Committee for Risk Assessment

RAC

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/F
ECHA/RAC/DOC No CLH-O-0000001745-71-01/F
ECHA/RAC/DOC No CLH-O-0000000944-70-02/F

Adopted

10 June 2011

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

10 June 2011
CLH-O-0000001193-82-03/F
CLH-O-0000001745-71-01/F
CLH-O-0000000944-70-02/F

OPINION OF THE COMMITTEE FOR RISK ASSESSMENT ON A DOSSIER PROPOSING HARMONISED CLASSIFICATION AND LABELLING AT COMMUNITY LEVEL

In accordance with Article 37 (4) of the Regulation (EC) No 1272/2008 (CLP Regulation), the Committee for Risk Assessment (RAC) has adopted an opinion on the proposal for harmonised classification and labelling of

1. **Substance Name:** ***Stoddard solvent***[4]

EC Number: 232-489-3
CAS Number: 8052-41-3

The proposed harmonised classification:

	Regulation (EC) No 1272/2008	Directive 67/548/EEC
Current entry in Annex VI of CLP Regulation (EC) No 1272/2008	Carc. 1B H350, Muta 1B H340, Asp. Tox. 1 H304 P	Carc. Cat. 2; R45, Muta Cat. 2; R46, Xn; R65 P
Proposal by dossier submitter for consideration by RAC	STOT RE 1, H372	Xn; R48/20
Resulting harmonised classification (future entry in Annex VI of CLP Regulation) as proposed by dossier submitter	Carc. 1B H350, Muta 1B H340, Asp. Tox. 1 H304 STOT RE 1, H372 P	Carc. Cat. 2; R45, Muta Cat. 2; R46, Xn; R48/20 Xn; R65 P

[4] *USA term for white spirit, which corresponds to white spirit type 1*

2. **Substance Name***: Naphtha (petroleum), hydrodesulphurized heavy*[5]

EC Number: 265-185-4
CAS Number: 64742-82-1

The proposed harmonised classification:

	Regulation (EC) No 1272/2008	Directive 67/548/EEC
Current entry in Annex VI of CLP Regulation (EC) No 1272/2008	Carc. 1B H350, Muta 1B H340, Asp. Tox. 1 H304 P	Carc. Cat. 2; R45, Muta Cat. 2; R46, Xn; R65 P
Proposal by dossier submitter for consideration by RAC	STOT RE 1, H372	Xn; R48/20
Resulting harmonised classification (future entry in Annex VI of CLP Regulation) as proposed by dossier submitter	Carc. 1B H350, Muta 1B H340, Asp. Tox. 1 H304 STOT RE 1, H372 P	Carc. Cat. 2; R45, Muta Cat. 2; R46, Xn; R48/20 Xn; R65 P

3. **Substance Name***: Solvent naphtha (petroleum), medium aliphatic*[6]**,**

EC Number: 265-191-7
CAS Number: 64742-88-7

The proposed harmonised classification:

	Regulation (EC) No 1272/2008	Directive 67/548/EEC
Current entry in Annex VI of CLP Regulation (EC) No 1272/2008	Asp. Tox. 1 H304	Xn; R65
Proposal by dossier submitter for consideration by RAC	STOT RE 1, H372	Xn; R48/20
Resulting harmonised classification (future entry in Annex VI of CLP Regulation) as proposed by dossier submitter	Asp. Tox. 1 H304 STOT RE 1, H372	Xn; R65 Xn; R48/20

The proposal was submitted by ***Denmark***
and received by RAC on **18 January 2010**

[5] *White spirit type 1*
[6] *White spirit type 0*

PROCESS FOR ADOPTION OF THE OPINION

Denmark has submitted a CLH dossier containing a proposal together with the justification and background information documented in a CLH report. The CLH report was made publicly available in accordance with the requirements of the CLP Regulation at ***http://echa.europa.eu/consultations/harmonised_cl/harmon_cl_prev_cons_en.asp*** on ***18 January 2010***. Parties concerned and MSCAs were invited to submit comments and contributions by ***3 March 2010***. It should be noted that the Danish report originally proposed the classification of five white spirits:

- Stoddard solvent
- Naphtha (petroleum), hydrodesulphurized heavy
- Naphtha (petroleum), solvent-refined heavy
- Naphtha (petroleum), hydrotreated heavy
- Solvent naphtha (petroleum), medium aliphatic

However, after the public consultation and during the opinion development process, Denmark decided to withdraw the proposals for the harmonised classification of naphtha (petroleum), solvent-refined heavy; and naphtha (petroleum), hydrotreated heavy. Therefore, this opinion only covers three white spirits.

ADOPTION OF THE OPINION OF RAC

Rapporteur, appointed by RAC: ***Erich Pospischil***
Co-rapporteur, appointed by RAC: ***Alicja Andersson***

The opinion takes into account the comments of MSCAs and parties concerned provided in accordance with Article 37 (4) of the CLP Regulation.

