June 2023

The SCOEL recommendation document covers the following substances:

Substance name	EC number	CAS RN
Naphtha (petroleum), hydrodesulfurized heavy - "White spirit, Type 1"	265-185-4	64742-82-1
Naphtha (petroleum), hydrotreated heavy - "White spirit, Type 3"	265-150-3	64742-48-9

Note; "White spirit" - Synonyms and trade names include: Mineral spirit, Shellsol D, Solvent naphtha, Turpentine substitute, Spirdane, Terpentinersatz, Testbenzin, lacknafta, Lakkabensiini

This text is not part of the official SCOEL Recommendation and is provided to give additional helpful information to the reader as regards chemicals addressed by the SCOEL Recommendation. The list is non-exhaustive and is presented for information purposes only.

SCOEL/SUM/87
August 2007
After Consultation

Recommendation of the Scientific Committee on Occupational Exposure Limits for "White Spirit"

8-hour TWA:	20 ppm (116 mg/m³)
STEL (15 min.):	50 ppm (290 mg/m³)
Further notation:	Skin

Conversion factor: 1 ppm = 5.8 mg/m³ 1 mg/m³ = 0.17 ppm
(calculated on an average mol weight of 142)

"White spirit" comprises groups of hydrocarbon mixtures, **for example** those classified by the EU as follows:

White Spirit Type 1: *Naphtha (petroleum), hydrodesulfurized heavy*

A complex combination of hydrocarbons obtained from a catalytic hydrodesulfurization process. It consists of hydrocarbons having carbon numbers predominantly in the range of C_7 through C_{12} and boiling in the range of approximately 90 ^{0}C to 230 ^{0}C (194^{0}F to 446 ^{0}F).

[CAS 64742-82-1]	Carc.Cat.2; R45 Xn; R65	May cause cancer. Harmful: may cause lung damage if swallowed.

(Labelling as a carcinogen is not obligatory if the content of benzene is < 0,1% w/v).

White Spirit Type 3: *Naphtha (petroleum), hydrotreated heavy*

A complex combination of hydrocarbons obtained by treating a petroleum fraction with hydrogen in the presence of a catalyst. It consists of hydrocarbons having carbon numbers predominantly in the range of C_6 through C_{13} and boiling in the range of approximately 65 ^{0}C to 230 ^{0}C (149 ^{0}F to 446 ^{0}F).

[CAS 64742-48-9]	Carc. Cat. 2; R45 Xn; R65	May cause cancer. Harmful: may cause lung damage if swallowed.

(Labelling as a carcinogen is not obligatory if the content of benzene is < 0,1% w/v).

The OEL for white spirit is considered to apply to all complex hydrocarbon mixtures with their main compounds in the range from C_6 to C_{12}.

SUBSTANCE

"White spirit"

Synonyms and trade names include: Mineral spirit, Shellsol D, Solvent naphtha, Turpentine substitute, Spirdane, Terpentinersatz, Testbenzin, lacknafta, Lakkabensiini.

White spirit is the name given to a group of commonly used hydrocarbon solvents, including aromatic solvents, which are products of crude oil after atmospheric fractional distillation into the appropriate boiling ranges. It is a clear colourless solvent with very low water solubility and characteristic odour (odour threshold: approx. 5 mg/m³). Hastings et al. (1984) determined the odour threshold level for Stoddard solvent to be 2 mg/m³. The concentration in air at saturation is approximately 29.000 mg/m³ [5000 ppm] (25 °C) and the vapour pressure (25 °C/101 kPa) is approximately 0.5 kPa.

Different feed stocks and differences in manufacturing lead to variations in composition. The most common variant of white spirit is a mixture of saturated aliphatic and alicyclic C_6-C_{12} hydrocarbons with content of 15-20 % (by weight) of aromatic C_6 – C_{12} hydrocarbons and a boiling range of 130 – 230 °C. The C_6 – C_{12} hydrocarbons (aliphatics, alicyclics and aromatics) are most abundant, constituting 70 - 80% (by weight) of the total (IPCS 1996). The content of aromatics varies between 13- 30%, the content of benzene is less than 0.01% by weight.

Solvent blends may be produced from two or more solvents of different CAS numbers. The resulting products are called "preparations" in regulatory terms and, as such, do not receive CAS numbers. White spirit is however assigned a CAS-number, depending on the type. Examples are given in Table 1 and Tables 4A and 4B.

Table 1. Types of "White spirit"

Types of "white spirit"	CAS No.	EINECS No.	Aromatic content
White Spirit type 1; Standard White Spirit, mineral spirit.	64742-82-1	265-185-4	13 – 30 %; usually in the market: 15-22 %
***White Spirit type** 1, Stoddard solvent; (used only by U.S. producers *)*	8052-41-3	232-489-3	10 – 20%**
White Spirit type 2 (not in use by hydrocarbon producers*)	64741-92-0	265-095-5	?
White Spirit type 3, dearomatized	64742-48-9	265-150-3	< 1 %

* personal communication (Nessel C., EXXON)
** Toxicological profile for Stoddard solvent, ASTDR, 1995

The composition of the various types of white spirit depends on the production process (Type 1: hydrodesulfurized, type 2: solvent extracted and type 3: hydrotreated). Each of the three types of white spirit exists in three different technical grades: low-flash grade (flash point < 30 °C), regular grade (flash point 31 –50 °C) and high-flash grade (flash point > 50 °C).

The following recommendation is based almost exclusively on data on white spirit type 1, CAS 64742-82-1 and on white spirit type 3 CAS 64742-48-9, the two types of white spirit that are mainly used in the European market. However, the recommendation also includes reference to some of the US studies dealing with exposures to Stoddard solvent, CAS 8052-41-3. Stoddard solvent is also considered to be a form of white spirit type 1, but with a different amount of aromatics (e.g. benzene, toluene). Table 2 provides more detail on the relative composition of white spirit on the North European market compared with the US Stoddard solvent.

Table 2. Composition of North European white spirit and Stoddart solvent (IPCS 1996)

	North European white spirit CAS 64742-82-1				**US white spirit (Stoddard solvent)** CAS 8052-41-3			
	Alkanes	**Mono-cyclic alkanes**	**Dicyclic alkanes**	**Aromatics**	**Alkanes**	**Mono-cyclic alkanes**	**Dicyclic alkanes**	**Aromatics**
C_6 –C_{12}	**37**	**26**	**8.9**	**15.4**	**48**	**26**	**12**	**14.7**
Benzene				**0.001**				**0.1**
Toluene				**0.005**				**0.4**
Xylene				**1.3**				**1.4**
Approx. (%w/w)	**72 % specified of total alkanes (12 % unspecified)**				**85 % total alkanes**			

Scope of the present recommendation:

The OEL for white spirit is considered to apply to all complex hydrocarbon mixtures with their main compounds in the range from C_6 to C_{12}. There may be specific identifiable mixtures included in this definition for which emerging scientific data become eventually available, suggesting that a different OEL would be appropriate. For such products, a separate evaluation should be carried out.

OCCURRENCE/USE

White spirit does not occur naturally. However, the single chemical substances in white spirit are present in crude oil. White spirit is used as an extraction solvent, as a cleaning solvent, as degreasing solvent, and as a solvent in aerosols, paints, wood preservative, asphalt products, lacquers and varnishes. Approx. 700.000 tonnes were used in Western Europe (IARC, 1989), with a trend towards higher consumption of dearomatised white spirit (type 3).

