Committee for Risk Assessment

RAC

Annex 2
Response to comments document (RCOM)
to the Opinion proposing harmonised classification and labelling at Community level of
white spirit

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

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

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

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

Adopted

10 June 2011

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

COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

[ECHA has compiled the comments received via internet that refer to several hazard classes and entered them under each of the relevant categories/headings as comprehensive as possible. Please note that some of the comments might occur under several headings when splitting the given information is not reasonable.]

Substance names:

1. **Substance Name:** ***Stoddard solvent***[4]
   EC Number: 232-489-3
   CAS Number: 8052-41-3

2. **Substance Name*****: Naphtha (petroleum), hydrodesulphurized heavy***[5]
   EC Number: 265-185-4
   CAS Number: 64742-82-1

3. **Substance Name*****: Solvent naphtha (petroleum), medium aliphatic***[6]
   EC Number: 265-191-7
   CAS Number: 64742-88-7

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2) and naphtha (petroleum), hydrotreated heavy (EC No 265-150-3; CAS No 64742-48-9, white spirit type 3) which were withdrawn by the dossier submitter.]

[4] *USA term for white spirit, which corresponds to white spirit type 1*
[5] *White spirit type 1*
[6] *White spirit type 0*

General comments

Date	Country/ Person/Organisation/ MSCA	Comment	Response	Rapporteur's comment
18/01/2010	**Germany / Tobias Jacobi / Ministerium fuer Umwelt, Forsten und Verbraucherschutz Rheinland-Pfalz**	I find the wording "biocides and pesticides" under "uses" of white spirits in the ECHA News Alert of Jan. 18, 2010 somewhat confusing: According to Directive 2009/128/EC (Art. 3, 10) "pesticide" is the generic term comprising both plant protection products and biocidal products. Hence a biocide is a pesticide. Best regards Tobias Jacobi	This may stem from section 1.2 in the dossier where data from the Nordic Product Registries are given and where the terms biocides and pesticides are used by the registries.	No additional comment
22/02/2010	**Norway / Climate and Pollution Agency**	We support the Danish proposal to classify white spirit, in addition to the existing classification, with Xn; R48/20, Harmful: danger of serious damage to health by prolonged exposure through inhalation, according to Directive 67/548/EEC and STOT RE 1, H372, Causes damage to the central nervous system through prolonged or repeated exposure via inhalation, according to Regulation 1272/2008.	We acknowledge your support to the proposed classification.	No additional comment
22/02/2010	**Denmark / Peter Feddersen /**	I agree with the Danish EPA on this - and that reactive naphtha´s and destillates also deserves to be classified with combinations of R50-53 if possible, since they exhibit such a common widespread general use in countless preparations.	The comment is noted. However, our aim with this dossier is to focus specifically on the Xn; R48/20 and STOT RE 1; H372 classification.	No additional comment
25/02/2010	**United Kingdom / John Wood /**	A warning using the words 'prolonged inhalation' (or prolonged anything) should be accompanied by a definition of what 'prolonged' means. Continually upgrading warnings leads to a numbing of users perception of what real dangers they are being exposed to.	The comment is noted. However, such further guidance is not part of the classification system, where only the adopted standard phrases can be applied.	No additional comment
26/02/2010	**Belgium / Dorothee Arns / Hydrocarbon**	The following conclusions are extracted from the full position paper stated below (under "any other hazard		

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	Solvents Producers Association (HSPA, CEFIC)	classes or endpoints"), and submitted as an attached pdf-file: It is the view of the HSPA (Hydrocarbon Solvents Producers Association, part of CEFIC) that high dose exposure to white spirit produces acute reversible CNS effects, commonly associated with narcosis, but that there is no consistent evidence of more profound neurological effects in humans or animals. To the contrary, the toxicology studies which have been conducted in accordance with international guidelines for such tests revealed negative results for neurological damage in exposed rats, even in studies involving very high exposure levels. In addition, in most of the experimental studies described in the Danish proposal no neurotoxic or behavioral effects were observed. It can be concluded that the experimental evidence does not support classification of white spirit as a target organ toxicant. Thus, the basis for classification relies on human case studies or epidemiological data. However, also in this case only acute CNS effects following high-level exposure to white spirits have been recognized. As described in the full document below, the human evidence has multiple weaknesses in study design, is highly susceptible to confounding, and as a whole does not support a conclusion that white spirits have long term neurological effects on humans at current exposure limits. In an intensive review, Gamble (ref. 13 in the full document) has described the shortcomings and uncertainties of the epidemiological data that is currently available. Moreover, Gamble conducted a study that is more specific (focus was on hydrocarbon solvents only, instead of exposure to	From the CLH-dossier it is clear that the classification for damage to the central nervous system through prolonged exposure first of all is based on the human data. It is acknowledged that data from experimental animal studies may look inconsistent. Nevertheless experimental animal studies with positive findings in relation to the CNS (as shown in table 9 & 10 in the CLH dossier) should not be dismissed but considered together with the findings from the human data, and in this regard we find the animal data as supportive for the classification. Our classification proposal relies on the conclusions of the experts groups of the IPCS and SCOEL, and both groups concluded based on the human epidemiological studies and using a WoE approach a causal association between long term repeated exposure and chronic toxic encephalopathy at concentration levels which are below acute neurotoxic effect levels. We are aware as indicated in your comments that several reviews on the neurotoxicity of solvents have been made by industry. (Gamble 2000; Amoruso et	In addition, Gamble et al summarise associations in appendices 2 and 3 to be 42 significant/201 non significant and 32 significant/200 non significant associations by functional modality. The authors conclude "exposure response showed no consistent or significant pattern for any tests of functional modality. The weight of evidence suggests that exposure to hydrocarbon solvent at current limits does not appear to cause adverse neurobehavioral effects." However, we are of the opinion that Gamble et al point to a number of positive significant associations and a number of inconclusive associations. Considering it unlikely that false D/R relationships occur positive D/R associations should be regarded as strong evidence for differences between groups. The "non significant" associations would rather be seen as inconclusive.