The RAC opinion on the proposed harmonised classification and labelling has been reached on ***10 June 2010,*** in accordance with Article 37 (4) of the CLP Regulation, giving parties concerned the opportunity to comment. Comments received are compiled in Annex 2.

The RAC Opinion was adopted by ***consensus***

OPINION OF RAC

The RAC adopted the opinion that the following substances should be classified and labelled as follows[1]:

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**

[1] Note that not all hazard classes have been evaluated

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*

SCIENTIFIC GROUNDS FOR THE OPINION

In developing this Opinion, RAC limited its assessment of the hazard potential of the substances concerned to the repeated dose toxicity endpoint; this was the only endpoint addressed in the proposal submitted by Denmark. Both human and animal toxicity data were assessed.

The proposal builds on a "category approach" applied by both IPCS (1996) and SCOEL (2007) in their evaluation of white spirits. This category approach has been based on the following:

(i) The different types of white spirits are mainly identified by production process, overall range for C-atoms and an overall boiling range.
(ii) The different types of white spirits consist up to 80-85% of identical aliphatic and alicyclic hydrocarbons with the same physical properties

Information about the chemical definitions of these substances and the available compositional data showed that these substances cover a range of identical constituents. Consequently, RAC concluded that the data presented by the dossier submitter was generally of relevance to all three substances.

In addition, RAC briefly assessed information on substance ID as provided in registration dossiers for white spirits type 0, type 1 and Stoddard solvent. This information was taken into account while developing the opinion.

Assessment of the original information presented by the dossier submitter

The proposal for harmonised classification of white spirits type 0, type 1 and Stoddard solvent provided by the dossier submitter was based on evaluations made by two different groups of experts (IPCS, 1996; SCOEL, 2007).The dossier submitter referred in its classification proposal to the data collected and evaluated by these groups, and builds its rationale for the classification on the conclusions reached by them. According to the dossier submitter, both IPCS and SCOEL concluded that there was an association between exposure to white spirits of all types (i.e. types of white spirits containing varying aromatic content in the typical range of 15-20% of aromatics like type 0, type 1 and Stoddard solvent but also types of white spirits with a much lower content of aromatics like type 2 (<5%) and type 3 (<1%)) and long-term adverse effects on the central nervous system (CNS) and, on this basis, white spirits type 0, type 1 and Stoddard solvent should be classified for repeated dose toxicity.

Thus the studies included in the dossier as a basis for the classification are the same animal and epidemiological studies as referred to in the IPCS and SCOEL publications. They include neurobehavioral, neurophysiological and neurochemical studies in rats and a high number of epidemiological studies describing human exposure.

Details about the levels of these substances on the market and the nature of the human exposures that have occurred were presented by the dossier submitter and industry. These data indicate that the qualities of white spirit containing varying aromatic content in the typical range of 15-20% aromatic hydrocarbons were the types most widely used from the 1960-ies and up to 1990-2000. From the 80-ies, a gradual shift towards the use of low-aromatic and aromatic-free white spirit occurred and today this quality (especially white spirit type 3) is most widely used in relation to these paint products. These data together with those from the

Nordic countries are in agreement with the various publications that states that occupational exposure of painters during the 60-80-ies predominantly was related to the white spirit types containing varying aromatic content in the typical range of 15-20% of aromatics.

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 effects on central nervous system 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 in the 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.

Assessment of the information received during the public consultation and RAC discussions

The stakeholders that commented during the public consultation offered varying views as to how white spirits should be classified. While representatives from six national institutions from five Member States expressed their support for the classification (one institution from a seventh Member State asked mostly for clarifications), the representatives from three industrial organisations questioned the proposal. The commenting representatives from the Member States were of the opinion that the presented results justify the classification. The industry representatives pointed, however, at the available data reviews (not included in the proposal however assessing mainly the study results provided in the classification proposal) which disregarded any clear association between exposure to white spirits and the chronic neurotoxic effects. In the opinion of the industry representatives, the animal data were inconclusive and failed to provide any molecular mechanism that could explain long-term effects. Further, the lack of exposure data, causality, the imprecise handling of confounders and no clear discrimi-

nation of acute and chronic effects in human studies may weaken the evidence and the significance of the results.

Denmark as dossier submitted concluded that the absence of adverse effects seen in certain animal studies (referred to in the comments from industry) did not influence the classification; the proposal was justified by the available human evidence.

As already mentioned, based on the assessments of IPCS and SCOEL, RAC concluded that long-term exposure to Stoddard solvent, White Spirit type 0 and White Spirit type 1 may cause chronic toxic encephalopathy. Although this conclusion rests upon the overall weight of evidence provided by all studies, appendix A summarises the key epidemiological studies selected by both IPCS and SCOEL.