TOXICOKINETICS

Since white spirit is a mixture of numerous hydrocarbons with very different chemical properties, the study of toxicokinetics is complex. Aromatic components are generally more soluble in blood than aliphatic and alicyclic hydrocarbon components. The relative percentage of the single compounds and their different physical and chemical properties greatly affect the toxicokinetics of white spirit, as with other hydrocarbon solvents. 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. It is widely distributed throughout the body of humans (brain, kidney, liver and fat).

Volunteers exposed to 0, 300, 600, 1200 mg/m³ (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).

In a single dose 6 hr exposure study by Pedersen et al. (1984c) 12 volunteers were exposed by inhalation to 610 mg/m³ (~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 (S.D.= 0.7).

Acute central nervous system (CNS) effects of white spirit (aromatics: 21.3%) were studied in rats and humans, and effects were compared with CNS concentrations. The CNS concentration was measured in rats, where exposures were for 9 hrs/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)

The overall half-life of white spirit in the body is 46-48 hrs, meaning that steady state in adipose tissue and in the brain will first be reached after approximately 3 weeks (Pedersen et al. 1987). In a single exposure study, 8 male subjects were exposed to 600 mg/m³ (~ 100 ppm) white spirit (< 1% aromatics) in an experimental exposure chamber for 3 hrs. After an interval of 6 to 8 weeks seven of the volunteers were then exposed in a multiple exposure study to 600 mg/m³ of the same white spirit, 6 hrs. 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 hrs after exposure. The study showed that the redistribution phase of white spirit in adipose tissue was very long (approx. 20 hrs. for the first 5 exposures). The total body clearance was estimated to be 263 ml/min. After 5 consecutive days of 6 hrs exposure per day the maximum steady state concentration was approximately 55 mg/kg fat and the minimum steady state concentration approx. 35 mg/kg fat. This is due to the poor blood flow in this tissue and the high solubility of white spirit.

In male rats exposed to 2320 and 4680 mg/m³ (400, 800 ppm) of white spirit (20% aromatics) for 3 weeks, 6 h/d, 5 d/w, 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).

The concentration of white spirit (11.7% aromatics) in adipose tissue was measured in rats exposed for 17 weeks (5 d/w, 6 h/d) to air concentrations of 575, 2875 and 5750 mg/m³ (100, 500 and 1000 ppm). Concentrations measured in fat were 180 mg/kg and 440 mg/kg, respectively (Savolainen and Pfäffli, 1982).

Following application of white spirit to a 12 cm² area of rat tail, Verkkala et al. (1984) reported the absorption of 210-260 mg in 3 h, corresponding to about 7 mg/cm^2/h. The Verkkala study cannot, however, be used to assess skin penetration since the absorbed dose was estimated from the weight loss of white spirit. Weight loss is a poor indicator of dermal absorption as evaporation is not taken into account. For comparison, dermal uptake rates of 0.0008 mg/cm³/h for n-hexane (Lodén 1986), 0.08 for toluene (Ursin et al., 1995), 0.1 (Lodén, 1986) and 1.8 (Blank and McAuliffe 1985) for benzene, and 0.13 mg/cm²/h for m-xylene (Riihimäki, 1979) have been reported from human *in vivo* studies. An uptake rate of 0.02 mg/cm²/h was reported for a jet fuel containing 18% C7-C16 aromatics and 82% C8-C17 aliphatics in rat skin in vitro. (McDougal, 2000). 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 (50% uptake x 10 m^3/d x 116 mg/m^3 = 580 mg/d).

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

Effects of different types of white spirit were studied after skin application in rats (Verkkala et al., 1984). Overall, these studies did not suggest major differences between products with high and low aromatic content.

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

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

There were no data on the transfer of white spirit through the placenta. There are two Russian reports dealing with occupational exposure levels of about 300 mg/m³ of unspecified petroleum solvents. Levels of non-specified solvents were found in the tissue of embryos aborted by female workers, newborn infants had solvents levels in the blood of 5 mg/l, while the umbilical cord of their mothers contained 3.5 mg/l. In the other report, solvent was present in the milk of all examined women (n=71) in concentrations of about 0.5 mg/l (IPCS, 1982).

Very little is known of 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, catalysed by monooxygenases, to alcohols.

There are only three reports on the urinary excretion of white spirit or its metabolites: dimethylbenzoic acids have been identified in the urine of occupationally exposed workers (Savolainen and Päffli, 1982) and in experimentally exposed rats (Verkkala et al., 1984). Dimethylbenzoic acids are metabolites of trimethylbenzene isomers, which account for

approximately 2 % of the aromatic fraction of white spirit. It appears that other components in white spirit interfere with the metabolic elimination of 1, 2, 4-trimethylbenzene (Järnberg et al., 1998).

HEALTH SIGNIFICANCE

ANIMAL STUDIES. Short-term and long-term pathological effects.

In short- and long-term inhalation studies on white spirits, the respiratory system, haematopoietic system, the central nervous system, liver and kidney were generally the target organs.

Respiratory depression was seen in mice following 1 min of exposure to 10,000 mg/m³ (1700 ppm, aerosol and vapour; Stoddard solvent, 15 % aromatics). Exposure to 350 or 1200 mg/m³ of dearomatised white spirit did not induce sensory irritation. Exposure to an aerosol level of 3200 mg/m³ of "High Aromatic Solvent" induced a reduction in respiratory rate of more than 50 % (Carpenter et al. 1977).

Riley et al. (1984) exposed two groups of six female rats to white spirit at a mean concentration level of 214 mg/m³ [37 ppm] (b. p. range 150-195 °C, 61 % aliphatics, 20 % cyclic aliphatics, 19% aromatics) for 4 h/d in 4 consecutive days. At the beginning of exposure on day 0 the mean atmospheric concentration of white spirit was 291 mg/m³ (~ 50 ppm), decreasing on day 1 to 191 (~ 33 ppm), on day 2 to 187 (~ 32 ppm) and on day 3 to at least 186 mg/m³ (~ 32 ppm), reflecting the technical problems at the beginning of the exposure period. In the exposed group, histopathological examination of the respiratory tract revealed the presence of inflammatory cell infiltrate in the nasal cavity, trachea and larynx, loss of cilia, hyperplasia of mucosa cells and basal cells, and squamous cell metaplasia. The constituent of white spirit responsible for the tissue damage is uncertain. No such findings were apparent in the control group. Since the exposure level was not clearly controlled and standardized and histopathological responses were suggestive of aerosol exposure, this study is not useful for setting an OEL.

Blair et al. (1979) performed a study in which rats of both sexes inhaled 0, 2000, 4000 and 7500 mg/m³ (345, 690, 1292 ppm) of white spirit (boiling point range 150 – 200°C, 56 % aliphatics, 19 % aromatics) for 6h/d, 5d/w, 13 weeks. No deaths and no clinical signs were seen, except for slight lethargy in the animals of the highest exposure group. There was evidence of extramedullary haematopoiesis, kidney lesions (hyaline droplets, tubular basophilia) in male rats in the lowest exposed group (2000 mg/m³). Female kidney weights were increased in the two higher exposure group as well, but marginally and without accompanying histopathology.

Brain weight in rats was not affected by exposures to white spirit up to 800 ppm with a high content of aromatics (Lam et al. 1995; Østergaard et al. 1993) nor with white spirit with a low content where concentrations were up to 922 ppm (Phillips and Egan 1984). Histopathology did not suggest adverse peripheral or central nervous system (CNS) effects in rats exposed to 1320 ppm of a white spirit with a high content of aromatics (Douglas et al. 1993), or dogs exposed to 300 ppm of a similar white spirit (Carpenter 1975a). A similar lack of effect was observed in mice, rats and dogs exposed to white spirit with a low content of aromatics (NTP 2004; Lund et al. 1996; Kulig 1990; Phillips and Egan 1984; Carpenter et al. 1975b) at concentrations up to 2200 ppm in rats (NTP 2004). The animal studies using long-term administration of white spirit consistently showed no decrease in brain weight and no exposure-dependent effect using conventional histopathology. The histopathological studies

did not indicate critical effects; a comprehensive summary of the studies can be found in Nielsen et al. (2006).