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		solvent mixtures) and more recent compared to the majority of data used in the Danish proposal (i.e. the proposal is largely based on data summarized in the WHO/IPCS Environmental Health Criteria report which was published in 1996), concluding that "the weight of evidence suggests there are no consistent associations between reduced neurobehavioral test performance and low-level hydrocarbon solvent exposures occurring at current exposure levels". Similar conclusions have been made in other reviews by Ridgeway et al. and, more recently, Amuroso et al. (refs, 7 and 3 in the document below), and in reviews on chronic solvent encephalopathy (which includes the "landmark study" of 187 paint-manufacturing workers (ref. 18 in the document below)) describing that the literature does not support chronic low-level solvent exposure as harmful to the CNS. (refs. 19 and 20 in the full paper) Moreover, in the same period as the IPCS review on which the Danish proposal is based, ECETOC concluded in a technical report that "there is no basis for a neurological syndrome in man that is causally related to low level organic solvent exposure (as defined by recent or current OELs)". (ref. 8 in the submitted document below) Especially because no animal evidence exists describing a molecular mechanism that could serve as evidence for the suggested long-term effects, it is unlikely that prolonged/repeated exposure to solvents via inhalation induces serious damage to the central nervous system as is suggested by this proposed classification. In summary, according to the guidelines, classification should normally be done based on evidence from animal data. Industry has conducted all required tests to assess the toxicity of white spirits, which was	al. 2008 and ECETOC 1996). However, *no further original data* compared to the evaluations of IPCS and SCOEL has been introduced and the reviews are not addressing white spirit in such a specific and focused way as the IPCS and SCOEL evaluations. Gamble (2000) performs a WoE approach on a series of studies with painters and includes references with exposure from various hydrocarbon solvents and does not specifically focus on white spirit. However the studies where white spirit exposure is mentioned are studies which are also covered by the IPCS and SCOEL evaluations. Furthermore, Gamble (2000) does not include or discuss the IPCS (1996) evaluation on white spirit in his work. Our classification proposal refers to two independent experts groups (IPCS and SCOEL) with groups of experts specifically nominated for the assessment of the white spirit data and therefore we find these evaluations to be more authoritative than the industry review presented by Gamble addressing hydrocarbon solvent exposure in general. Ridgway et al (2003), and Schaumburg & Spencer (2000) also address many different kind of organic solvents, and	

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		currently re-assessed through REACH, and no long-term neurological effects could be observed in laboratory animals. Subsequently, additional information can be obtained from data in humans; however, these data have many weaknesses and remain inconclusive. Therefore, due to the high level of uncertainty surrounding the possible long-term effects of exposure to white spirits and the absence of supportive animal data, it is concluded that the weight of evidence does not warrant classification for specific target organ toxicity via the inhalation route of exposure.	make an assessment of this overall database. Again we do not find that a detailed evaluation of the evidence in relation to white spirit has been performed in these reviews. The most extensive toxicological review of white spirit is performed by Amoroso (2008). However, in relation to RDT and neurotoxicity emphasis is mainly put on the animal studies covering the same studies as evaluated by SCOEL. Only two epidemiological studies (from 1990 and 1994 and which are also included in the assessment by IPCS and SCOEL) are described in relation to neurotoxicity, and the conclusion by Amoruso et al. 2008 is then further based on the reviews by Gamble (2000); Ridgway et al. (2003); ECETOC (1996) and Schaumburg & Spencer (2000) . Also the ECETOC (1996) evaluation on chronic neurotoxicity of solvents covers a broad series of organic solvents and white spirit is only specifically covered in relation to experimental animals studies (all of which also are covered by the IPCS and SCOEL evaluations). So overall, since no new data are introduced, we think that an evaluation of white spirit should rely on documents	The studies included by Gamble (2000) included working populations exposed to hydrocarbons other than white spirits, eg. toluene, xylene, ethylbenzene, acetates.

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			which specifically address white spirit. The most detailed and authoritative evaluations that have been made on white spirit are by the two independent expert groups under IPCS and SCOEL.	
26/02/2010	**United Kingdom / Adam Mather / Tetrosyl Ltd**	I have no issue with the upgraded classification for the material where it would be mobile and easily transportable to air, water and consumer etc. However, where the substances is used in a formulation, where that formulation has structure and viscosity, and to a degree, the solvent is 'locked in' then I think the classification is severe. If a viscosity derogation could be applied, in the same way as R65 is applied to certain hydrocarbons, but this phrase can be excluded if the preparation is higher than 30 seconds in a 3mm ISO cup or a kinematic viscosity higher than 7 x 10 (-6) m squared per second. This would be more fair, consistent, and helpful to formulators.	The comment is noted. Our classification proposal addresses the substances as such. For preparations/ mixtures in which these substances are used the general rules for classification of mixtures have to apply.	No additional comment
03/03/2010	**Belgium / Bohdan Dmytrasz / CONCAWE**	It should be noted that while white spirits and refinery naphtha process streams have historically shared the EINECS/CASRN identifiers listed in the supporting documentation prepared by Denmark, white spirits and refinery naphtha process streams will be considered as different substances under REACH. The identifiers cited in the documentation will be retained for refinery naphtha process streams; new identifiers will be assigned to the substances referred to as white spirits. It should also be noted that the predominant use of refinery naphtha process streams is as a fuel components and chemical feedstock streams. Refinery process naphtha streams are not used in aerosols, paints, lacquers and varnishes.	The comment is noted. We have recently been aware of the new substance identification system developed by the Hydrocarbon Solvents Producers (HSPA) to be used in REACH registration of hydrocarbon solvents. However, at this stage we have to rely on the substance identification of EINECS. Thus it may be a task for the future to transfer the classifications from the EINECS substances to the new substance categories defined by the new HSPA identification system.	No additional comment

