Significantly more painters reported nausea, feelings of drunkenness, mucous membrane irritation, parasthesia, vertigo and impaired sense of smell. No notable group differences were found in EEG and NCV measurements. *This study is also included in the evaluation by SCOEL (2007), see section 5.6.2.2.1.*

In a cross-sectional study (Lindström and Wickström 1983), 219 housepainters and 229 reinforcement workers were examined by using a questionnaire and 8 neuropsychological tests determining intelligence and psychomotor performance. The mean exposure period was 22 years. The average exposure to white spirit was estimated to be 40 ppm (232 mg/m³) during working hours. Among painters, there were significantly increased prevalence of acute symptoms such as nausea, runny noses and malaise, and significantly poorer performance in 4 tests. Short-term visual memory and simple reaction time were most affected functions. For these functions, a slight correlation between performance and total exposure/exposure level was demonstrated. *This study is also included in the evaluation by SCOEL (2007), see section 5.6.2.2.1.*

In a cross-sectional study (Cherry et al. 1985), 236 painters and 128 non-exposed joiners were examined by using questionnaires, and 44 painters and 44 non-exposed joiners went through neurological examination (nerve conduction measurements) and 9 neuropsychological tests determining intelligence and psychomotor function. Exposure was to mixed solvents. The average levels of white spirit were under two working conditions measured to be 125 and 578 mg/m^3. The mean exposure period was 11.7 years. The questionnaires revealed that painters significantly more often reported of tingling in hands and feet, depression, difficulties in concentration and increased irritability. The neuropsychological tests revealed significantly impaired scoring in 10 out of 14 test parameters. After re-matching with other controls and allowance for a lower preceding intellectual level of the painters, no significant differences were noted. *This study is also included in the evaluation by SCOEL (2007), see section 5.6.2.2.1.*

In a cross-sectional study (Fidler et al. 1987), 101 construction painters and 31 dry wall tapers (the control group was not used in the evaluation because of pronounced differences compared to the painter group) were examined by a questionnaire and neuropsychological tests (8 tests for intellectual functions and psychomotor performance). The painters were exposed to mixed solvents. Exposure indices were calculated on the basis of duration of exposure (years as a painter), type of work, frequency of exposure, amount of solvent used, exposure during the latest year, etc. The mean exposure period was 18 years. Among painters, dose-related increase in symptoms such as dizziness, nausea, fatigue, feeling of drunkenness and mood tensions were observed. Impaired performance in one psychomotor performance test and in one short-term memory test was

associated with the exposure during the latest year. Because signs of mental impairment did not form a consistent pattern the findings in the study were judged to be in accordance with the WHO definition of the mildest form of chronic solvent toxicity.

In a cross-sectional study (Baker et al. 1988), 186 construction painters were examined by a questionnaire and a neuropsychological test battery (9 tests determining verbal ability, psychomotor performance and memory). Information about intensity and duration were combined and different exposure indices were calculated. Stratification to 6 sub-groups, according to the index of lifetime exposure intensity (LEI), was done. The mean exposure period was 12 years. Unadjusted as well as adjusted (adjustments were made by regression analysis to account for the factors age, race, education, social status and alcohol habits) prevalence rates of symptoms such as forgetfulness, lassitude, disorientation, dysphoria and numbness of fingers and toes increased significantly with increasing LEI. Significant dose (LEI)-response relationship was also found for five mood parameters and in the symbol-digit test. When stratifying according to exposure duration without accounting for the exposure intensity, the neuropsychological parameters were affected to a minor degree.

In a cross-sectional study (Mikkelsen et al. 1988), 85 painters and 85 bricklayers were examined by a neuropsychological test battery (13 tests intellectual functions and psychomotor performance), by neurological tests (motor performance, coordination, reflexes, sensitivity) and by neurophysiological examination (CT). White spirit was estimated to account for about 75% of the total solvent exposure. The mean exposure period was 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 (n=33). Average exposure level (all painters) was estimated to be 40 ppm. Twenty-one painters had been exposed during the latest week before examination. The following odds ratios (OR) for painters compared to bricklayers were found for the development of dementia (the presence and degree of dementia evaluated from the overall performance in the test battery): high exp.: OR= 5.0 ($p < 0.05$); medium exp.: OR= 3.6 ($p < 0.05$); low exp.: OR= 1.1. Only a weak correlation was found between exposure and performance in specific neurological tests. However a strong correlation was found between exposure levels and the total number of abnormal scores. In CT scanning, exposure and dose relationship for differences were noted in 3 out of 11 different parameters. An average no-observed-effect level of 40 ppm (232 mg/m³) for 13 years was estimated (possible confounders were identified and taken into account). *This study is also included in the evaluation by SCOEL (2007), see section 5.6.2.2.1.*

A historical follow-up study (Gubéran et al. 1989) used information from register files of 1916 painters and 1948 electricians awarded disability pensions. The painters were exposed to paint solvents (no further specific data with regard to the solvent exposure). A relative risk (RR) of 1.8 (not significant) was calculated for the painters compared to the electricians for receiving disability pension because of neuropsychiatric diseases.

In a cross-sectional study (Bove et al. 1989), 93 construction painters and 105 unexposed controls were examined by vibration thresholds and temperature sensitivity. The painters were exposed to mixed solvents with a mean exposure period of 18 years. Different exposure indices were calculated on the basis of intensity and duration of exposure. The vibration thresholds were significantly higher in the older painters than in the comparable controls. The painter group had a significant excess of high-level temperature sensitivity compared to controls. Among painters, there was a positive association between vibration threshold and exposure level and cumulative exposure over the past year.

In a cross-sectional study (Bazylewicz-Walczak et al. 1990), 226 rubber footwear industry workers and 102 non-exposed hosiery plant workers were examined in a neuropsychological test battery (7 tests for intellectual functions and 5 tests for psychomotor performance). The rubber footwear workers were exposed solely to white spirit from gluing. The mean exposure period was about 500 mg/m^3 in the last 13 years. The two groups were divided into three sub-groups with respect to age. Further the exposed subjects were divided according to exposure duration: I: 5-10 years (n=51); II: 11-15 years (n=103); III: 16-30 years (n=72). The performance of the exposed groups (as a total), compared to the controls, was significantly worse with regard to 4 of the 7 tests for intellectual functioning and with regard to 3 of the 5 tests for psychomotor performance. The affected variables were: correctness of perception and reproduction of visual material, projection of spatial relationships, concentration, speed of reactions to single and complex light stimuli, and manual dexterity. Variables such as simple and complex reaction time and coordination were found to deteriorate with duration of exposure. *This study is also included in the evaluation by SCOEL (2007), see section 5.6.2.2.1.*

In a cross-sectional study (Bolla et al. 1990, Bleecker et al. 1991), 187 workers selected from two paint manufacturing plants were examined by questionnaires, neuropsychiatric evaluation, vibration threshold test, and a neuropsychological test battery (13 tests for intellectual functions and psychomotor performance). There were no unexposed controls. The painters were mainly exposed to aromatic hydrocarbons (toluene, xylene) and aliphatic hydrocarbons. Average lifetime exposures were estimated to be 2, 7, 12 and 18 ppm (as total hydrocarbons) for 4 sub-groups of workers (n = 44 in each group). The mean exposure period was 15-16 years for the four groups. Significant dose-related response was observed in test for vibration threshold and in 5 test parameters for sustained attention and concentration. The effects were judged to be sub-clinical. No differences between the exposure groups were observed regarding symptoms typically related to the “painter’s syndrome”.