Vitamin C status and effects of white spirit in guinea pig studies

The water soluble vitamin C (the active form is L-ascorbic acid (AA), which may be regenerated from the oxidised form, dehydroascorbic acid) constitutes an important part of the vital antioxidant defence (e.g. Bertinato et 2007; Burk et al. 2006). Man, guinea pigs, bats, monkeys, and anthropoid apes are among the few mammals which are not able to synthesize vitamin C (Ginter 1979) due to loss of L-gulono-γ-lactone oxidase (Ginter 1979; Nishikimi et al. 1994); they rely on vitamin C supply in foods. This is in contrast to the commonly used laboratory animals, e.g. the mouse, rat, rabbit, hamster, dog and pig (Ginter 1979).

Food rich in vitamin C is seasonal in the cold and temper belts. Thus, a proportion of the human population may suffer from latent vitamin C deficiency. Also, a proportion of the population has been shown to have raised vitamin C requirement, which includes smokers and women using oral contraceptives (Ginter 1979). In the commonly used laboratory animals, the interplay between low vitamin C and white spirit can only be investigated in the guinea pig. For reference of vitamin C status, antioxidant levels and growth rate are considered.

Daily doses from 0.2 to 0.7 mg/100 g b.w. of AA resulted in dose-dependent increase in AA in the liver, spleen and adrenal gland (Collins and Elvehjem 1958). The liver vitamin C was increased 48 times in the 20 mg/day group compared with the 0.8 mg/day group and 58 times in the 420 mg/day group. Vitamin E, glutathione (GSH), superoxide dismutase, catalase, GSH peroxidase, and cytochrome oxidase were similar in the three groups, whereas uric acid and GSH reductase were highest in the 20 mg/day group and similar in the other two groups. The unsaturated lipid content was also highest in the 20 mg/day group (Barja et al. 1994). Although, tissue saturation are considered to occur at about 50 mg AA/day/animal (c.f. Stanya et al. 1984), an increase in tissue vitamin C level may still occur with higher doses although blood level shows a plateau at about 250 mg AA/kg diet (about 60 mg AA/day/animal) (c.f. Ginter 1979).

In guinea pigs, a daily dose of 0.5 mg vitamin C per animal is considered sufficient to prevent scurvy (Ginter 1979). Body weight gain has been used as an indicator of optimal vitamin C supply. In young guinea pigs with a body weight from 150-450g, a daily dose per animal of AA of less than 0.5 mg/100 g b.w. was less efficient in promoting growth than 0.5 to 2 mg/100 g b.w., which was equally efficient (Collins and Elvehjem 1958). Similarly, in guinea pigs with a body weight of about 250 g, 0.8 mg AA/day/animal (33 mg AA/kg diet) was suboptimal for growth, whereas 20 mg AA/day/animal (660 mg AA/kg diet) showed a higher growth rate. However, a very high dose, about 420 mg AA/day/animal (13 200 mg AA/kg diet), was less efficient for promoting growth, which was approximately equal to the 0.8 mg AA/day dose (Barja et al. 1994). In adults with a body weight of about 400g, 0.2 to 250 mg AA/day/animal was equally efficient in promoting growth (Stanya et al. 1984).

Overall, for vitamin C in tissue and growth rate, the following crude ranges are used for evaluations of the interplay with white spirit: 0.5-5 mg AA/day is suboptimal for growth and resulted in low tissue vitamin C content, 5-250 mg AA/day is sufficient for optimal growth whereas about 400 mg AA/day is suboptimal for growth. These limits will be used for the evaluation of the interplay between vitamin C supply and effects of white spirit, which are available from two studies (Rector et al. 1966; Jenkins et al. 1971).

Rector et al. (1966) exposed Long-Evans and Sprague-Dawley rats, guinea-pigs, New Zealand albino rabbits, squirrel monkeys and beagle dogs for 90 continuous days to white spirit (b.p. range, 140-190 °C, 80-86 % aliphatics and cyclic alkanes, 13-19 % aromatics) at nine different exposure levels in the range of 114 – 1271 mg/m³ (20-219 ppm), together with an air-exposed control group. In addition, groups of the same five species were exposed repeatedly (rather than continuously) for 8h/d, 5d/w, to 0, 596 or 1353 mg/m^3 (0, 103 or 233 ppm) for 30 exposures; half of the rats and guinea pigs that had received 596 mg/m^3 then received a further 30 exposures to 593 mg/m^3 (102 ppm). Body weight was monitored for each animal in the study, and limited haematology, serum biochemistry and, at termination, histopathology examinations were performed.

For the continuous exposure regime, the guinea pig responded in a much more pronounced manner than the other four species. Exposure-related deaths occurred in guinea pigs continuously exposed to 363 mg/m^3 (63 ppm) and above. The cause of death was unclear; the only clear changes evidently caused by the exposure to white spirit were a body weight loss of 4%, congested lungs and histopathological evidence of lung inflammation at the highest exposure concentration(1271 mg/m^3; 219 ppm) and possibly "vacuolar changes" in the peripheral cells of liver lobules at 513 mg/m^3 (88 ppm) and above.

As regards the other species exposed continuously, there were no exposure-dependent deaths and the only clear evidence of toxicity was histopathological evidence of lung inflammation at the top concentration (1271 mg/m^3; 219 ppm), which occurred in all species. Additionally at this dose level a body weight loss of 9% was also recorded in the monkey study only. There were no clear effects in any of these four species at 619 mg/m^3 (107 ppm) and below.

For the repeated exposure regime, there were no deaths, including in guinea pigs, at any exposure level, from 593 mg/m³ (103 ppm) up to 1353 mg/m^3 (233 ppm). During and at the end of the first 6-week exposure period the only evidence of toxicity was some histopathological evidence, not totally convincing according to the authors, for lung congestion and emphysema in guinea pigs at 1353 mg/m^3 (233 ppm). In the guinea pigs (but not in the rats) receiving the two 30-exposure periods to 596/593 mg/m^3 (103/102 ppm) there was a suggestion, again not convincing, of slight lung inflammation. No other effects were seen for any of the species/exposure regimes used in the repeated exposure part of the study, i.e. the NOAEL in rats, rabbits, monkeys and dogs was 1353 mg/m^3 (233 ppm).

The NOAEL in the guinea pigs is accepted to be about 100 ppm (~580 mg/m^3). The vitamin C status of the guinea pigs can be estimated from the quarter of the lettuce each animal received daily (assumed to weigh 50 g) and the vitamin C content, which may vary from 9.3 to 12.2 mg/100g fresh weight (FW) (Hassimotto et al. 2005), about 4 mg/100 g FW (Nicolle et al. 2004) to less than 2 mg/100 g FW (Proteggente et al. 2002), suggesting an estimate of about 5 mg/100 g FW. Thus, each animal received about 2.5 mg vitamin C per day, which classifies the intake as suboptimal for growth and tissue content of vitamin C.