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Carcinogenicity

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22/02/2010	**Denmark / Peter Feddersen /**	Most naphtha´s are officially classified with Carc2;R45, which rarely comes into use due to the "P" label. This gives rise to much confusion for the downstream user. If it can be shown that the benzene content is less than 0,1 Wt% the Carc2 classification can be omitted. However - it is rarely "shown" - and it is rarely documented on the SDS. It is just the "de facto" standard that naphthas remain unclassified. If this really is the case - the general official classification should be omitted - and the label "P" should read the opposite: If it can be shown that the benzene content exceeds 0,1 wt.% benzene, the substance must be classified Carc2:R45	The comment is noted. According to the present classification it is the obligation of industry to document that the benzene content is below 0.1 % if the classification with Carc2; R45 should not apply. We support this current approach.	No additional comment

Mutagenicity

Date	Country/ Person/Organisation/ MSCA	Comment	Response	Rapporteur's comment

Toxicity to reproduction

Date	Country/ Person/Organisation/ MSCA	Comment	Response	Rapporteur's comment

Respiratory sensitisation

Date	Country/ Person/Organisation/ MSCA	Comment	Response	Rapporteur's comment

Other hazards and endpoints

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22/02/2010	**Norway / Climate and Pollution Agency**	From the CLH report it is evident that animal studies not alone would meet the classification criteria for Xn; R48/20 or STOT RE 1, H372. However, due to the numerous amounts of epidemiological studies with exposure to white spirit, showing clear impaired CNS performance, with a dose-response relationship in some of the studies, a classification as proposed by Denmark is warranted. We also agree to the approach made by Denmark to include all types of white spirit in the proposal. This was based on the large overlap of constituents between the various types of white spirit and the difficulties in the identification of toxic responses from the various types. A harmonized classification of white spirit in Europe is also important since white spirit is classified differently in Europe for effects on health.	We acknowledge your support for the proposed classification.	No additional comment
22/02/2010	**Norway / Climate and Pollution Agency**	We support the Danish proposal to classify white spirit, in addition to the existing classification, with Xn; R48/20, Harmful: danger of serious damage to health by prolonged exposure through inhalation, according to Directive 67/548/EEC and STOT RE 1, H372, Causes damage to the central nervous system through prolonged or repeated exposure via inhalation, according to Regulation 1272/2008.	-	No additional comment

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		(ECHA: transferred from general comments)		
26/02/2010	**Belgium / Dorothee Arns / Hydrocarbon Solvents Producers Association (HSPA, CEFIC)**	Industry objections to the Danish proposal for harmonized classification and labeling of white spirits The Hydrocarbon Solvents Producers Association (HSPA) asserts that the Danish Environmental Protection Agency has failed to justify the proposal to classify white spirits based upon the guidelines as harmful; danger of serious damage to health by prolonged exposure through inhalation (R48/R20) or serious damage to the central nervous system through prolonged/repeated exposure via inhalation (STOT RE 1, H372). In accordance with regulation (EC) 1272/2008 on the classification, labeling and packaging of substances1, the classification requirements for specific target organ toxicity via inhalation (previously R48/20 classification) include the following: - Category 1: Substances that have produced significant toxicity in humans or that, on the basis of evidence from studies in experimental animals, can be presumed to have the potential to produce significant toxicity in humans following repeated exposure. When considering results of animal studies, the guidance vapor concentration in rats for category 1 is < 0.2 mg/l. - Category 2: Substances that on the basis of evidence from studies in experimental animals can be presumed to have the potential to be harmful to human health following repeated exposure. Substances are classified in category 2 for target organ toxicity (repeated exposure) on the basis of observations from		It should be noted that there is (has been) no substantial discussion in the available literature on differences in toxicity of white spirit in experimental animals of different strains and in humans.

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		appropriate studies in experimental animals in which significant toxic effects, of relevance to human health, were produced at generally moderate exposure concentrations. The guidance concentration (vapor, in rats) for category 2 is < 1 mg/l (6 hr). In addition, under the previous Dangerous Substances Directive (67/548/EEC)2, the guidance value for classification of R48/20 is lower than 0.25 mg/l, 6h/day (inhalation, rat, 90-day subchronic study; for a sub-acute 28 day toxicity study, the value should be increased approximately 3-fold). The HSPA position is based on a critical review of the currently available data from toxicological- and epidemiological studies, concluding that the current available toxicological data do not support classification according to these guidelines. Animal studies (non-neurological) There have been numerous repeated dose/exposure studies of full range and de-aromatized white spirits, which were recently summarized by Amoruso et al.3 Repeated exposure by inhalation at levels up to and including 800 ppm (approximately 4 mg/l, which is significantly higher than the classification guidelines) has produced no consistent findings other than alpha 2-U-globulin mediated renal effects in male rats. The renal effects, which were previously referred to as "light hydrocarbon nephropathy", are male rat specific and not considered to have any human relevance4. None of these studies would be a basis for classification as either R48/20 or a target organ toxicant.	RCOM to your comments on animal data: As indicated in our RCOM above we find the experimental animal data as	