A cross-sectional study (Brackbill et al. 1990) used information from register files of 3565 people receiving disability pensions because of chronic neuropsychiatric conditions and 83,245 people receiving disability pensions because of other reasons (not mental). Included in the two groups were 4291 painters and 1641 bricklayers. Painters were selected as a group highly exposed to solvents. The odds ratio was 1.42 ($p < 0.05$) for painters for getting disability pension because of chronic neuropsychiatric diseases compared to unexposed bricklayers.

In a cross-sectional study (Demers et al. 1991), 28 solvent-exposed painters and 20 non-exposed boilermakers were evaluated for subjective symptoms and examined by a vibration perception threshold test. The exposure was to mixed solvents. Seventy-six percent of the painters reported white spirit exposure and 42% of the painters were solvent exposed more than 50% of the working time. The mean exposure period was 30 years. Dizziness was experienced by 82% and syncopal episodes during work by 11% of the painters. Vibration tests were performed with a “Vibrometer” on the index fingers and the big toes to assess peripheral nerve functioning. The tests demonstrated significantly reduced vibration perception thresholds compared to the control group.

In a cross-sectional study (Spurgeon et al. 1990, 1992), two study groups were examined by a questionnaire (concerning symptomatology and psychiatric state) and by a neuropsychological test battery for intellectual functions and perceptual speed. Study group 1: 90 brush painters and 90 unexposed age-matched controls. Study group 2: 144 solvent-exposed brush painters, spray painters, printers and others, and 144 unexposed age-matched controls. Study group 1 was mainly exposed to white spirit with an estimated average level of 50 ppm for 2 days a week. Study group 2 was more diversely exposed because of the inclusion of several different occupations. Both groups were divided into four subgroups of exposure duration: < 10 years, 10-20 years, 21-30 years, > 30 years. In both studies, significantly impaired performance was observed in the symbol-digit substitution test for the exposed groups. In study 2, the performance of workers exposed for more

than 10 years was worse in paired associate learning test. After accounting for other possible influences on performance, a significant effect from exposure remained only for the sub-groups exposed for more than 30 years. It was concluded that the investigation provided some evidence for effects on cognitive functioning after long-term solvent exposure. *These studies are also included in the evaluation by SCOEL (2007), see section 5.6.2.2.1.*

In a cross-sectional study (Hooisma et al. 1993a), 47 young painters (30-40 years old), 45 older painters (55-72 years old), 53 young controls (30-40 years old) and 43 older controls (55-72 years old) were examined by a neuropsychological test battery (8 WHO core tests and 14 computerised tests). The 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 group differences were found between young and old painters and their age-matched controls. For young painters, the test scores for immediate memory were related to non-protected spray painting in the last 5 years and the time spent in painting during the last 5 years. For the older painters, the test scores for visuomotor performance and memory were related to the time spent in painting during the last 5 years and the total number of pre-narcotic episodes, respectively. However, these isolated findings were found to be inconsistent.

In a cross-sectional study (Hooisma et al. 1993b), 120 young painters (30-40 years old), 169 young controls (30-40 years old), 127 older painters (55-72 years old) and 157 older controls (55-72 years old) were examined by a questionnaire containing 43 questions regarding subjective symptoms and 9 questions regarding personality. The exposure was to paint solvents. Individual data were collected on total hours of painting or spray-painting, hours of non-protected spray-painting, and numbers of pre-narcotic episodes. Younger and older painters experienced significantly more complaints in 21/43 and 18/43 questions concerning symptoms. In no cases did the controls experience significantly more complaints. The two exposed groups had more complaints concerning core symptoms in relation to solvent exposure such as fatigability, bad memory and impaired concentration. The symptoms appeared to be related to periods of heavy exposure rather than to other exposure measures. No significant differences were observed in questions concerning personality.

In a cross-sectional study (Bolla et al. 1995, Ford et al. 1991), 144 workers from two paint-manufacturing plants (from same exposure group as Bolla et al. (1990) and Bleecker et al. (1991)) and 52 unexposed workers were examined by a neuropsychological test battery. At both plants, aliphatic hydrocarbon mixtures (white spirits), toluene and xylene were the three most widely used solvents. The cumulative hydrocarbon exposure was 180 ppm x years and 97 ppm x years at the two plants, respectively. Lifetime-weighted average exposure was 11.7 ppm and 7.6 ppm, respectively. The performance of the exposed group was worse in 14 out of 15 test parameters. Significantly impaired performance was noted in 5 tests for motor function and manual dexterity. In 10 out of the 15 tests, there was a positive trend between impaired performance and duration of exposure (for 3 tests $p < 0.05$). The scorings were adjusted for the cofactors age, vocabulary and race.

In addition to the epidemiological studies summarised above, there are further 15 epidemiological studies listed (Table 17 in IPCS 1996) in which white spirit exposure is considered to be part of the exposure. These studies are not further addressed in this CLH report as the exposure conditions have not been defined with the same degree of certainty and exposure is most often referred to as mixed solvent exposure from painting.

Discussion of findings in the epidemiological studies (IPCS 1996):

One of the major limitations regarding the epidemiological studies on long-term neurotoxic effects in painters is the lack of exact knowledge about exposure levels and the nature of exposure. Although white spirit was 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 epidemiological studies addressed in this section contain more specific exposure information (duration and exposure levels) with respect to white spirit (Seppäläinen & Lindström 1982, Lindström and 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 was 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 decades. 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, 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).

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 addressed in this section. 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).

Conclusion, human data from IPCS (1996):

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.

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-hour 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, 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/m^3 (40 ppm) white spirit for more than 13 years could lead to chronic central nervous system effects. However, considerable reservations apply to this estimate as a no-observed-adverse-effect level for occupational exposure to white spirit could not be estimated 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”.

5.6.2.2.3 Overall MSCA conclusion, neurotoxic effects in humans

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.

Dose-response relationships for different end-points have been demonstrated in a few of the epidemiological 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).

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.

The adverse neurotoxic effects of white spirit, including disabling and irreversible effects on mental functioning, have been demonstrated by many different investigators and in different countries. It is unlikely, therefore, that the combined set of findings could be explained by the same potential confounders or types of potential biases.

Most of the human data originate from exposure to 'white spirit', i.e., the type of white spirit in use was generally not characterised or not specified in the reports. However, the white spirit in use when most of the human studies were performed was generally high in aromatics, and less human information is thus available on de-aromatised white spirit. Based on the available human data, no conclusion can be drawn with respect to possible differences in the neurotoxic profiles of the various types of white spirit as a result of differences in the composition.

Both expert evaluations made by IPCS (1996) and SCOEL (2007) conclude that there is an association between long-term exposure to white spirit and chronic central nervous system effects. Based on the Mikkelsen et al. (1988) study, the IPCS evaluation indicates that an average exposure level at 40 ppm (240 mg/m^3) for more than 13 years may lead to chronic toxic effects of the central nervous system. The SCOEL evaluation, which is based on the more recent Lundberg et al. (1995) study (not included in the IPCS evaluation), concludes that the NOAEL for long-term neurobehavioural effects can be no higher than 90 ppm (540 mg/m^3) and recommends an OEL of 20 ppm (116 mg/m^3) for the different types of white spirit.

RAC assessment of the data:

In forming an opinion, RAC examined whether the assessments from IPCS and SCOEL could be used to develop a position on how white sprits should be classified for repeated dose toxicity.