In a 90-day continuous exposure study with white spirit (18-20% aromatics), guinea pigs were exposed to about 900 mg/m^3 (~150 ppm) (Jenkins et al. 1971); in a crude evaluation, the daily supply of vitamin C was estimated from the supply of lettuce (c.f. the evaluation of the Rector et al. (1966) study) and the content of vitamin C in the diet, assuming an intake of 25 g diet/animal/day. In the first part of the study, the A group received the same diet as that used by Rector et al. (1966), i.e. about 2.5 mg vitamin C/animal/day. The B group received a quarter of a lettuce/week and a diet with 200 mg vitamin C/100g diet, corresponding to about 50 mg vitamin C/animal/day. The C group was on a diet with 2000 mg vitamin C/100 g diet and each animal received a quarter of a lettuce per week, corresponding to about 500 mg

vitamin C/day/animal. The mortality in the Hartley strain on the A, B or C diet was 5/10, 5/10 and 3/10, respectively, and the mortality in the NMRI:(ASH) strain was 8/10, 6/10 and 6/10, respectively. Across the diets, the mortality was approximately doubled in the males (9/15 in the Hartley strain and 13/15 in the NMRI: (ASH) strain) compared to the female guinea pigs (4/15 in the Hartley strain and 7/15 in the NMRI: (ASH) strain). In this case, vitamin C in the diet had no clear influence on mortality.

In the second part of the study (Jenkins et al. 1971), male Hartley guinea pigs were exposed to white spirit using a similar protocol to the first part. However, a Rockland diet (60 mg vitamin C/100 g of diet) and the diet with 2000 mg vitamin C were used. Additionally, each animal received a quarter of a lettuce three times per week. The low vitamin C group corresponded to about 16 mg vitamin C/animal/day whereas the high vitamin C group corresponded to about 500 mg vitamin C/animal/day. The increase in mean weight (±SD) during the 90-day period was in white spirit unexposed (control) animals from 362±33 to 658±80 g in the low vitamin C group and from 341±23 to 648±45 g in the high vitamin C group, i.e. a similar weight gain. In the white spirit exposed groups, the weight gain of surviving animals in the low vitamin C group increased from 363±7 to 527±30 g and in the high group from 340±30 to 591±34 g. None of the 15 control animals died in each of the two diet groups, whereas in the white spirit exposed groups, 10/15 animals died in the low vitamin C group and 2/15 in the high group. Thus, death occurred in guinea pigs on a growth sufficient diet in white spirit exposed animals, but death was largely prevented with a diet with a pharmacologically high vitamin C content. From the urinary vitamin C excretion in the two control groups, no support for an insufficient vitamin C supply was found in the low dose group as the urinary ascorbic acid excretion was 19.4±9.5 mg ascorbic acid/24 hrs and the excretion was 19.2±12.9 mg/24 hrs in high vitamin C group. Overall, about 900 mg/m^3 (~150 mg/m^3) at continuous exposure both caused death and impairment of growth in animals not protected by a pharmacological high vitamin C supply.

HUMAN STUDIES

Lack of pathological effects in animal studies is in agreement with experiences in humans. No decrease in brain weight was observed in 103 subjects (98 men and 5 women) with solvent exposures (probably mixed solvent exposure) for at least 10 years and with suspected chronic toxic encephalopathy when compared with two control groups of 643 (forensic controls) and 733 (hospital controls) individuals, respectively. Of the 98 men, 46 were house painters and 14 were spray painters, car painters or ship painters, while 38 had other occupations. Among the five women, two were industrial laboratory workers, one an industrial worker in a plastic goods factory, one a dry cleaner, and one a nurse anaesthetist. The majority of the solvent exposed workers had considerably reduced working capacity assessed by meticulous evaluations by medical specialists and psychologists. Nevertheless, chronic alcoholism was correlated with slightly reduced brain weight (~2 %) (Klinken and Arlien-Søborg 1993).

Irritation in humans

In a controlled chamber study (Lammers et al. 2007), twelve healthy males, 20-23 years old, were exposed to 57 mg/m^3 (10 ppm) or 570 mg/m^3 (100 ppm) white spirit for 4 hours spaced 7 days apart; the content of aromatics was 21.3 %. Reporting of symptoms showed no treatment-related effect as seen from headaches (1/12, low dose), coughing and tearing or stinging eyes (1/12 in each group), drunken feeling (2/12, low dose), and other complaints (3/12 in each group). A small exposure-dependent elongation of the simple reaction time was observed consistently. Although other statistically significant values were reported, they were

either not exposure-dependent or inconsistent with other results from the same domain. Overall, 570 mg/m^3 (100 ppm) white spirit can be considered the NOAEL or close to the NOAEL.

Carpenter et al. (1975a) exposed six volunteers (25 – 59 years old) to Stoddard solvent (47.7% alkanes, 37.6% cycloalkanes, 14.1% aromatics) for 15 min at a vapour concentration of 2700 mg/m³ (470 ppm), the volunteers reported eye irritation (6:6) and lacrimation (3:6), throat irritation (1:6), slight injection of sclera (2:6) and dizziness (2:6). However, all symptoms disappeared 15 min after leaving the chamber. No symptoms were seen in volunteers exposed to 140 mg/m³ (24 ppm), but one of six volunteers had slight and transitory eye irritation when exposed to a level of 850 mg/m³ (150 ppm).

Mild irritation symptoms were found by Hastings et al. (1984) in 25 subjects exposed to white spirit vapour (Stoddard solvent, 35 % aliphatics, 40 % cyclic aliphatics, 25 % aromatics) at a concentration of 600 mg/m³ (102 ppm). Irritation of the nose was experienced by 31 % (15 % in the control group) after 30 min and eye irritation by 36% (24% in the control group). No changes in the rates of eye-blinking, swallowing or breathing were noted. After exposure to 1200 mg/m³ (200 ppm) significantly more volunteers reported irritation of the throat (control group n= 12: 17%, 102 ppm –group: 30%; 204 ppm-group: 60%).

In a 7- hr chamber study, 9 male students with a mean age of 23 years were exposed to 0, 34, 100, 200 or 400 ppm white spirit containing 17% aromatics (Stokholm & Cohr , 1979a,b). A concentration-dependent increase occurred in eye irritation, which was significantly increased in the 400 ppm group. A similar trend was seen for headache and tiredness, which were both increased significantly at 400 ppm. Nine male house painters, mean age 49 years, were also exposed to 0, 50 or 100 ppm white spirit for 7 hrs. A concentration-dependent increase occurred in eye irritation, which was significantly increased at 100 ppm. The irritation effect increased over time.

In a metal works, a questionnaire study was performed after replacement of white spirit containing 18 % aromatics with white spirit with less than 1 % aromatics; white spirit was used for degreasing and as a solvent for lubricating oil. Excessive skin exposure was also present. The unexposed reference group comprised 71 subjects (65 men (m), 6 women (w), mean age of the group was 51y and 30% were smokers). The white spirit only group comprised 148 subjects (135m, 33w, mean age 48y, and 46 % smokers). A group of 146 subjects (139m, 7w, mean age 40y, and 50% smokers) was exposed both to white spirit and a mist of lubricating oil; previously performed measurements showed an oil level of 2-3 mg/m^3. In the white spirit group, 57% was exposed more than 4 hours/day. The mean breathing zone level of white spirit was 37 ppm (120 mg/m^3) with short term peaks up to 120 ppm (700 mg/m^3). The prevalence of nose and throat symptoms was increased significantly in the white spirit group (38 %) and in the mixed exposed group (42 %) compared to the control group (15 %). No significant increase occurred in lower airway symptoms in the white spirit group. Of 175 subjects, 26 felt that the replacement had improved the working environment, whereas 32 subjects reported worsening. It is noted that the difference between the symptom prevalence in the control group and the white spirit group cannot be explained by the difference in age, which is three years.