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		Animal studies (neurological) One of the key references used by the Danish EPA is a review by Nielsen et al., in which they summarize a number of neurotoxicity studies of full range and de-aromatized white spirits.5 An overall conclusion from their review was that there was no consistent evidence of structural changes in the nervous system detectable by routine histopathology after inhalation of white spirits. They did, however, point to certain behavioral and neurochemical studies which they considered to have provided evidence of effects of white spirits in animals. In the Danish EPA report, conclusions of these studies suggesting an effect on the central nervous system (CNS) detected by electrophysiological- and neurobehavioral endpoints are highlighted. However, it is difficult to assess these parameters. For example, it is not well established what the normal range in laboratory animals is in these types of tests; when is a finding different from what is considered 'normal' or even adverse? Moreover, are the very minor statistical significant differences that are observed also biologically significant, i.e. toxicologically relevant? For changes in behavior or motor function in animals, this is hard to assess, especially if these are not related to any neuro-pathology. Therefore, it is difficult to use these studies for regulatory purposes. An example is the study by Lund et al.6 that is used in the Danish proposal as the major evidence for neurotoxic effects in laboratory animals. Here, the authors report a significant decreased activity of the animals during the dark period after exposure to 800 ppm dearomatized white spirit for 6 months and a 2 month exposure-free period. However, these results were (slightly)	supportive and we agree that the data on its own do not comply with the criteria for R48/20 or STOT RE classification. However, as the MoA for chronic neurotoxicity in humans is not established and the most relevant toxicological parameter in experimental animals can not be defined, positive findings with respect to the various neurobehavioural, neurophysicological and neurochemcial end-points in experimental animals should be considered carefully, as such data indicate that certain parameters indeed are affected by the white spirit exposure. Also we find it important to consider the toxicokinetic data from animal experiments as these data show that the various hydrocarbon components from white spirit actually reach the brain and that they accumulate in the brain tissue.	

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		statistically significant (P=0.045) only the first weekend that these measurements were done, whereas in the second weekend only a trend was observed towards a decrease in activity (P=0.217). No data are shown for the light period (although it is mentioned that the activities were not different between groups), and moreover, no results are shown or described for the 400 ppm dose group. In addition, both concentrations are very high and far above the current exposure limits. In addition, there are numerous studies describing that there is no association between chronic solvent exposure and neurological effects, which is already apparent from the review by Nielsen et al. This is supported in other reviews, for example in a similar review conducted by Amoruso et al. in 2008.3 One of the main conclusions of the Amoruso review is, that most associations described by authors as evidence for long-lasting or even irreversible changes, are generally subtle in nature, and not related to functional deficits, behavioral- or pathological changes. Ridgway et.al. came to similar conclusions after reviewing the information on neurotoxicity studies of animals summarized by the World Health Organization.7 Moreover, in the ECETOC technical report on chronic neurotoxicity of solvents, it is concluded that "subchronic or chronic inhalation exposure to white spirits did not have any post exposure behavioral or neuro-pathological effects".8 They therefore determined the NOAEL from the highest concentration tested with respect to neurotoxicity endpoints (800 ppm (4.2-4.8 mg/L), which is far above the guidance values for classification), showing no evidence of chronic CNS damage.		

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		Described below are two publications , documenting studies which separately evaluated the neurotoxic potential of the aliphatic and aromatic constituents of white spirit in rats. These were conducted in accordance with regulatory guidelines for neutoxicity investigations, followed Good Laboratory Practice (GLP) requirements and were fully audited by quality assurance specialists. In both studies animals were exposed by inhalation, 6 hours/day, 5 days/week for 13 weeks. The rats were assessed both during and after the exposure period using standard methods for functional observations and motor activity, and were then sacrificed and examined histologically for pathological changes in the nervous system. The first of these studies by Douglas9 aimed to address the neurotoxic potential of the aromatic constituents of full range white spirits, which are C9-C14 aliphatic solvents containing up to 25% of essentially C9-, aromatics. The tested substance is called "high flash aromatic naphtha" compositionally is a good match for the aromatic constituents found in full range white spirit. The highest concentration used in this study (1320 ppm, approximately 6600 mg/m3) was the maximally attainable vapor concentration under these test conditions. All animals survived the exposure period and there was little evidence of treatment related effects other than reduced weight gain in the highest exposure group. There were no consistent changes in motor activity or functional observations during or after exposure, and examination of the nervous system tissues provided no evidence of pathological or degenerative changes. This study demonstrated that the aromatic constituents of white spirit do not cause either pathological or		

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		neurobehavioral changes even after repeated exposures at levels up to 6600 mg/m3, significantly higher than the current classification guidelines. The second study evaluated a substance called light alkylate distillate which is an essentially pure isoparaffinic substance with constituents having carbon numbers predominantly in the range of C5-C8, and similar to the more volatile aliphatic constituents of white spirit.10 In this study rats were exposed 6 hours/day, 5 days/week for 13 weeks at vapor concentrations up to 6646 ppm. As in the Douglas study, animals were examined after 5, 9 and 13 weeks of exposure for functional observations and motor activity. At study termination the animals were sacrificed for pathological investigation. There was no evidence of impairment in the functional observation battery, no changes in motor activity were observed and no evidence of pathological changes was identified in the microscopic investigation of nervous system tissue. The only effects of treatment were evidence of male rat kidney effects which is a male-rat specific effect, not relevant to humans, and significantly enlarged livers in the high dose animals, which can be regarded as an adaptive effect to the high exposure. As stated in the CLP guidance, changes in organ weight without any sign of organ dysfunction and substance-induced species specific mechanisms of toxicity like the kidney effects observed here, do not justify classification. In the Danish proposal it is concluded that data from experimental animal studies are inconclusive with respect to long-term neurological effects. Currently in the process of REACH registration, all available data are being reviewed, and there is no animal data		