IPCS and SCOEL discussed in detail most of the available human and animal studies relating to the neurotoxic effects of white spirits of all types. They evaluated core issues in relation to the identification of different types of white spirit, exposure levels, and the interpretation of the human data, which consisted of both clinical and epidemiological data. The aim of IPCS was to carry out a risk assessment, which included all toxic effects, whereas SCOEL aimed at an evaluation of all toxic effects considering an NOAEL to determine an OEL (Occupational Exposure Level). Both evaluations attempted to clarify the complexity of neuropsychological testing and other methodological problems; confounders or bias factors (e.g. alcohol intake) were taken into account.

IPCS concluded that a NOAEL could not be derived; IPCS made an attempt to model exposure/effect of white spirit on house painters. This led to the suggestion that exposure to an average of 240 mg/m^3 (40 ppm) white spirit for more than 13 years could lead to chronic central nervous system effects. According to IPCS, considerable reservations apply to this estimate. However, the frequent occurrence of neuropsychological signs among workers in house painting implicates white spirit in the development of chronic toxic encephalopathy.

In the SCOEL recommendation for setting an OEL a neurobehavioural and neurophysiological study from Lindström and Wickström (1983) was cited. At an estimated average exposure to white

spirit of 232 mg/m³ (40 ppm) 219 house painters and 229 reinforcement workers, showed that the exposed painters showed significantly inferior performance in 4 functional tests (simple reaction time and short-time visual memory test being the most affected). In contrast, Mikkelsen et al. (1988) found no impairment in neurobehavioural tests and examinations by computer tomography of workers with an estimated exposure to white spirit below 230 mg/m³ (40 ppm) for more than 10 years. From a cohort study (Lundberg et al. 1995), the LOAEL for long-term effects was estimated by SCOEL that it should be no higher than about 540 mg/m^3 (90 ppm). SCOEL departed from the narrow range of NOAELs and LOAELS from 40 ppm in human studies applying a safety factor of 2 for the recommended Occupational Exposure Level (OEL) of 116 mg/m3 (20 ppm) in order to prevent subtle chronic nervous system effects and organic brain damage. The OEL covers white spirit with the different content of aromatic, de-aromatised white spirit and various aliphatics.

According to SCOEL, animal studies support a common OEL for aromatized and dearomatized white spirits. In a long-term inhalation animal study in guinea pigs, a NOAEL for pathological effects was 100 ppm, In rats, rabbits, monkey and dogs a NOAEL was seen at 233 ppm. Neurochemical and electrophysiological effects in animals were observed at 400 ppm and above. SCOEL summarised how there were no major differences in neurotoxic patterns in the animal studies, when comparing aromatized and dearomatized white spirit, taking all endpoints into account. However, SCOEL observed that there was only limited information about the effects of de-aromatized white spirits on humans.

It is also important to mention that the effects observed in humans are mainly related to neurobehavioral effects and these effects are difficult to detect in laboratory animals. However, persistent changes were apparent in important neurotransmitters and in enzymes of the Krebs cycle in the mitochondria in animals at exposures to white spirit with high content of aromatics. Electrophysiological animal studies indicate that de-aromatized white spirit can induce long-lasting effects at 400 and 800ppm, but not white spirit with high content of aromatics. Overall, the animal studies failed to demonstrate adverse histopathological findings, which might suggest proliferation of the glial cells than demyelination after exposure. Therefore, the animal data may be seen as inconsistent.

After careful evaluation, RAC agreed with the assessments of IPCS and SCOEL, concluding that long-term exposure to white spirit may lead to the impairment of brain function and can therefore be associated with a high risk for the development of a chronic toxic encephalopathy (CTE). The corresponding decline in the number of diagnosed CTE-cases with the decreasing use of solvent-based paints supports the theory of white spirit as the causative agent.

Of further relevance to this assessment, the European Commission has previously recommended that Member States acknowledge chronic encephalopathy related to exposure to white spirit as an occupational disease (EC, 2009). White spirits and other hydrocarbons (toluene, xylene, styrene and pentane) were listed as causative agents for encephalopathies due to organic solvent exposure. Painters are the first occupational group mentioned as a risk group in relation to chronic toxic encephalopathy. In order to induce chronic encephalopathy, the EC stated that exposure duration of at least 5-10 years (usually 10 years or more) is required.

There is no scientific evidence available that would link the adverse effects on CNS to a single component of white spirits. Therefore, in considering the need for classification, RAC concluded that the adverse effects observed could be related to exposure to the substances as a whole, not to one or more of their individual components. Because the adverse effects measured in the epidemiological studies (as assessed IPCS and SCOEL) followed the exposure to white spirit types containing varying aromatic content with a typical range of 15-20% of aromatic and 80-85% of

aliphatic and alicyclic hydrocarbons, RAC concluded that this composition of the substances may have caused the adverse effects.

5.6.3 Repeated dose toxicity: dermal

5.6.4 Other relevant information

5.6.5 Summary and discussion of repeated dose toxicity:

The various types of white spirit consist of a complex mixture of hydrocarbons in the C_7-C_{12} range (predominantly in the C_9-C_{11} range; see section 1.2). Although differences exist in the complex hydrocarbon mixture, especially in regard to the content of aromatic hydrocarbons, this difference may be less clearly expressed in the actual vapour exposure under normal conditions of use, as the vapours will be dominated by the most volatile hydrocarbon components in the solvents, i.e. aliphatic, alicyclic components and the lower aromatic components.

Due to the large overlap of constituents between the various types of white spirit and also due to the difficulties to identify differences in the toxic responses from the various types, this evaluation covers all types of white spirit. This is in accordance with the conclusions from the evaluations performed by IPCS (1996) and SCOEL (2007) that also covers the various types of white spirit.

The overall evaluation given below is based on the conclusions from the expert group evaluations by IPCS (1996) and SCOEL (2007):

Animal data

Studies in experimental animals are available on different specific types as well as on unspecified types of white spirit, which was not further characterised in the study reports. Based on the available toxicological data from electrophysical and neurochemical testing there is no indications of overt differences in the neurotoxicity of the various types of white spirit as a result of differences in the composition.

Most long-term studies showed no adverse effect in most behavioural testing, using white spirit concentrations in the range of 101 to 1320 ppm. In the Lund et al. (1996) study, decreased activity in the dark period was observed with exposures to de-aromatised white spirit at 800 ppm. Furthermore, this study also indicates an effect on the CNS using electrophysiological endpoints. Additional support for an exposure-related CNS effect of de-aromatised white spirit is available from a study with prenatal exposures (Hass et al. 2001) where the offspring showed memory and learning deficit at 800 ppm. (SCOEL 2007, Nielsen et al. 2006).

Persistent or irreversible induced neurochemical changes are indicative of neurotoxicity. An overall comparison of the studies on neurochemical effects of the white spirit with a high or a low content of aromatics is difficult as several end-points were not identical. However, the increased glial fibrillary acidic protein fulfils the requirement being a directly interpretable end-point (US-EPA 1998) and, thus white spirit with a high content of aromatics can be considered neurotoxic at 400 ppm. The interpretation of the changes in enzyme activity at 100 ppm is more difficult, but the changes are considered as supporting evidence. A product with a low content of aromatics increased glutathione in the synaptosomal fraction at 400 ppm. When generalising, fewer neurochemical parameters were affected with white spirit with a low content of aromatics compared to white spirit with a high content of aromatics, but as several different end-points were studied, no definite

conclusion can be drawn about the relative toxicity of the two types of white spirit from these studies. The neurochemical changes should be interpreted with reference to presumed neurotoxic consequences. For example, many neuroactive substances may increase or decrease neurotransmitter levels. Thus, only substances, which cause adverse neuropathological, neurobehavioural or neurophysiological effects (neural dysfunctions or lesions), should be considered neurotoxicants. (Nielsen et al. 2006).