In a 6 h single-dose experiment 12 volunteers were exposed to 100 ppm of several different types of white spirit (Varnolene, 17.8% w/w aromatics, mean molecular weight of 145; Shellsol TS, low aromatics, mean molecular weight of 170; Exxsol D 40, low aromatics, mean molecular weight of 138) . There was an interval of 1 week between each exposure. Subjects were exposed to all products in a balanced Latin square design and used as their own

controls. According to the self-administrated questionnaires there was no difference during and after exposure in either study in the following symptoms: dryness of the mucous membranes, headache, dizziness, feeling of inebriation, visual disturbances, tremor, feeling of muscle weakness, impairment of coordination, loss of appetite, nausea, vomiting, diarrhoea and fatigue (Pedersen and Cohr (1984a).

In a toxicokinetic study on trimethylbenzene, Järnberg et al. (1996) reported an absence of symptoms such as headache, fatigue, dizziness and irritation of the eyes, nose and throat in volunteers exposed to 290 mg/m³ (50 ppm) white spirit (16% aromatics) after 2 h exposure. The authors suggested that symptoms occur only at exposure levels > 300 mg/m³ (50 ppm).

Recently, a calculating system has been proposed, which estimates acute central nervous system depression and eye and respiratory tract irritation of complex hydrocarbon solvents. The estimation is based on grouping of compounds, guidance values for the groups, and a reciprocal calculation procedure (McKee et al. 2005). It is noted that the system may be able to predict the acute effects, however, it is also agreed as stated by the authors that "there is no known toxicological relationship between acute and chronic central nervous system effects".

White spirit was not found to be sensitizing in a guinea pig test (API 1986). White spirit can irritate the skin and cause contact eczema as a result of repeated dermal contact, which is worsened by occlusion (Adams, 1983).

In general, the controlled chamber studies suggest a NOAEL for the different types of symptoms at about 100 ppm white spirit. Occupationally exposed subjects have reported symptoms at about this or lower exposure levels. In this case, it is not possible to evaluate a potential confounding from odour and a potential increased sensitivity due to occupational exposures.

Nephrotoxicity

Animal studies.

Pathological changes in the kidney were seen in a study by Phillips and Cockrell (1984), who exposed three groups of 50 Sprague-Dawley and Fisher rats to 0, 570 and 4580 mg/m³ (0, 100 and 800 ppm, respectively) of white spirit (boiling range, 156-204 °C; 55% aliphatics, 27% cycloalkanes and 18% aromatics) for 6 h/d, 5 d/w, for 8 weeks. In a similar study with Fisher rats exposed to C_{10}-C_{11} isoparaffinic solvent (boiling range, 156-176 °C, mainly C_{10}-C_{11} aliphatics) at 1830 and 5480 mg/m³ (300 and 900 ppm) electron microscopic changes ("hyaline droplets") were seen in the kidney. The ultrastructural changes were not totally reversible after a recovery period of 4 weeks following exposure, but the animals regained normal kidney function.

In male rats exposed to 1100 mg/m³ (190 ppm) for 65 days, 2 of 9 animals had changes in kidney tubules (Carpenter et al., 1975).

A 2-year inhalation study with Stoddard solvent IIC (CAS no. 64742-88-7) was carried out in F344/N rats (NTP 2005). Exposures were to 0, 138 (males only), 550, 1100 or 2200 (females only) mg/m^3, 6 h/d, 5 d/w for 104 and 105 weeks. Renal toxicity was evaluated in subgroups of animals at 3 months. In males, kidney cell proliferation increased at ≥ 550 mg/m^3 and α2μ-globulin increased with increasing exposure concentration. Also, the incidences of granular casts and cortical tubule degeneration and regeneration were generally increased, as was the severity of hyaline droplets. These effects did not occur in females.

Generally, the nephrotoxic effects have been found to be species- and sex-specific, since they have only been observed in male rats. The male rat-specific protein alpha 2-microglobulin has been observed to accumulate in protein droplets, and the hindered catabolism of this protein is thought to be a crucial point in the initiation of the nephrotoxic response (Swenberg et al., 1989).

Studies in Humans

Stevenson et al. (1995) investigated the potential for hydrocarbon solvents exposure to induce renal damage in workers of a manufacturing plant (Group 1: solvent-based paint production, group 2: exposure to petroleum-based mineral oils, group 3: low back ground exposure to hydrocarbon solvents, group 4: no exposure to solvents). In a small but significant proportion of these workers exposed to hydrocarbons/mixed solvents there were renal changes, both in the basement membranes, resulting in auto-antibody production (anti–Goodpasture-Syndrome-membrane - GBM), and in the overlying vascular endothelial cells. It is unclear whether white spirit alone or a mixture of solvents may play a role in these adverse effects.

The association between hydrocarbon exposure and anti-basement membrane antibody-mediated disease has been reviewed by Bombassei *et al* (1992). The results from this review suggest that hydrocarbon exposure may be a causal agent in Goodpasture's syndrome, although most reported cases are of individuals developing symptoms rapidly following acute exposure to hydrocarbons.

However, the promotion of autoimmune diseases is not supported from other endpoints, c.f. the section *Connective tissue disease*.

Neurotoxicity and neurobehavioural toxicity

Animal studies.

Neurobehavioural studies

In a recent study (Lammers et al. 2007), male rats were exposed 8 h/d for three consecutive days to 600, 2400 and 4800 mg/m³ (approximately 100, 400 and 800 ppm, respectively) white spirit. The content of aromatics was 21.3%. After the third exposure, a small statistically significant exposure-dependent decrease occurred in body weight at the two highest exposure levels. A reduced body temperature was observed only at the highest exposure level. The test results in the Functional Observational Battery were not affected exposure-dependently, except for a possible effect on gait. However, this effect was not apparent on the third exposure day, which was suggested to be due to enzyme induction, lowering the body burden of white spirit. After the third exposure, the spontaneous motor activity was decreased only at the highest exposure level. Most study parameters in the Visual Discrimination Performance (light stimuli and water reinforcement performance) were not affected by white spirit exposures. Nevertheless, the psychomotor speed was affected exposure-dependently at the two highest levels. Overall, the NOAEL was 600 mg/m^3 (approximately 100 ppm).

Kulig (1989) found minor behavioural changes in male Wistar rats exposed to white spirit vapour levels of 0, 1200, 2400 and 4800 mg/m³ (0, 200, 400 and 800 ppm) (boiling range 158-193 °C; 44% aliphatics, 36% cycloalkanes, 18% aromatics) 8 h/d for three consecutive days. Before exposure, rats were trained to react to a light stimulus on either of two panels and to depress a lever at the illuminated site to access to water. Immediately after the first day of exposure, the latency time from stimulus to reaction was significantly increased in an

exposure-related manner (low-dose 46%, mid-dose 96%, high dose 156%). When tested at the end of day 2 and 3, similar but less marked and less clearly dose-related effects were seen. The dose-related effect was only significant after an acute exposure, but not in the following days.

In an abstract, Kulig (1990) reported the results from exposures of rats to 0 (controls), 1200 (~200 ppm), 2400 (~400 ppm) or 4800 (~800 ppm) mg/m^3 white spirit 8 h/d, 5 d/w for 26 weeks. Psychomotor slowing was observed, but there was no carry over of effect into the post-exposure period.

Most long–term studies showed no adverse effect in most behavioural testing (table 3, Appendix), 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 dearomatised white spirit, 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, the study suggests an effect on the CNS using electrophysiological endpoints (c.f. the section *Electrophysiological studies*); interpretation of effects on electrophysiological endpoints are discussed e.g. by the EPA (1998). Additional support for an exposure-related CNS effect is available from two studies with prenatal exposures although both studies have limitations. Exposures to dearomatized white spirit (Exxsol D-40, cf table 3 for composition), 400 and 800 ppm for 6 h/d on gestation days 7-20 in rats caused long-lasting, but not concentration-dependent-changes in calcium homeostasis in the CNS in the offspring (Edelfors et al. 1999). At 800 ppm, the offspring also showed memory and learning deficit (Hass et. 2001). However, the exposed dams gained less weight than the unexposed control animals.