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		showing neurological effects after prolonged exposure to white spirits. The test concentrations used are in most cases far above the values as described in the classification guidance, keeping also in mind that long-term human exposure is generally to low concentrations. In conclusion, the available data from repeated dose animal studies alone do not meet the requirements for classification as STOT RE1/H372 or R48 (serious damage; clear functional disturbance or morphological change which has toxicological significance). Effects in Humans The only findings in humans which have been clearly associated with exposure to white spirits are acute CNS effects.3, 11 However, some have suggested that repeated high exposure to white spirits may cause more profound and long lasting neurological changes (e.g., World Health Organization, 1996).12 Whether such an association exists is controversial and complicated. Most of the human data are from epidemiological studies, including the data discussed in the Danish proposal, which are often confounded by numerous factors, leading to a high degree of uncertainty. First of all, the cross-sectional design that is used in most of the studies (26 out of the total of 29 studies that are described are cross-sectional) is highly susceptible to confounding, in particular with the endpoints that are assessed here, such as cognitive functioning.13 In this study design, it is not possible to assess change (in contrast to a prospective study design, in which each individual can be used as its own control), but the performance of an individual is		

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		compared to a different individual. Obviously, in this case an individual's baseline state of e.g. intelligence, socio-economic status, age, disease state, drug history, alcohol use, computer skills, language, cultural differences, etc. can have a significant impact on performance in the conducted tests, which is clearly unrelated to exposure. Moreover, if there are indeed associations observed, these are generally weak, implying that it is likely that bias/ confounding factors caused the observed effect as a consequence of the inadequate control for these variables. Most of the described studies only partially succeeded in controlling for these variables, and therefore the reliability of the outcome is highly questionable. The importance of this potential for confounding was illustrated by Gade et al., who did a reanalysis of individuals previously reported to have 'painters syndrome' (neurological dysfunction after prolonged exposure to solvents).14, 15 When the influences of age, intelligence and education were considered, the previously observed significant reduction in neuro-psychological test scores was not evident. Gade et al. also showed that years of education, often used as a surrogate to asses baseline intelligence, is not an adequate measure. In addition to these weaknesses, there is the problem of multiple exposure comparisons to a common control that exists in these studies, which increases the likelihood of false positive findings and weakens statistical power.11 Most of the studies did not control for multiple comparisons or if they did adjust, results were not significant any more. As such, the validity of associations of neurologic deficit following exposure to hydrocarbon solvents are suspect.		

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		In addition to the statistical issues described above, the variety of test batteries that are used in the described studies make it difficult to assess consistency in order to verify and compare results from different studies and to establish generally agreed relationships.16 Van der Hoek16 argued that the somewhat vague symptoms that are observed (irritability, fatigue and impaired memory or concentration) lead to the need of widely accepted diagnostic criteria, which would make it possible to deduct a confident conclusion from these types of tests. Moreover, if long term low-level exposure to these solvents would indeed be causally related to neurobehavioral or -psychological test performance, one would expect a consistent pattern of response observed in most studies, but consistency is not apparent in the currently available data. In addition, the causality of the relationship is often questionable because in most cases, they are only proved in external and not in internal comparisons (i.e. dose-response is needed, not only exposure-response, to improve causality) and the described 'long-term' findings are often confounded by recent (acute) exposures.13 With respect to these confounders, in the Danish EPA proposal it is stated that adverse neurotoxic effects, including disabling and irreversible effects on mental functioning, have been demonstrated by different investigators and in different countries. On that basis, they conclude that it is unlikely that "the combined set of findings could be explained by the same potential confounders". However, because different types of tests are used, there is a lack of consistency and the studies are difficult (if not, impossible) to compare.	RCOM to your comments on human data: We very much agree that the evaluation of the human data is not straight forward, as the interpretation, the evaluation of significance of the symptoms, and the results from neurobehavioural testing very much is a specialist task and relies on expert judgement. Important factors that have to be considered in the effect assessment and which may impact the test results from the neurological examinations and neurobehavioural testing are selection bias, confounding factors, the comparison to adequate controls or to an ´preexposure´ baseline level of performance. A thorough discussion of this has been made in the IPCS evaluation and this is also reflected in the CLH report p 46 under ´Discussion of findings in the epidemiological studies (IPCS 1996)´. Another crucial aspect is the causal association in relation to white spirit exposure as in many studies the exposure to a greater or lesser extent is to mixed exposure and often also with poor quantification of the exposure. Therefore studies have to be selected carefully in	