Human data

Most of the human data originate from exposure to 'white spirit', i.e., the type of white spirit in use was generally not characterised or not specified in the reports. However, the white spirit in use when most of the human studies were performed was generally high in aromatics, and less human information is thus available on de-aromatised white spirit. Based on the available human data, no conclusion can be drawn with respect to possible differences in the neurotoxic profiles of the various types of white spirit as a result of differences in the composition.

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. (IPCS 1996).

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. (IPCS 1996).

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. (IPCS 1996).

The adverse neurotoxic effects of white spirit, including disabling and irreversible effects on mental functioning, have been demonstrated by many different investigators and in different countries. It is unlikely, therefore, that the combined set of findings could be explained by the same potential confounders or types of potential biases.

Dose-response relationships for different end-points have been demonstrated in a few of the epidemiological 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). (IPCS 1996).

Both expert evaluations made by IPCS (1996) and SCOEL (2007) conclude that there is an association between long-term exposure to white spirit and chronic central nervous system effects. Based on the Mikkelsen et al. (1988) study, the IPCS evaluation indicates that an average exposure level at 40 ppm (240 mg/m^3) for more than 13 years may lead to chronic toxic effects of the central nervous system. The SCOEL evaluation, which is based on the more recent Lundberg et al. (1995) study (not included in the IPCS evaluation), concludes that that the NOAEL for long-term neurobehavioural effects can be no higher than 90 ppm (540 mg/m^3) and recommends an OEL of 20 ppm (116 mg/m^3) for the different types of white spirit.

As the animal studies would not alone meet the classification criteria for R48/20, but provide further support and understanding in relation to the findings in the human studies, the classification proposal is based on the human evidence. As the human data generally originate from exposure to 'white spirit' not further characterised or specified, a 'grouping approach' of the neurotoxicity data for 'white spirit' seems reasonable and valid for the purpose of a classification as R48/20 for the various types of white spirit covered in this proposal for harmonised classification and labelling: Stoddard solvent, white spirit type 1, and white spirit type 0.

5.6.5.1 Dose-response estimation

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 a 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-hour exposure of 240 mg/m^3 (40 ppm) has been used in the studies. It should be noted, however, that 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, an attempt has been made to model exposure/effect of white spirit on house painters. This leads, according to IPCS (1996) to the suggestion that exposure to an average of 240 mg/m^3 (40 ppm) white spirit for more than 13 years could lead to chronic central nervous system effects. However, IPCS also noted that considerable reservations apply to this estimate as a No-Observed-Adverse-Effect Level (NOAEL) for occupational exposure to white spirit could not be estimated based on the studies available.

According to SCOEL (2007), Mikkelsen et al. (1988) found no impairment in neurobehavioural tests and examinations by computer tomography of workers with an estimated exposure below 230 mg/m^3 (40 ppm) for more than 10 years. Moreover, Spurgeon et al. (1994) found no effects on cognitive functions and mental health in a cross-sectional study of paint makers predominantly exposed to white spirit (aromatic content not specified) as well as other solvents. The performance of the paint makers was not inferior to that of the controls in any neurobehavioral outcome, neither in the highest exposed (> 40 ppm), nor in those with the longest exposure duration (> 30 years). From a cohort study (Lundberg et al. 1995), the LOAEL for long-term effects was estimated by SCOEL that it should be no higher than about 540 mg/m^3 (90 ppm). SCOEL departed from the narrow range of NOAELs and LOAELS from 40 ppm in human studies applying a safety factor of 2 for the recommended Occupational Exposure Level (OEL) of 116 mg/m3 (20 ppm) in order to prevent subtle chronic nervous system effects and organic brain damage. The OEL covers white spirit with the different content of aromatic, de-aromatised white spirit and various aliphatics.

5.6.5.2 Proposed Classification

The following classification was proposed by Denmark to be added to the existing classification of white spirit* covering the substances: Stoddard solvent (CAS-no. 8052-41-3), white spirit type 1 (CAS-no. 64742-82-1), and white spirit type 0 (CAS-no. 64742-88-7).

Additional classification proposed according to Dir 67/548/EEC:

> **Xn; R48/20, Harmful: danger of serious damage to health by prolonged exposure through inhalation**

Additional classification proposed according to Regulation (EC) no. 1272/2008:

> **STOT RE 1, H372 Causes damage to the central nervous system through prolonged or repeated exposure.**

*The various types of white spirit consist of a complex mixture of hydrocarbons in the C_7-C_{12} range (predominantly in the C_9-C_{11} range, see section 1.2). Due to the large overlap of constituents between the various types of white spirit and also due to the difficulties to identify differences in the toxic responses from the various types, this classification proposal covers all types of white spirit. This is in accordance with the evaluations performed by IPCS (1996) and SCOEL (2007) that also covers the various types of white spirit.

The justification proposed by Denmark as dossier submitter is reproduced below.

Effects

White spirit causes neurotoxic / neurobehavioural effects after prolonged exposure, which are relevant for assigning the R-phrase R48 (CLP: Hazard Statement H372) to white spirit as these effects are not covered by other R-phrases (CLP: Hazard Statements).

Numerous epidemiological studies on occupationally exposed humans have identified symptoms of central nervous system effects in relation to white spirit exposure. The signs of neurotoxicity range from dizziness and headache to mood disturbances and impaired neurobehavioural performance. In severe cases, typically with more than 10 years of exposure, chronic toxic encephalopathy has been diagnosed.

The adverse neurotoxic effects of white spirit, including disabling and irreversible effects on mental functioning, have been demonstrated by many different investigators and in different countries. It is unlikely, therefore, that the combined set of findings could be explained by the same potential confounders or types of potential biases.

Nervous system effects have also been reported following repeated exposure of rats by inhalation including neurobehavioural and neurophysiological effects as well as effects on neurochemical end-points. Neurochemical and neurophysiological studies did not show overt differences in the adverse neurological long-term effects between white spirit with high and with low aromatic content. The animal data alone are not considered sufficient in order to meet the classification criteria for R48/20; however, the data provide further support and understanding in relation to the findings in humans. Furthermore, a recent study (Lammers et al. 2007) evaluated neurobehavioural effects in both humans and rats. According to the authors, these studies demonstrated a qualitative similarity in response between rats and humans, adding support to the view that the rodent tests can be used to predict levels of response in humans.

Criteria for classification

Below, findings from the animal and epidemiological studies are concluded on and related to the regulatory criteria for classification according to Directive 67/548/EEC Annex VI (Table 10) as well as to Regulation (EC) no. 1272/2008 Annex I (Table 11).