Neurochemical studies

Comparison of the 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 (table 4A, Appendix). However, persistent changes were apparent (table 4A) in important neurotransmitters at exposures to white spirit with high content of aromatics for six months (Lam et al. 1995; Østergaard et al. 1993).

The upregulation of glial fibrillary acidic protein (table 4B) following exposure to white spirit with a high content of aromatics indicates that the high aromatic-containing product shows more neuronal injury than a product with a low content of aromatics, based on this endpoint,. In general, the high aromatic white spirit had little effect on glutathione levels (table 4B), 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 increased formation of reactive oxygen species (table 4B). Glutamine synthetase was upregulated by high aromatic white spirit, but unaffected by a low aromatic product. As no downregulation occurred, excessive formation of reactive oxygen species is not apparent, which is in agreement with the findings from the GSH content in the CNS.

Finally, the persistent increase in creatine kinase (table 4B), almost exclusively associated with astroglial cells, might suggest proliferation of the glial cells (Savolainen and 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 histopathological studies. 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.

Electrophysiological studies

Central nervous system effects of Exxsol D 40, CAS No. 64742-48-9, boiling range from 145 to 200 °C, and with an aromatic content of <0.4% by weight were studied in rats. Exposures were 6 hrs/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 ppm (2339 mg/m^3) and 800 ppm (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 dearomatized white spirit can induce long-lasting and possibly irreversible effects at 400 and 800 ppm (Lund et al. 1996).

Studies in Humans

Carpenter et al. (1975a) reported slight dizziness in two of six volunteers (between 25 and 59 yr.) exposed to Stoddard solvent vapour (15.1% aromatics) at 2700 mg/m³ (470 ppm) for 15 min.

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

Cohr et al. (1980) exposed house painters (Group II; n=9, mean age 49 y, occupational exposure duration > 10 y) to 0, 290, and 580 mg/m³ (0, 50, 100 ppm) and students (Group I; n=9; mean age: 23 y) to 0, 200, 580, 1160 and 2320 mg/m³ (0, 34, 100, 200, 400 ppm) of white spirit containing 17% of aromatic hydrocarbons, for seven hours. The two groups were divided into subgroups of three persons each, the exposure sequence was partially balanced using block design. The odour of white spirit was masked with perfume. Beside clinical neurological examinations (e.g. Romberg-test) neurobehavioural tests (simple continuous reaction time, paced auditory serial addition test, verbal learning and memory test, purdue pegboard test) were performed before and during exposure (at 1, 3.5 and 6.5 h). Symptoms were registered during exposures (0.25, 1, 3.5, 5 and 6.5 h) and after the exposure (0-1, 1-3, 3-8 hours, during the night, and the next morning) by a self-administered questionnaire.

An increase in CNS symptoms (headache, tiredness, giddiness) was reported by the painters during exposure to 580 mg/m³ (100 ppm), but was reported by students to increase only at higher levels of exposure (1160-2329 mg/m³ or 200-400 ppm). In the group of painters the only neurobehavioural parameter that changed significantly during exposure was short-term memory, with a decrease occurring already at 290 mg/m³ (50 ppm). However, the performance in the long-term memory function test was too inconsistent to allow a reliable evaluation. In students, reaction time and attention function were affected significantly during exposure to 580 mg/m³ (100 ppm) and higher levels. It was not clear whether the effects observed in the painters group and the differences in the performance between the groups were an effect of age, or an age-dependent increase in sensitivity or an occupational increase in sensitivity.

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 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 prevalences of acute symptoms such as nausea, runny noses and malaise. The chronic symptoms, forgetfulness, sensitization, 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, 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 ill defined and thus the study is not useful for setting an OEL for 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 approx. 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 brick layers. 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 was 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 approx. 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.

In this study, 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 y, 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 (~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 (~ 85 ppm) for the past 13 years. It was not clear whether confounding factors such as having (had) a neurological disease, alcohol consumption, and premorbid intelligence were adequately taken into account. Exposure data did not report exposure patterns.

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. Neither showed physical (e.g. blood pressure and eczema of the hands) and neurological (e.g. reflex status, polyneuropathy, paresthesia, nerve conduction velocities, vibration thresholds, hand tremor, gait and ataxia) examinations 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 computerized 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 the setting of an OEL for 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).

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.

Haematological Effects

Case reports and epidemiological studies of humans exposed to unspecified levels of Stoddard solvent or white spirits in the workplace have shown conflicting results. From the limited data available, it is not possible to conclude whether Stoddard solvent adversely affects the haematological system or not. It should be taken into account that US white spirit has a higher content of benzene and toluene than European white spirit. Benzene is a known hematotoxicant.

Reproductive toxicity

Female rats were exposed to 0, 600 and 1400 mg/m³ (0, 100 and 400 ppm) white spirit (Stoddard solvent; boiling range, 157-204 °C; 43 % aliphatics, 33% cycloalkanes, 24 % aromatics) for 6 h/d on days 6 to 15 of gestation. No maternal toxicity was observed and there were no differences in litter size or average foetal weight between the groups. An increased incidence of pups with skeletal variations was observed in the exposed groups. The details of the variations were not reported. However, these effects were considered to be expression of retarded growth and not malformations (API, 1983).

Jakobsen et al. (1986) found signs of maternal toxicity (decreased weight gain and eye irritation) when pregnant Wister rats were exposed 6 h/d to 5700 mg/m³ (950 ppm) of white spirit on days 3 to 20 of gestation. The average foetal body weight was reduced significantly and an increased incidence of delayed ossification and increased number of foetuses with extra ribs were noted. The effects were thought to be primarily a result of maternal toxicity.

No firm conclusions can be drawn from these studies regarding developmental toxicity of white spirit, although the limited data indicate that white spirit type 1 is not likely to be teratogenic.

In a human study, 11 men in a printing factory were occupationally exposed to a wide variety of solvents, including 294 mg/m³ (~ 50 ppm) of white spirit for 1-17 years. Sperm counts, motility, and morphology were monitored for 2 months, and all values were normal (Tuohimaa and Wichmann 1981). This study had several limitations including a small test population, the degree of accuracy of the exposure assessment, exposure to mixed solvents, and variability of sperm parameters.

Other human biochemical effects

12 volunteers were exposed to 0 or 100 ppm of 3 different white spirits, containing 99 % paraffins, 52 % paraffins and 48 % naphthenes, or 57 % paraffins, 25 % naphthenes and 18 % aromatics, respectively, in a 6 hours single exposure experiment (Pedersen and Cohr 1984a). Concentrations of serum α-amylase, cholesterol, triglycerides, sodium, creatine kinase, urate, and glucose were analysed 6 and 48 hrs. after the start of exposure. The only significant changes reported were a decrease (9 %) in serum alpha-amylase concentration (an increase is a marker of acute pancreatitis), and serum (S-)potassium concentrations falling similarly by 9 % ($P < 0.05$) 48 h after exposure to the white spirit high in naphthenes. It is noted that the short term S-potassium level is regulated by the kidney and by the shift of potassium between

the intracellular and extracellular compartment. In general, S-potassium is regulated around 3.5-5.0 mmol/L (Rastergar and Soleimani 2001). Thus, the observed decrease lay within the normal range. Overall, none of the statistically significant values are considered clinically relevant, indicating that the effects on biochemical parameters do not point to an acute effect on the pancreas or the kidney.