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		As was described in a review by Gamble13, in most of these studies the design makes it difficult to adequately control for uncertainties, so often the only constant factors affecting the outcome observed in these tests are confounders like the types described above. Therefore, in contrast to the conclusion in the Danish proposal, it is likely that large portions of the variance observed can be explained by other factors than the actual exposure. Most of the summarized studies in the classification proposal by the Danish EPA are taken from the assessments on white spirits by SCOEL17 and IPCS12, and although these sources mention 'some positive results in some tests at some concentrations', at the same time it they also state that 'considerable uncertainties still surround the results'. Many studies that are cited describe contradictory results, and are confounded by (at least one of) the factors described above. This is also acknowledged in the SCOEL report, and, in contrast to what is suggested in the Danish EPA proposal, it can be concluded from the SCOEL review that only acute, reversible neurological symptoms are observed, and, although some subtle chronic effects are described in some studies, there is still too much uncertainty to conclude on chronic effects of white spirit exposure. Hence, correctly, no classification for chronic neurological effects is proposed in the SCOEL document. One particular complication arising in most (both case- and epidemiological) studies, is that estimates of exposures are consequently imprecise (in terms of concentration, duration and type), which makes it difficult to relate exposure to white spirits to any sort of observed effect. Exposure to white spirits often	order to minimize possible influence from other exposures. Thus expert judgement and a WoE approach has to be applied when a conclusion shall be made on the basis of this highly diverse database. Due to the huge complexity of this task we think it is important to take advantage of the assessments made by expert groups in this field and therefore our classification proposal is based on the conclusions from the two expert groups of WHO/IPCS and SCOEL that in detail has assessed all the available data in relation to white spirit. We agree that SCOEL do not express any recommendation with regard to the classification of white spirit. However, this has never been the task of SCOEL to evaluate whether a substance is classified correctly or not. We therefore take note of the overall evaluation of SCOEL in which they conclude an OEL of 20 ppm for white spirit based on a NOAEL of 40 to 90 ppm in relation to organic brain damage. Overall, we take note that HSPA/ CEFIC, based on their evaluation and conclusion do not intend to classify white spirit for chronic neurotoxicty after repeated exposure. In our view this is in conflict with the	The study of Gade et al. showed some weakness in number of cases and in the control sample. The controls were recruited in the hospital, some was underwent surgery and narcosis. The results in neurobehavioural testing presents an impairment at higher degree in younger exposed persons without brain atrophy and controls

Date	Country/ Person/Organisation/ MSCA	Comment	Response	Rapporteur's comment
		occurs in combination with that of other solvents. When exposed to mixtures, which might include white spirits, it is difficult to determine what is causing the effect, if any effect is observed at all. To avoid the complication of mixed solvent exposures, Gamble13 identified and reviewed studies of individuals who had been exposed only to hydrocarbon solvents. His overall conclusion was that the "exposure-response showed no consistent or significant pattern for any tests of functional mortality. The weight of evidence suggests that exposure to hydrocarbon solvents at current limits does not appear to cause adverse neurobehavioral effects." Gamble reviewed the data again and published the same conclusion in 2008.3 In addition, a similar conclusion was published after another recent review of the information by Ridgway et al.7, in which they concluded that "it is not possible to draw reliable conclusions with respect to the presence or absence of nervous system damage related to the common properties of organic solvents." In short, whether or not white spirit causes neurological effects other than those associated with acute central nervous system effects is not supported by the available data in humans. Conclusions It is the view of the HSPA that high dose exposure to white spirit produces acute reversible CNS effects, commonly associated with narcosis, but that there is no consistent evidence of more profound neurological effects in humans or animals. To the contrary, the toxicology studies which have been conducted in accordance with international guidelines for such tests revealed negative results for neurological damage in	available data and thus this leads to under-classification of the white spirit substances by industry. This for us is an important argument for obtaining a harmonized classification for this end-point.	than in older exposed workers with brain atrophy and the controls. These results were not very well discussed.

Date	Country/ Person/Organisation/ MSCA	Comment	Response	Rapporteur's comment
		exposed rats, even in studies involving very high exposure levels. In addition, in most of the experimental studies described in the Danish proposal no neurotoxic or behavioral effects were observed. It can be concluded that the experimental evidence does not support classification of white spirit as a target organ toxicant. Thus, the basis for classification relies on human case studies or epidemiological data. However, also in this case only acute CNS effects following high-level exposure to white spirits have been recognized. As was described above, the human evidence has multiple weaknesses in study design, is highly susceptible to confounding, and as a whole does not support a conclusion that white spirits have long term neurological effects on humans at current exposure limits. In an intensive review, Gamble13 has described the shortcomings and uncertainties of the epidemiological data that is currently available. Moreover, Gamble conducted a study that is more specific (focus was on hydrocarbon solvents only, instead of exposure to solvent mixtures) and more recent compared to the majority of data used in the Danish proposal (i.e. the proposal is largely based on data summarized in the WHO/IPCS Environmental Health Criteria report which was published in 1996), concluding that "the weight of evidence suggests there are no consistent associations between reduced neurobehavioral test performance and low-level hydrocarbon solvent exposures occurring at current exposure levels". Similar conclusions have been made in other reviews by Ridgeway et al.7 and, more recently, Amuroso et al.3, and in reviews on chronic solvent encephalopathy (which includes the		

Date	Country/ Person/Organisation/ MSCA	Comment	Response	Rapporteur's comment
		"landmark study" of 187 paint-manufacturing workers18) describing that the literature does not support chronic low-level solvent exposure as harmful to the CNS.19,20 Moreover, in the same period as the IPCS review on which the Danish proposal is based, ECETOC concluded in a technical report that "there is no basis for a neurological syndrome in man that is causally related to low level organic solvent exposure (as defined by recent or current OELs)".8 Especially because no animal evidence exists describing a molecular mechanism that could serve as evidence for the suggested long-term effects, it is unlikely that prolonged/repeated exposure to solvents via inhalation induces serious damage to the central nervous system as is suggested by this proposed classification. In summary, according to the guidelines, classification should normally be done based on evidence from animal data. Industry has conducted all required tests to assess the toxicity of white spirits, which was currently re-assessed through REACH, and no long-term neurological effects could be observed in laboratory animals. Subsequently, additional information can be obtained from data in humans; however, these data have many weaknesses and remain inconclusive. Therefore, due to the high level of uncertainty surrounding the possible long-term effects of exposure to white spirits and the absence of supportive animal data, it is concluded that the weight of evidence does not warrant classification for specific target organ toxicity via the inhalation route of exposure. References:		