Table 10. Criteria for classification and labelling according to Directive 67/548/EEC Annex VI

Criteria Annex VI	**Compliance with criteria**
Section 3.2.4. 'Comments regarding the use of R48' *"…serious damage to health is to be considered to include death, clear functional disturbance or morphological changes which are toxicologically significant. It is particularly important when these changes are irreversible."*	After repeated or prolonged exposure to white spirit, various central nervous system (CNS) symptoms and impaired neurobehavioural functioning have been observed and in severe cases, the persons have been diagnosed with chronic toxic encephalopathy. This has to be considered as serious damage to health.
Section 3.2.4. 'Comments regarding the use of R48' *"It is also important to consider not only specific severe changes in a single organ or biological system but also generalised changes of a less severe nature involving several organs, or severe changes in general health status."*	Thus, for a solvent such as white spirit, which affects a number of functional areas of the central nervous system, the criteria emphasise the importance to consider the whole scale of effects.
Section 3.2.4.1 (b) (i) *"Major functional changes in the central or peripheral nervous systems, including sight, hearing and the sense of smell, assessed by clinical observations or other appropriate methods (e.g. electrophysiology)"*.	The diverse pattern of chronic CNS symptoms and the impaired CNS performance following repeated exposure to white spirit are all considered as being clinical relevant and therefore, to be judged as major functional changes according to the classification criteria. Thus, R48 is warranted.
Section 3.2.4.1 "*When considering data from practical experience special attention should be given to exposure levels."* and in the general introduction to Annex VI, section 1.1 it is stressed that *"… all the toxicological … properties of substances … which may constitute a risk during normal handling and use …"* should be identified.	The human data on white spirit is generally from occupational exposure and thus, from practical experience. SCOEL (2007) indicates that an average long-term level no higher than 90 ppm should be regarded as a NOAEL with respect to chromic effects on the CNS. Thus, exposure levels above 90 ppm (about 540 mg/m^3) may be considered as exposure levels of concern in relation to effects from repeated or prolonged exposure.

Table 11. Definitions and general considerations for classification and labelling according to Regulation (EC) no. 1272/2008 Annex I

Annex I	**Compliance with criteria**
Section 3.9.1.2. *"Classification for target organ toxicity (repeated exposure) identifies the substance as being a specific target organ toxicant and, as such, it may present a potential for adverse health effects in people who are exposed to it."*	After prolonged or repeated exposure to white spirit, the central nervous system (CNS) has been identified as a specific target organ in humans. This is supported by animal toxicokinetic data, which indicate that white spirit is distributed to and accumulates in the CNS and animal data indicating neurobehavioural, neurophysiological, and neurochemical findings after repeated inhalational exposure to white spirit.
Section 3.9.1.3. *"The adverse health effects include consistent and identifiable toxic effects in humans, or, in experimental animals, toxicologically significant changes which have affected the function or morphology of a tissue/organ… and these changes are relevant for human health."*	After prolonged or repeated exposure to white spirit, various central nervous system (CNS) symptoms, mood disturbances and impaired neurobehavioural functioning have been observed and in severe cases, the persons have been diagnosed with chronic toxic encephalopathy, which is to be considered as consistent and identifiable toxic effects in humans. The CNS is also a specific target organ in experimental animals following repeated exposure and CNS effects similar to those in humans have been observed, e.g., neurobehavioural and neurophysiological changes. Neurochemical changes have also been observed in experimental animals exposed to different types of white spirit. Thus, the changes observed in experimental animals are support for the findings in humans.
Section 3.9.2.4. *"Weight of evidence of all data …, including human incidents, epidemiology, and studies conducted in experimental animals, is used to substantiate specific target organ toxic effects that merit classification."*	Numerous epidemiological studies of painters with long-term exposure to white spirit have revealed CNS symptoms and impaired neurobehavioural functioning. In several cases, an overall reduction in cognitive functioning was noted to a degree that corresponded to a diagnosis of

	chronic toxic encephalopathy. 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. Studies in experimental animals have revealed CNS effects similar to those in humans, e.g., neurobehavioural and neurophysiological changes. Overall, the human data supported by the findings in studies of experimental animals merit a classification of white spirit as STOT RE 1.
Section 3.9.2.10.2 *"When well-substantiated human data are available showing a specific target organ toxic effect that can be reliably attributed to repeated or prolonged exposure to a substance, the substance shall normally be classified. Positive human data, regardless of probable dose, predominates over animal data. Thus, if a substance is unclassified because no specific target organ toxicity was seen at or below the dose/concentration guidance value for animal testing, if subsequent human incident data become available showing a specific target organ toxic effect, the substance shall be classified."*	Well-substantiated human data are available showing that the CNS is a specific target organ after repeated or prolonged exposure to white spirit even at relatively low exposure levels (exposure levels above 90 ppm may be considered as exposure levels of concern in relation to effects from repeated or prolonged exposure) and thus, merit a classification of white spirit as STOT RE 1. Animal data are supportive for the classification based on human data as some CNS effects are observed in animals at exposure levels above the guidance value for classification.

STOT RE 1 is proposed as the basis for the classification is driven by the *human evidence* which is covered under category 1 of the criteria given in table 3.9.1:

Table 3.9.1

Categories for specific target organ toxicity-repeated exposure

Categories	Criteria
Category 1	Substances that have produced significant toxicity in humans or that, on the basis of evidence from studies in experimental animals, can be presumed to have the potential to produce significant toxicity in humans following repeated exposure. Substances are classified in Category 1 for target organ toxicity (repeat exposure) on the basis of:

	– reliable and good quality evidence from human cases or epidemiological studies; or – observations from appropriate studies in experimental animals in which significant and/or severe toxic effects, of relevance to human health, were produced at generally low exposure concentrations. Guidance dose/concentration values are provided below (see 3.9.2.9), to be used as part of a weight-of- evidence evaluation.
Category 2	Substances that, on the basis of evidence from studies in experimental animals can be presumed to have the potential to be harmful to human health following repeated exposure. Substances are classified in category 2 for target organ toxicity (repeat exposure) on the basis of observations from appropriate studies in experimental animals in which significant toxic effects, of relevance to human health, were produced at generally moderate exposure concentrations. Guidance dose/concentration values are provided below (see 3.9.2.9) in order to help in classification. In exceptional cases human evidence can also be used to place a substance in Category 2 (see 3.9.2.6).

Exposure levels

According to IPCS (1996), an average exposure of 40 ppm (240 mg/m^3) white spirit for more than 13 years could lead to chronic central nervous system effects.

According to SCOEL (2007), the NOAELs range from 40 to 90 ppm (230-540 mg/m^3) for subtle chronic nervous system effects and organic brain damage.

Classification

White spirit produces a number of serious health effects in the central nervous system progressing to chronic toxic encephalopathy after prolonged exposure by inhalation in humans. The exposure levels inducing neurotoxicity in humans are in the order of 40 to 90 ppm (230-540 mg/m^3). Based on the data assessed by an WHO/IPCS expert group (IPCS 1996) and by SCOEL (SCOEL 2007), a classification as Xn; R48/20, Harmful: danger of serious damage to health by prolonged exposure through inhalation (according to Regulation (EC) no. 1272/2008: STOT RE 1, H372 Causes damage to the central nervous system through prolonged or repeated exposure via inhalation*) is warranted for the five types of white spirit covered in this CLH-report, irrespective of eventual differences in the evidence of their respective toxicity. The justification for proposing the same classification for all five types of white spirit is that the reports of the epidemiological studies do not specify the type of white spirit in use when the workers were exposed. The data from experimental animal studies are inconsistent; however, the findings in a number of these studies including irreversible effects in the central nervous system support the proposed classification.

*only the inhalation route is considered relevant. Although SCOEL (2007) applied a skin notation on white spirit this was based on a rather low estimated absorption rate of 7%, and therefore the STOT RE 1, H372 classification is not considered to apply to the dermal exposure route on its own.

RAC conclusion on the classification:

RAC supports the Danish proposal for the three white spirits covered by this opinion and background document. The proposal for white spirits type 2 and 3 was withdrawn and therefore RAC has not assessed the information covering these types.