In a clinical study, seven volunteers (students) were exposed to 615 mg/m³ (~ 100 ppm) of white spirit (99 % aliphatic alkanes, < 1 % aromatics), 6h/day for 5 days. Five subjects were used as unexposed controls. After exposures the serum creatine kinase activity had increased up to 76 % above the pre-exposure level, and the serum follicle stimulating hormone (FSH) had significantly decreased at maximum by 11 % below the initial level; both were determined 4 days after initiation of exposure. No changes were found in plasma immunoglobulins and orosomucoid (Pedersen and Cohr 1984b). The most marked effect, an increase in plasma creatine kinase (CK), may indicate a neuromuscular effect. However, no consensus exists about the normal range of CK; in one study with 1537 subjects, CK in men varies from 35-520 U/L. Also, exercise may increase CK up to 10 times normal (c.f. Morandi et al. 2006). It is noted that the modest increase in CK may well be within a normal range and be caused by normal physical activity. Overall, no convincing neuromuscular effect is apparent.

Connective tissue disease

Case reports suggest that solvents are associated with various connective tissue diseases (systemic sclerosis, scleroderma, undifferentiated connective tissue disease, systemic lupus erythematosis, and rheumatoid arthritis), particularly systemic sclerosis. A small number of epidemiological studies have shown statistically significant but weak associations between solvent exposure, systemic sclerosis, and undifferentiated connective tissue disease. Existing studies, on balance, do not show conclusively that solvents (either as a group of chemicals or individual chemicals) are causally associated with any connective tissue disease (Garabrant and Dumas 2000).

A case-control study by Diot et al. (2002) investigated 80 case of systemic sclerosis matched with 160 controls. The occupational exposures to silica dust and organic solvents (such as trichloroethylene and other chlorinated solvents, and benzene and other aromatic solvents) were investigated by semiquantitative estimates of exposure. An exposure score was calculated for each of these persons' employment period during which exposure to these toxic agents occurred. The main duration of exposure was more than 10 years in systemic sclerosis patients exposed to silica, chlorinated solvents, white spirit, epoxy resin, ketone, or welding fumes. Mean duration of exposure of less than 10 years was only found for aromatic solvents (8.9 years). Some exposures were shorter, approximately 4–5 years, but with higher level daily exposures. Information on the type of solvents, especially with regard to white spirit, and data on ambient workplace exposure are lacking in this study.

Significantly increased odds ratios for systemic sclerosis were observed in female patients for crystalline silica, trichloroethylene, chlorinated solvents, toluene, aromatic solvents, ketones, white spirit (odds ratio 3.46 95 % CI, 1.48 – 8.11), epoxy resins and welding fumes. No correlation was found among men between occupational exposures and systemic sclerosis, except for "solvents as a whole" (odds ratio 7.11, 95 % CI 1.40 - 36.12), The authors cited Bovenzi et al. (1995), who stated that solvents bind to nucleic acids and proteins, reduce humoral and cell mediated immune responses, and stimulate the production of fibrogenic proteins and growth factors, such as interleukin 1, platelet derived growth factor, transforming growth factor ß, and fibronectin, which are generated in scleroderma. However,

these studies failed to differentiate between single and mixed solvent exposure and ambient air measurements or exposure levels were not reported.

Risk factors from scleroderma in women were investigated in a case-control study from Michigan (1980-91) and Ohio (1980-92). The study included 660 cases, which were at least 18 years old at the time of diagnosis, and 2227 controls, who were matched for race, age and geographic region. Risk factors in self-reported exposures were paint thinners and removers (OR (95 %CI): 1.9 (1.4-2.6)), mineral spirit, naphtha, or white spirit (1.5 (1.1-2.0)), and gasoline (1.8 (1.1-3.1)). However, the risk factors were no longer statistically significant after expert review to address misclassification of self-reported exposure. Neither was there any increasing risk with increasing duration of exposure (Garabrant et al. 2003).

Occupational exposures were assessed in 105 patients with systemic sclerosis (SSc) from 1998 to 2002 in a study by Magnant et al. (2005). Exposure to silica dust, welding fumes, solvents, and epoxy resins were investigated. Groups of 39 exposed and 66 unexposed systemic sclerosis patients were identified and compared according to the severity markers of SSc. There were significant or close to significant associations between toxic exposure and diffuse scleroderma (p=0.06), pulmonary involvement (p=0.10), and negative anticentromere antibodies (p=0.03). The most incriminated products seemed to be epoxy resins (p=0.06), white spirit (p=0.07), aromatic solvents (p=0.07), and silica coupled to welding fumes (p= 0.10). Information on exposure patterns and ambient air concentrations of white spirit were not given in this study.

Genotoxicity

Results obtained in bacterial, yeast and *in vivo* mammalian assays were negative (API, 1984a; API, 1984b; Gochet et al., 1984). However, white spirit (boiling range, 161-199 °C, 14.5 % aromatics) was judged to be positive in an *in vitro* mammalian cell assay both with and without metabolic activation at a cytotoxic level (API, 1987). In a recent study (NTP 2004), Stoddard solvent IIC (CAS no. 64742-88-7) was tested for mutagenicity in S*almonella typhimurium* strains TA97, TA98, TA100 and TA1535, with and without S9 metabolic activation enzymes; all results were negative. *In vivo*, the frequency of micronucleated erythrocytes was assessed in peripheral blood samples from male and female $B6C3F_1$ mice after 3 months of inhalation exposure, and results were negative (NTP 2004). Based on these studies it can be concluded that white spirit is not mutagenic.

Carcinogenicity

The carcinogenic properties of petrochemical products are usually ascribed to the content of benzene or polyaromatic hydrocarbons, especially benzo[a]pyrene. Several epidemiological studies of cancer in workers with potential exposure to white spirit, e.g. painters, metal machinists, construction workers and dry cleaners, are available. Increased relative risks for certain cancers (e.g., lung, kidney, prostate, Hodgkin's lymphoma) had been observed after hydrocarbon solvent exposure (Hardell et al., 1981, 1984; Siemiatycki et al., 1987; Duh and Asal, 1984; Nakamura, 1985; Spirtas et al., 1991), but the studies are insufficient to demonstrate causal association with exposure to white spirits.

A case-referent study using cases of Hodgkin’s disease and non-Hodgkin’s lymphoma among Swedish workers exposed to white spirit implied a slight increase in crude odds ratios, but the study was limited by an insufficient number of cases (Persson et al. 1993).

IARC has published an evaluation on the carcinogenic risk of occupational exposure to petroleum solvents, including white spirit (Group 3) and concluded that there is *inadequate evidence* for the carcinogenicity of petroleum solvents in humans (IARC 1989).

A 2-year inhalation study with Stoddard solvent (CAS no. 64742-88-7) was carried out in F344/N rats (NTP 2005). Exposures were to 0, 138 (males only), 550, 1100 or 2200 (females only) mg/m^3, 6 h/d, 5 d/w. In males, benign pheochromocytoma was observed in 5/50, 9/50, 13/50 and 17/50 and malignant pheochromocytoma in 1/50, 0/50, 0/50 and 2/50, respectively. At 2 years, the incidences of benign and benign or malignant pheochromocytoma (combined) of the adrenal medulla occurred with positive trends in males, and the incidences in the 550 and 1100 mg/m^3 groups were significantly increased. No neoplastic effect was observed in the females. The study concluded that there was some evidence of carcinogenic activity in male F344/N rats, based on increased incidences of adrenal medullary neoplasms.