Date	Country/ Person/Organisation/ MSCA	Comment	Response	Rapporteur's comment
		1 EU (2008). Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labeling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending regulation (EC) No 1907/2006. 2 Council Directive 67/548/EEC of 27 June 1967 on the approximation of laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances. 3 Amoruso, M., Gamble, J., McKee, R., Rohde, A., and Jaques, A. (2008). Review of the toxicology of mineral spirits. International Journal of Toxicology 27:97-165. 4 Alden, CL. (1986). A review of unique male rat hydrocarbon nephropathy. Toxicol Pathol. 14(1):109-11. 5 Nielsen, G. et al. (2006). Neurological effects of white spirit: Contributions of animal studies during a 30-year period. Basic and Clinical Pharmacology and Toxicology 98:115-123. 6 Lund SP, Simonsen L, Hass U, Ladefoged O, Lam HR, Østergaard G (1996). Dearomatized white spirit inhalation exposure causes long-lasting neurophyiological changes in rats. Neurotoxicol Teratol 18, 67–76. 7 Ridgway, P., Nixon, T., and Leach, J.-P. (2003). Occupational exposure to organic solvents and long-		The aim of SCOEL is to establish OEL`s and STEL´s on basis of NOAEL´s; SCOEL concluded, that 20/50 ppm prevent acute effects and organic brain damage. See above,

Date	Country/ Person/Organisation/ MSCA	Comment	Response	Rapporteur's comment
		term nervous system damage detectable by brain imaging, neurophysiology or histopathology. Food and Chemical Toxicology 41:153-187. 8 European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC) (1996). Chronic Neurotoxicity of solvents. Technical report No. 70. ECETOC, Brussels, Belgium. 9 Douglas, J. (1993). A neurotoxicity assessment of high flash aromatic naphtha. Toxicology and Environmental Health 9:1047-1058. 10 Schreiner, C. et al. (1998). Toxicity evaluation of petroleum blending streams: Inhalation subchronic toxicity/neurotoxicity study of a light alkylate naphtha distillate in rats. Journal of Toxicology and Environmental Health, Part A. 55:277-296. 11 Agency for Toxic Substances and Disease Registry (ATSDR). 1995. Toxicological profile for Stoddard solvent. Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service. 12 World Health Organization (1996). White spirit (Stoddard Solvent). IPCS Environmental Health Criteria 187. World Health Organization, Geneva. 13 Gamble, J. (2000). Low-level hydrocarbon solvent exposure and neurobehavioural effects. Occupational Medicine 50:81-102. 14 Gade A, Mortensen EL, Bruhn P (1988). "Chronic painter's syndrome". A reanalysis of psychological		

Date	Country/ Person/Organisation/ MSCA	Comment	Response	Rapporteur's comment
		test data in a group of diagnosed cases, based on comparison with matched controls. Acta Neurol Scand 77, 293-306. 15 Arlien-Soeborg P, Bruhn P, Gyldensted C, Melgaard B (1979). Chronic painter's syndrome: Chronic toxic encephalophaty in house painters. Acta Neurol Scand 60, 149-156. 16 Van der Hoek JAF, Verberk MM, van der Laan G, Hageman G (2001). Routine diagnostic procedures for chronic enecphalopathy induced by solvents: survey of experts. Occup Environ Med 58, 382-385. 17 SCOEL (2007). Recommendation of the Scientific Committee on Occupational Exposure Limits for "White Spirit". SCOEL/SUM/87, August 2007. 18 Bleecker ML, Bolla KI, Agnew J, Schwartz BS, Ford DP (1991). Dose- related subclinical neurobehavioral effects of chronic exposure to low levels of organic solvents. Am J Ind Med 19, 715-728. 19 Rosenberg NL (1995). Neurotoxicity of organic solvents. In: Rosenberg NL, ed. Occupational and Environmental Neurology. Newton, MA: Butterworth-Heinman, pp 71-113. 20 Schaumburg HH, Spencer PS: organic solvent mixtures, in Spencer PS, Schaumburg HH (eds.): Experimental and clinical neurotoxicology, 2nd ed. New York: Oxford University Press, 2000, pp 894-897.		Amoruso et al. summarize, that at current occupational exposure levels, there is no compelling evidence that mineral spirits produce irreversible CNS effects, although this remains controversial. SCOEL has recommended an OEL of 20 ppm on basis of a LOAEL of 40 ppm which follows also

Date	Country/ Person/Organisation/ MSCA	Comment	Response	Rapporteur's comment
				the authors statement protecting exposed workers.
26/02/2010	**Ireland / Health & Safety Authority**	REPEAT DOSE TOXICITY: Based upon the weight of evidence provided, the Irish CA agrees with the MSCA proposal to classify the group of substances for repeat dose toxicity of the central nervous system as R48/20; STOT RE 1 H372. However the Irish CA does not agree with the wording of the hazard statement which states: "Causes damage to the central nervous system through prolonged or repeated exposure via inhalation". When classifying for repeat dose toxicity using CLP criteria, a route may only be specified if it is conclusively proven that no other routes of exposure cause the hazard (Table 3.9.5 of CLP Annex I). The Irish CA considers that insufficient evidence has been provided to discount the possibility that dermal exposure will also cause the effects seen. It could be expected that the dermal route would be a major occupational route of exposure for the painters studied. It is noted that no animal studies are reported for the dermal or oral routes. The Irish CA believes that the hazard statement should be as follows "Causes damage to the central nervous system through prolonged or repeated exposure ".	We acknowledge your support to our classification proposal. You are right that very few data are available regarding the degree of skin absorption of white spirit and thus due to lack of these data it is difficult to exclude the relevance of absorption from dermal exposure. However, in the SCOEL documentation some further consideration has been made with regard to skin absorption and the conclusion from this is that the dermal exposure may contribute to systemic exposure: ´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/cm2/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,	No additional comment Referring to the Irish comment on the wording of the hazard statement, we agree that exposure route (inhalation) should not be included.