The classification is based on human evidence.

The results from animal studies do not warrant the classification for long-term effects as they are recorded at levels above the recommended guidance values (recommended guidance values for cat.1: Inhalation (rat) ≤ 0,2 mg/l/6h/day and for cat2 0,2 < C ≤ 1,0). It is also important to mention that the type of the adverse effects as measured in humans may be difficult to detect in animals. Since the main adverse effects in humans are related to behavioural changes, in contrast to humans there are only methods available to examine the neurobehavioral or neurophysiological performance in laboratory animals.

Based on the epidemiological studies assessed by IPCS and SCOEL RAC finds that there is an association between exposure to the three types of white spirits proposed for classification by the dossier submitter and chronic toxic encephalopathy. This association can be established with high certainty since the composition of these types of white spirits correspond to the composition of the white spirits that were investigated in the epidemiological studies, i.e. white spirit types containing varying aromatic content with the typical range of 15-20% of aromatics and 80-85% of aliphatic and alicyclic hydrocarbons..

Based on the evaluations of IPCS and SCOEL, rather than a completely independent assessment of all the individual studies, RAC summarizes both evaluations and states, that Stoddard solvent, white spirit type 0 and white spirit type 1 all can produce a number of serious health effects in the central nervous system progressing to chronic toxic encephalopathy after prolonged exposure in humans. Therefore, classification with STOT RE 1 - H372 (CLP Regulation) and Xn; R48/20 (Directive 67/548/EEC) is warranted for the three types of white spirit covered in this Opinion.

Overall, the summaries of the human data provided by IPCS and SCOEL exclusively address the inhalation route of exposure. A hazard statement covering this exposure route specifically would be informative. However, dermal exposure may also contribute to systemic exposure. Assuming a dermal uptake rate of white spirit of 0.02 mg/cm²/h, an exposed area of 2000 cm², and an exposure duration of 1 h, the daily dermal dose would be 40 mg, i.e. 7% of the daily dose via inhalation at the proposed OEL (SCOEL). Since both inhalation and dermal exposures may contribute to the hazard of white spirits, RAC is of the opinion that the label H372 (CLP Regulation) should be applied without specifying the exposure route: i.e. causes damage to the central nervous system through prolonged or repeated exposure.

As already mentioned RAC considered in its opinion development the available data on substance ID provided for white spirits type 0, type 1 and stoddard solvent in the registration dossiers. It was found that a part of the registrants applies a new naming system while the rest applies the old one as presented by the dossier submitter. Although the new naming system has a number of consequences for some types of white spirits (as mentioned above), the data from the registration dossiers have

shown that the composition of the types of white spirits covered by the dossier (i.e. Stoddard solvent, white spirit type 0 and 1) is in general in agreement with the classification proposal.

Additional recommendation:

It should be noted that at a late stage in the forming of this opinion, some information was put forward by industry stakeholders regarding white spirit substances registered under REACH using a new naming proposal for hydrocarbons. The document provided by the Hydrocarbon Solvent Producers' Association (HSPA) identifies seven substances registered under the new proposed naming strategy for hydrocarbons (which includes over 40 substances) which in their view largely correspond to white spirits identified with the conventional EC numbers. Four of these substances are said to correspond to either White Spirit type 0, White Spirit type 1 or Stoddard's Solvent. These substances were automatically allocated provisional EC numbers during the registration process and are currently undergoing a compliance check in order to confirm their substance identity by ECHA.

As the outcome of the ECHA evaluation will not be available before the deadline for the RAC opinion, RAC cannot address the issue in its opinion.

RAC considers that further reflection is necessary on how to apply the new identification developed for REACH for those UVBC substances which are on the market with similar composition to the current entries in Annex VI covered by this opinion.

5.7 Mutagenicity

5.7.1 In vitro data

5.7.2 In vivo data

5.7.3 Human data

5.7.4 Other relevant information

5.7.5 Summary and discussion of mutagenicity

5.8 Carcinogenicity

5.8.1 Carcinogenicity: oral

5.8.2 Carcinogenicity: inhalation

5.8.3 Carcinogenicity: dermal

5.8.4 Carcinogenicity: human data

5.8.5 Other relevant information

5.8.6 Summary and discussion of carcinogenicity

5.9 Toxicity for reproduction

5.9.1 Effects on fertility

5.9.2 Developmental toxicity

5.9.3 Human data

5.9.4 Other relevant information

5.9.5 Summary and discussion of reproductive toxicity

No proposal for harmonised classification for reproductive toxicity.

5.10 Other effects

5.11 Derivation of DNEL(s) or other quantitative or qualitative measure for dose response

Not relevant for this type of dossier.

6 HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

6.1 Explosivity

Including C&L

6.2 Flammability

Including C&L

6.3 Oxidising potential

Including C&L

7 ENVIRONMENTAL HAZARD ASSESSMENT

7.1 Aquatic compartment (including sediment)

7.1.1 Toxicity test results

7.1.1.1 Fish

Short-term toxicity to fish

Long-term toxicity to fish

7.1.1.2 Aquatic invertebrates

Short-term toxicity to aquatic invertebrates

Long-term toxicity to aquatic invertebrates

7.1.1.3 Algae and aquatic plants

7.1.1.4 Sediment organisms

7.1.1.5 Other aquatic organisms

7.1.2 Calculation of Predicted No Effect Concentration (PNEC)

Not relevant for this type of dossier.

7.2 Terrestrial compartment

7.2.1 Toxicity test results

7.2.1.1 Toxicity to soil macro organisms

7.2.1.2 Toxicity to terrestrial plants

7.2.1.3 Toxicity to soil micro-organisms

7.2.1.4 Toxicity to other terrestrial organisms

Toxicity to birds

Toxicity to other above ground organisms

7.2.2 Calculation of Predicted No Effect Concentration (PNEC_soil)

Not relevant for this type of dossier.

7.3 Atmospheric compartment

7.4 Microbiological activity in sewage treatment systems

7.4.1 Toxicity to aquatic micro-organisms

7.4.2 PNEC for sewage treatment plant

Not relevant for this type of dossier.

7.5 Calculation of Predicted No Effect Concentration for secondary poisoning (PNEC_oral)

Not relevant for this type of dossier.

7.6 Conclusion on the environmental classification and labelling

JUSTIFICATION THAT ACTION IS REQUIRED ON A COMMUNITY-WIDE BASIS

As can be seen from the comments made by industry (the Hydrocarbon Solvents Producers Association and CEFIC) which have been received in connection with the public consultation of this classification proposal industry do not at present and do not in future intend to classify the white spirit substances with Xn; R48/20 or STOT RE 1, H372. This is also seen from the available SDSs (from outside Denmark) on the white spirit substances. Thus on EU-wide community basis the white spirit substances are not classified correctly according to the present knowledge on the intrinsic hazardous properties of the substances.

Classification with Xn; R48/20 or STOT RE 1, H372 is to be considered as a toxicity end-point of serious nature as impaired CNS performance and the diverse pattern of CNS symptoms and the irreversible nature of these effects should be considered as adverse effects of concern. Furthermore, the very high tonnage levels of white spirit (EU annual tonnage levels of above 1,000,000 tonnes for some of the types of white spirit) and the disperse and widespread use in several thousands of different chemical products for various purposes (see section 2.2) in combination with the volatility of the substance result in a very high potential for human exposure both in relation to workers and consumers. Thus, it is important that white spirit itself and products containing white spirit are classified and labelled according to the potential hazards in order to warn against the hazard in relation to repeated or prolonged inhalational exposure.