In its evaluation of neurological findings IPCS described in section 8.2.1.2 of the monograph the available studies. For most of the subjects included in this 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. However, occupational hygiene measurements and exposure estimation by cumulative exposure indices let derive LOAEL´s and NOAELS. Since ongoing ambient air measurements of white spirit indicate a decrease of occupational exposure to aromatized white spirit in painters and better performance in workers protection was seen, an intense reduction of CTE was found out. This observation may support a dose-relationship, which was yet seen in animal studies.

Beside lacking exact ambient air exposure data in most of the epidemiological or case studies co-exposure to other solvents were described. It should be taken into account that the paint technology in the 70ies to 80ies was mainly based on white spirit as a solvent and thinner. In contrast to studies on painters other studies on solvent exposed groups should not be taken into account. Mikkelsen et al. (1988) critically reviewed the literature and presented several items that could bias the studies, as stated in the IPCS-document. The "healthy worker effect" may be present in all cross-sectional studies conducted with active workers. Acute effects caused by recent solvent exposure may lead to an overestimation of the chronic effects on the one hand, or alternatively they may mask an underlying chronic dose-response relationship.

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

Overview of the scientific evidence:
Comparison of available information with the criteria for STOT RE 1(CLP) and R48/20 (Directive 67/548/EEC)

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 cat.2 (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 in 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.

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

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

EU-Commission (2009). Information notices on occupational diseases: a guide to diagnosis. Directorate- General for Employment, pp 279. http://www.beroepsziekten.nl/sites/default/files/documents/Information-Notices-2009.pdf

Appendix A. Epidemiological studies on workers predominantly exposed to white spirit and dose-response related findings (from IPCS 1996 and SCOEL 2007)

Additional information

The Background Document, attached as Annex 1, and Annex 2 gives the detailed scientific grounds for the Opinion.

ANNEXES:

Annex 1	Background Document (BD)
Annex 2	Comments received on the CLH report, response to comments provided by the dossier submitter and rapporteurs' comments (excl. confidential information)

Appendix A.

Epidemiological studies on workers predominantly exposed to white spirit and dose-response related findings (from IPCS 1996 and SCOEL 2007)

Reference/type of study	Groups studied	Exposure	Results
Lindström and Wickström (1983) Cross-sectional study. Questionnaire and 8 neuropsychological tests determining intelligence and psychomotor performance	219 housepainters and 229 reinforcement workers	The mean exposure period was 22 years with an estimated average level of white spirit of 40 ppm (232 mg/m³) during working hours; exposure indices made for total lifetime exposure and average exposure levels	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.
Fidler et al. (1987), Cross-sectional study. Questionnaire Neuropsychological tests (8 tests for intellectual functions and psychomotor performance).	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)	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.
Baker et al. (1988) Cross-sectional study Questionnaire Neuropsychological test battery (9 tests determining verbal ability, psychomotor performance and memory).	186 construction painters	Information about intensity and duration were combined and different exposure indices were calculated. Stratification to 6 subgroups, according to the index of lifetime exposure intensity (LEI), 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.

Mikkelsen et al. (1988) Cross-sectional study Neuropsychological test battery (13 tests intellectual functions and psychomotor performance), by neurological tests (motor performance, coordination, reflexes, sensitivity) and by neurophysiological examination (CT).	85 painters and 85 bricklayers	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)
Bove et al. (1989) Cross-sectional study Vibration thresholds and temperature sensitivity.	93 construction painters and 105 unexposed controls	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.
Bazylewicz-Walczak et al. (1990)	226 rubber footwear industry workers and 102 non-exposed	Solely white spirit exposure from gluing. The mean exposure period was about 500 mg/m^3	The performance of the exposed groups (as a total), compared to the controls, was

Cross-sectional study Neuropsychological test battery (7 tests for intellectual functions and 5 tests for psychomotor performance).	hosiery plant workers	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).	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.
Spurgeon et al. (1990,1992) Cross-sectional study Questionnaire concerning symptomatology and psychiatric state 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: Mainly exposed to white spirit with an estimated average level of 50 ppm for 2 days a week. Study group 2: Exposure more diverse 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.
Bolla et al. (1995), Ford et al. (1991) Cross-sectional study Neuropsychological test battery.	144 workers from two paint-manufacturing plants (from same exposure group as Bolla et al. (1990) and Bleecker et al. (1991)) 52 unexposed workers	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.
Lundberg et al. (1995) Cross-sectional study Neuropsychological test bat-	135 house painters and 71 house carpenters, affiliated with their respective trade	In the latter part of the 1950s and in the 1960s, white spirit was the dominating solvent in alkyd-based paints. Their lifetime	Neuropsychiatric symptoms compatible with chronic toxic encephalopathy were more common among the painters than

tery, 12 psychometric tests	unions for at least 10 years before 1970	organic solvent exposure was evaluated through the aid of an interview	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).