A 2-year inhalation study was also conducted in B6C3F$_1$ mice (NTP 2005) with exposure concentrations of 0, 550, 1100 or 2200 mg/m^3, 6 h/d, 5 d/w. In females, hepatocellular adenomas were seen in 9/50, 12/50, 15/50 and 18/50, respectively. No neoplastic or non-neoplastic effect was observed in the males. The incidences of hepatocellular adenoma occurred with a positive trend in females, and the incidence of multiple hepatocellular adenomas in females exposed to 2200 mg/m^3 was significantly increased. However, the incidences of hepatocellular adenomas or carcinomas (combined) and hepatocellular carcinoma alone in exposed males and females were not significantly increased. The study concluded that there was equivocal evidence of carcinogenic activity in female B6C3F$_1$ mice.

The limited epidemiological data available are inadequate to estimate the potential cancer risk of white spirit in humans.

RECOMMENDATION

White spirit is a complex mixture of hydrocarbons, mainly saturated aliphatic, alicyclic and aromatic hydrocarbons with the hydrocarbon number of the main components in the range from C_6 to C_{12}. The wide range in composition limits the comparisons that can be made between different studies. In general, the content of aromatics is less than 20 % and dearomatized white spirit is nowadays more commonly in use. However, most of the human data originate from exposure to white spirit which was high in aromatics, and less information is available on dearomatized white spirit.

The recommended OEL for white spirit is set to prevent eye and airway irritation and impairment of neurobehavioural functions.

In a long-term inhalation animal study a NOAEL for pathological effects was 580 mg/m³ (100 ppm) in an 8 h/d, 5 d/w exposure regime in guinea pigs on a low vitamin C diet. The NOAEL in rats, rabbits, monkeys and dogs was 1353 mg/m^3 (233 ppm). Neurochemical and electrophysiological effects were observed at 2320 mg/m³ (400 ppm) and above (Table 4 and the section "*Electrophysiological studies*"). Thus, there are no major differences in neurotoxic potency in these studies, when comparing aromatized and dearomatized white spirit, taking all endpoints into account. Further, there are few human data on effects of dearomatized white spirit. Overall, there is no basis for suggesting different OELs for different types of white spirit.

With respect to occupational exposure, significantly more painters reported acute symptoms (nausea, mucous membrane irritation, vertigo and impaired sense of smell) at an estimated

average exposure to white spirit of 232 mg/m³ (40 ppm) (Seppäläinen and Lindström. 1982). An extended neurobehavioural and neurophysiological study from the same group, but extended to 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) (Lindström and Wickström 1983). In contrast, Mikkelsen et al. (1988) found no impairment in neurobehavioural tests and examinations by computer tomography of workers with an estimated exposure below 230 mg/m³ (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), toluene, xylene, methyl ethyl ketone, methyl isobutyl ketone and 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 NOAEL for long-term effects can be estimated to be no higher than about 540 mg/m^3 (90 ppm).

Departing from the broad range of NOAELs from 40 to 90 ppm, an OEL of 116 mg/m³ (20 ppm) is recommended to prevent subtle chronic nervous system effects and organic brain damage. The OEL covers white spirit with the different content of aromatic, dearomatized white spirit and various aliphatics.

Considering acute effects, several controlled exposure experiments with volunteers have been performed with exposure durations from 2 and up to 7 h (e.g. Cohr et al. 1980, Järnberg et al. 1996, Pedersen and Cohr 1984a, Stokholm and Cohr 1979a, 1979b, Hissink et al, 2007, Lammers et al, 2007). According to Pedersen and Cohr (1984a), there was no increase in self reported symptoms during or after exposure at 100 ppm for up to 6 h. Similarly, exposures at lower levels were negative with respect to self reported symptoms (50 ppm for 2 h, Järnberg et al. 1996) and neurophysiological tests (34 ppm for 7 h, Cohr et al. 1980). However, a significant increase in eye irritation was reported in house painters exposed for 7 h at 100 ppm (Stokholm & Cohr , 1979a, 1979b).

Based on these studies and the one by Seppäläinen and Lindström (1982), a STEL of 290 mg/m³ (50 ppm) is recommended to prevent acute irritation and acute neurological symptoms.

The OEL for white spirit is considered to apply to all complex hydrocarbon mixtures with their main compounds in the range from C_6 to C_{12}. New scientific data for specific identifiable mixtures included in this definition may become available that suggest that a different OEL would be appropriate. For such products, a separate evaluation should be carried out.

White spirit is permeable through human skin and the uptake may contribute substantially to the body burden. Therefore a skin notation is appropriate.

Metabolites in urine such as dimethylbenzoic acids, metabolites of trimethylbenzenes, may be used to estimate the exposure to specific white spirits. However, since the composition of white spirit varies, no biological limit value based on single components or metabolites is proposed.

Difficulties of air measurement are not expected at the recommended limits. There are fully validated analytical methods using gas chromatography with flame ionization detector to

determine a wide range of petroleum distillate fractions such as white spirit, Stoddard solvent, naphthas and mineral spirits.

Standard solutions of the compounds of interest in the elution solvent should be prepared gravimetrically in order to avoid the need for calibration of volumetric apparatus and to reduce errors caused by evaporation of very volatile compounds. Then, the OELs should be reported as mg/m^3. Nevertheless, for practical reasons, airborne concentrations and the OELs of the hydrocarbon mixtures (petroleum fractions) can be reported in ppm by using the conversion factor calculation based on a particular average molecular weight of the fraction considered.

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APPENDIX

Table 3. Comparison of behavioural effects of white spirit with high and low content of aromatics in rats.

I: Product II: CAS No. III: Boiling range in °C	**Aromatics[a] (%)**	**Exposure period**	**Concentration ppm (mg/m^3) and group size (N)[b])**	**Effect**	**Reference**
I: Shell K-30 II: - III: 148-200	20 (v/v)	6 hrs/day 5 days/week for 6 months. 2-month rest: behavioural tests.	400 (2290) N=36 800 (4580) N=36	Three month old rats at start of exposures. No exposure-effect on motor activity, in a functional observational battery, on passive avoidance test, eight-arm radial test and Morrise maze testing. Dito	Østergaard et al. 1993
I: High Flash Aromatic Naphtha II: 64742-95-6	~100 (w/w) ~75% C9	6 hrs/day 5 days/week for 13 weeks	101 (497) N=20 432 (2125) N=20 1320 (6494) N=20	No biological relevant effects on total motor activity or functional tests (grip strength, auditory startle response, hot plate test, and hind limb foot splay). Dito Dito	Douglas et al. 1993
I: Exxsol D 40 II: 64742-48-9 III: 145-200	<0.4 (w/w)	6 hrs/day 5 days/week for 6 month followed by an exposure free period of 70-80 days	400 (2339) N=36 800 (4679) N=36	NOAEL in behavioural tests. Decreased motor activity in the dark period. No significant exposure-effect in functional observational battery, passive avoidance test, Morris water maze tests, and radial arm maze.	Lund et al. 1996
I: Low aromatics (?) II:- III:-	Low aromatics(?)	8 hrs/day 5 d/week for 26 weeks	~200 (1200), ~400 (2400), ~800 (4800) N/group?	No post-exposure effect on learrned performance, and sensory or peripheral nerve function	Kulig 1990

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.

Table 4A. Comparison of central nervous system (CNS) effects in rats at exposures to white spirit with high and low content of aromatics. Transmitter related neurochemical effects.

I: Product II: CAS No. III: Boiling range in °C	**Aromtics (%) [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 hrs/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, Dearomatized 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 forbrain, ↓ 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-HT_{2A} receptor (5-HT_{2A} R); 5-HT_4 receptor (5-HT_4 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 4B. 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.

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 Dearomatized 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 Dearomatized 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 cell creatine kinase. Cerebellar glial cells: No effect on GSH, ↓ succinate dehydrogenase, ↑ creatine kinase (overall: dose-dependent). 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.