OTHER INFORMATION

Please, note: the original CLH proposal presented in the ECHA Public consultation included also naphtha (petroleum), solvent-refined heavy (EC No 265-095-5; CAS No 64741-92-0, white spirit type 2) and naphtha (petroleum), hydrotreated heavy (EC No 265-150-3; CAS No 64742-48-9, white spirit type 3) which were withdrawn by the dossier submitter.

REFERENCES

Key references:

IPCS (1996). White Spirit (Stoddard Solvent). Environmental Health Criteria 187. International Programme on Chemical Safety, World Health Organization, Geneva.
http://www.inchem.org/documents/ehc/ehc/ehc187.htm

Nielsen GD, Lund SP and Ladefoged O (2006). Neurological Effects of White Spirit: Contribution of Animal Studies during a 30-Year Period. Basic Clin Pharmacol Toxicol **98**, 115-123.

SCOEL (2007). Recommendation of the Scientific Committee on Occupational Exposure Limits for "White Spirit". SCOEL/SUM/87, August 2007.

References quoted from the above-mentioned key references:

Aastrand I, Kilbom A, Övrum P (1975). Exposure to white spirit. I. Concentration in alveolar air and blood during rest and exercise. Scand J Work Environ Health **1**, 15-30.

Arlien-Soeborg P, Bruhn P, Gyldensted C, Melgaard B (1979). Chronic painter's syndrome. Acta Neurol Scand **60**, 149-156.

Arlien-Soeborg P, Zilstorff K, Grandjean B, Pedersen LM (1981). Vestibular dysfunction in occupational chronic solvent intoxication. Clin Otolaryngol **6**, 285-290.

Arlien-Soeborg P, Henriksen I, Gade A, Gyldensted C, Paulson OB (1982). Cerebral blood flow in chronic toxic encephalopathy in house painters exposed to organic solvents. Acta Neurol Scand **66**, 34-41.

Axelson O, Hane M, Hogstedt C (1976). Case reports on chronic psycho-organic syndrome in house painters. Läkartidningen **73**, 317-318 (in Swedish, with English summary).

Baker EL, Letz RE, Eisen EA, Pothier LJ, Plantamura DL, Larson M, Wolford R (1988). Neurobehavioral effects of solvents in construction painters. J Occup Med **30**, 116-123.

Bazylewicz-Walczak B, Marszal-Wisniewska M, Siuda A (1990). The psychological effects of chronic exposure to white spirit in rubber industry workers. Pol J Occup Med **3**, 117-127.

Berstad J, Flekkoey K, Pedersen ON (1989). Encephalopathy and polyneuropathy induced by organic solvents. J Oslo City Hosp **39,** 81-86.

Bleecker ML, Bolla KI, Agnew J, Schwartz BS, Ford DP (1991). Dose- related subclinical neurobehavioral effects of chronic exposure to low levels of organic solvents. Am J Ind Med **19**, 715-728.

Blume J, Hane M, Sundell L, Ydreborg B (1975). Mental function changes among house painters. Läkartidningen **72**, 702-706 (in Swedish, with English summary).

Bolla KI, Schwartz BS, Agnew J, Ford PD, Bleecker ML (1990). Subclinical neuropsychiatric effects of chronic low-level solvent exposure in US paint manufacturers. J Occup Med **32**, 671-677.

Bolla KI, Schwartz BS, Stewart W, Rignani JE, Agnew J, Ford DP (1995). Comparison of neurobehavioral function in workers exposed to a mixture of organic and inorganic lead and in workers exposed to solvents. Am J Ind Med **27**, 231-246.

Bove FJ, Letz R, Baker EL (1989). Sensory thresholds among construction painters: A cross-sectional study using new methods for measuring temperature and vibration sensitivity. J Occup Med **31**, 320-325.

Brackbill RM, Maizlish N, Fischbach T (1990). Risk of neuropsychiatric disability among painters in the United States. Scand J Work Environ Health **16**, 182-188.

CEFIC (1989). Classification and labelling of White Spirits. Document forwarded to the Chairman for the Working Group Classfication and Labelling of Dangerous Substances, August 1989. EC no. XI/748/86-Add. 20.

CEFIC (1991). Classification and labelling of White Spirits. Document forwarded to the Chairman for the Working Group Classfication and Labelling of Dangerous Substances, September 1991. EC no. XI/748/86-Add. 28.

Cherry N, Hutchins H, Pace T, Waldron HA (1985). Neurobehavioural effects of repeated occupational exposure to toluene and paint solvents. Brit J Ind Med **42**, 291- 300.

Demers RY, Markell BL, Wabeke R (1991). Peripheral vibratory sense deficits in solvent-exposed painters. J Occup Med **33**, 1051-1054.

Douglas JF, McKee RH, Cagen SZ, Schmidt SL, Beatty PW, Swanson MS, Schreiner CA, Ulrich CE, Cockrell BY (1993). A neurotoxicity assessment of high flash aromatic naphtha. Toxicol Ind Health **9**, 1047-1058.

Eide I (1990). A review of exposure conditions and possible health effects associated with aerosol and vapour from low-aromatic oil-bases drilling fluids. Ann Occup Hyg **34**, 149-157.

ExxonMobil (2009). Safety data sheets on White Spirit type 1 (Varsol 30, Varsol 40, Varsol 60); White Spirit type 3 (Exxsol D30; Exxsol D40; Exxsol D60, and Exxsol D180/200 SP), and Stoddard solvent (Varsol 1 napthta anti-static).

Fidler A, Baker EL, Letz RE (1987). Neurobehavioural effects of occupational exposure to organic solvents among construction painters. Br J Ind Med **44**, 292-308.

Flodin U, Edling C, Axelson O (1984). Clinical studies of psycho-organic syndromes among workers with exposure to solvents. Am J Ind Med **5**, 287-295.

Ford DP, Schwartz BS, Powell S, Nelson T, Keller L, Sides S, Agnew J, Bolla K, Bleecker M (1991). A quantitative approach to the characterization of cumulative and average solvent exposure in paint manufacturing plants. Am Ind Hyg Assoc J **52**, 226-234.

Gade A, Mortensen EL, Bruhn P (1988). ”Chronic painter’s syndrome”. A reanalysis of psychological test data in a group of diagnosed cases, based on comparison with matched controls. Acta Neurol Scand **77**, 293-306.

Gregersen P, Mikkelsen S, Klausen H, Doessing M, Nielsen H, Thygesen P (1978). A chronic cerebral syndrome in painters. Dementia due to inhalation or of cryptogenic origin? Ugeskr Laeger **140**, 1638-1644 (in Danish, with English summary).

Gregersen P, Klausen H, Elsnab CU (1987). Chronic toxic encephalopathy in solvent-exposed painters in Denmark 1976-1980: Clinical cases and social consequences after a 5-year follow-up. Am J Ind Med **11**, 399-417.

Gubéran E, Usel M, Raymond L, Tissot R, Sweetnam PM (1989). Disability, mortality, and incidence of cancer among Geneva painters and electricians: a historical prospective study. Br J Ind Med **46**, 16-23.

Gyldensted C, Gyldensted M, Arlien-Soeborg P, Bruhn P, Melgaard B (1980). Chronic painter’s syndrome. Toxic encephalopathy with brain atrophy and dementia in professional house painters. In: Proceedings of the 8th Congress of the European Society of Neuroradiology, Strasbourg, 7-8 September 1979. Amsterdam, Kugler Publications, pp 137-140.

Hane M, Axelson O, Blume J, Högstedt C, Sundell L (1977). Psychological function changes among house painters. Scand J Work Health **3**, 91-99.

Hane M and Högstedt C (1980). Subjective symptoms among occupational groups exposed to organic solvents. Läkartidningen **77**, 435-436, 439 (in Swedish, with English summary).

Hass U, Ladefoged O, Lam HR, Østergaard G, Lund SP, Simonsen L (2001). Behavioural effects in rats after prenatal exposure to dearomatized white spirit. Pharmacol Toxicol **89**, 201–207.

Henriksen HR (1980). Kemiske miljøfaktorer ved bygningsarbejder: Mineralsk terpentin. Kemisk sammensætning. Arbejdsmijøinstituttet.

Hissink AM, Krüse J, Kulig BM, Verwei M, Muijser H, Salmon F, Leenheers LH, Owen DE, Lammers JHCM, Freidig AP, McKee RH (2007). Model studies for evaluating the neurobehavioral effects of complex hydrocarbon solvents. III. PBPK Modeling of white spirit constituents as a tool for integrating animal and human test data. Neurotoxicol **28**, 751-760.

Hooisma J, Hänninen H, Emmen HH, Kulig BM (1993a). Behavioral effects of exposure to organic solvents in Dutch painters. Neurotoxicol Teratol **15**, 397-406.

Hooisma J, Hänninen H, Emmen HH, Kulig BM (1993b). Symptoms indicative of effects of organic solvent exposure in Dutch painters. Neurotoxicol Teratol **16**, 613-622.

Kulig BM (1989). The effects of white spirit on neurobehavioral functioning in the rat. Rijswijk The Netherlands TNO Medical/Biological Laboratory (Unpublished report).

Kulig BM (1990). Neurobehavioral effects of white spirits during acute and chronic exposure. Toxicologist **10**, 308.

Lam HR, Löf A, Ladefoged O (1992). Brain concentration of white spirit components and neurotransmitters following three weeks of inhalation exposure of rats. Pharmacol Toxicol **70,** 394-396.

Lam HR, Østergaard G, Ladefoged O (1995). Three weeks' and six months' exposure to aromatic white spirit affect synaptosomal neurochemistry in rats. Toxicol Lett **80**, 39–48.

Lam HR, Plenge P, Jørgensen OS (2001): Effects of white spirits on rat brain 5-HT receptor functions and synaptic remodelling. Neurotoxicol Teratol **23**, 603–608.

Lindström K, Wickström G (1983). Psychological function changes among maintenance house painters exposed to low levels of organic solvents mixtures. Acta Psychiatr Scand **67**, 81-91.

Lund SP, Simonsen L, Hass U, Ladefoged O, Lam HR, Østergaard G (1996). Dearomatized white spirit inhalation exposure causes long-lasting neurophyiological changes in rats. Neurotoxicol Teratol **18**, 67–76.

Lundberg I, Michélsen H, Nise G, Högstedt C, Högberg M, Alfredsson L, Almkvist O, Gustavsson A, Hagman M, Herlofson J, Hindmarsh T, Wennberg A. (1995). Neuropsychiatric function of housepainters with previous long-term heavy exposure to organic solvents. Scand J Work Environ Health **21** (Suppl. 1) , 3-44.

Mikkelsen S (1980). A cohort study of disability pension and death among painters with special regard to disabling presenile dementia as an occupational disease. Scand J Soc Med Suppl **16**, 34-43.

Mikkelsen S, Joergensen M, Browne E, Gyldensted C (1988). Mixed solvent exposure and organic brain damage. Acta Neurol Scand **78**, 1-143.

Pedersen LM, Larsen K, Cohr K-H (1984). Kinetics of white spirit in humans fat and blood during short-term experiment exposure. Acta Pharmacol Toxicol **55**, 308-316.

Pedersen LM, Rasmussen S, Cohr K-H (1987). Further evaluation of the kinetics of white spirit in human volunteers. Pharmacol Toxicol **60**, 135-139.

Savolainen H and Pfäffli P (1982). Neurochemical effects of exposure to white spirit vapour at three concentration levels. Chem Biol Interact **39**, 101-110.

Seppäläinen AM, Lindström K (1982). Neurophysiological findings among house painters exposed to solvents. Scand J Work Environ Health **8**, 131-135.

Spurgeon A, Gray CN, Sims J (1990). An investigation of the possible chronic neuropsychological effects of long-term occupational exposure to organic solvents. Birmingham, University of Birmingham, Institute of Occupational Health (Unpublished report).

Spurgeon A, Gray CN, Sims J, Calvert I, Levy LS, Harvey PG, Harrington JM (1992). Neurobehavioural effects of long-term occupational exposure to organic solvents: two comparable studies. Am J Ind Med **22**, 325-335.

Spurgeon A, Glass DC, Calvert IA, Cunningham-Hill M, Harrington JM (1994). Investigation of dose related neurobehavioural effects in paintmakers exposed to low levels of solvents. Occup Environ Med **51**, 626-630.

Triebig G, Barocka A, Erbguth F, Höll R, Lang C, Lehrl S, Rechlin T, Weidenhammer W, Weltle D (1992a). Neurotoxicity of solvent mixtures in spray painters. II. Neurologic, psychiatric, psychological, and neuroradiologic findings. Int Arch Occup Environ Health **64**, 361-372.

Triebig G, Schaller KH, Weltle D (1992b). Neurotoxicity of solvent mixtures in spray painters. I. Study design, workplace exposure, and questionnaire. Int Arch Occup Environ Health **64**, 353-359.

Triebig G and Hallermann J (2001). Survey of solvent related chronic encephalopathy as an occupational disease in European countries. Occup Environ Med **58**, 575-581.

US-EPA (1998). Guidelines for neurotoxicity risk assessment. U.S. Environmental Protection Agency, Federal Register 1998, 63, 26925-26954.

Van der Hoek JAF, Verberk MM, van der Laan G, Hageman G (2001). Routine diagnostic procedures for chronic enecphalopathy induced by solvents: survey of experts. Occup Environ Med **58**, 382-385.

Zahlsen K, Nilsen AM, Eide I, Nilsen OG (1990). Accumulation and distribution of aliphatic (*n*-nonane), aromatic (1,2,4-trimethylbenzene) and naphthenic (1,2,4-trimethylcyclohexane) hydrocarbons in the rat after repeated inhalation. Pharmacol Toxicol **67**, 436-440.

Zahlsen K, Eide I, Nilsen AM, Nilsen OG (1992) Inhalation kinetics of C6 to C10 aliphatic, aromatic and naphthenic hydrocarbons in rats after repeated exposures. Pharmacol Toxicol **71**, 144-149.

Østergaard G, Lam HR, Ladefoged O, Arlien-Søborg P (1993). Effects of six months' white spirit inhalation exposure in adult and old rats. Pharmacol Toxicol **72**, 34–39.

Other references:

Concawe (2005). Classification and labelling of petroleum substances acccording to EU dangerous substances directive (CONCAWE recommandations – July 2005), report no 6/05, Brussels, 178.

Lammers JHCM, Emmen HH, Muijser H, Hoogendijk EMG, McKee RH, Owen DE, Kulig BM (2007). Model studies for evaluating the neurobehavioral effects of complex hydrocarbon solvents. II. Neurobehavioral effects of white spirit in rat and human. Neurotoxicol **28**, 736-750.