Date	Country/ Person/Organisation/ MSCA	Comment	Response	Rapporteur's comment
			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 m3/d x 116 mg/m3 = 580 mg/d).´ Still, SCOEL concluded to apply a skin notation for white spirit to the OEL value. Overall, we find that the available human data as presented by IPCS and SCOEL exclusively addresses the inhalation route of exposure and we find that a hazard statement covering this exposure route would be the most adequate and informative hazard statement. Although dermal exposure may contribute to systemic exposure we do not think that dermal exposure on its own and with an absorption rate around 7% would warrant	

Date	Country/ Person/Organisation/ MSCA	Comment	Response	Rapporteur's comment
			classification. However, this may be an issue for further discussion in the RAC.	
01/03/2010	**Germany / Jan Averbeck / MSCA**	regards "Translation" of classification: The German CA principally agrees with the classification of white spirit as neurotoxic after repeated exposure. However, there is some uncertainty with the translation of the classification categories. According to CLP regulation, white spirit is classified as STOT RE Cat.1 (H372), which is comprehensible due to human data. This would in our view translate into T, R48/23. If you would like to abide by this combination, some explanation on this would be appreciated. (ECHA: transferred from general comments)	We acknowledge your support to our classification proposal. Our starting point was the Xn; R48/20 classification as this is how white spirit is classified in DK, and also we find this classification as most appropriate taking account of the data and the DSD criteria. A classification as T; R48/23 indicates a very potent substance which does not seem to be the case for white spirit. According to the CLP criteria STOT RE Cat. 1 is the most appropriate classification when the evidence is based on human data. You are right that this classification is comparable to T, R48/23 when using the translation table in annex VII.. However the criteria for STOT RE and R48 are not quite identical and therefore the conversion is not as straight forward as the translation table may indicate. The translation table can be used as a practical tool but does not take precedence compared to use of the relevant criteria.	No additional comment
02/03/2010	**Sweden / Marie Cardfelt / Swedish Work Environment Authority**	The Swedish Work Environment Authority supports the proposal for harmonised classification and labelling of white spirits. It is important that employers and workers are warned of the toxic effects of prolonged or repeated exposure to white spirits.	We acknowledge your support to our classification proposal.	No additional comment

Date	Country/ Person/Organisation/ MSCA	Comment	Response	Rapporteur's comment
		Self-classification of products containing white spirit has lead to a situation where adequate warnings are not always given. Many users have the opinion that the present white spirits are less hazardous than the earlier, although available studies not have been able to show this. (ECHA: transferred from general comments)		
02/03/2010	**Poland / Mariusz Godala / Biuro ds Substancji i Preparatów Chemicznych**	The five substances included in "Proposal for harmonized classification and labelling of white spirit" are included in Annex VI to regulation (EC) No 1272/2008. Danish Environmental Protection Agency proposes additionally to classify these substances also as Xn; R48 (Harmful; Danger of serious damage to health by prolonged exposure through inhalation). According to the article 36.3 of regulation 1272/2008, where a substance fulfils for other hazard classes or differentiations than those referred to in art. 36.1 (CMR) and does not fall under art. 36.2 (active substances in plant protection products or in biocide products), a harmonized classification and labelling may also be added to Annex VI on a case-by-case basis, if justification is provided demonstrating the need for such action at Community level. We are not sure if it is a need to add a new classification to these substances according to the article 37.3 of regulation No 1272/2008. According to the article of 4 .3 of this regulation if a substance is subject to harmonized classification and labeling in accordance with Title V, the hazard classes or differentiations not covered by an entry in Part 3 of Annex VI shall be evaluated and, if there is a scientific background, classify by manufacturers, importers.	As indicated in the section for justification in the CLH-report we find it important that HPV substances used in a great variety of preparations with a large exposure potential for workers as well as consumers are classified in a way that gives warning about serious health effects such as e.g. chronic neurotoxicity. The harmonized classification is also important to avoid unevenly classification throughout EU. As can be seen from various Safety Data Sheets on the substances and also from the comments from HSPA/ CEFIC the solvent industry do not find that there is sufficient evidence for a classification for neurotoxicity in relation to repeated exposure and do not on their own intend to classify for this end-point. However from our view we find the practice used in Denmark where a classification with Xn; R48/20 for white spirit apply is most in accordance with the criteria. Due to your comments we intend to expand our argumentation in the CLH report concerning the need for a	No additional comment

Date	Country/ Person/Organisation/ MSCA	Comment	Response	Rapporteur's comment
		We also think that in section "Justification that action is required on a community-wide basis" shall be added more information which demonstrate the need for a new harmonized classification for these substances (for example, if there are information from poison centers that indicate that these substances or mixtures which contain these substances cause hazard to human health, such information should be included in this section). For the assessment of repeated dose toxicity a grouping approach was used. A five different types of white spirit is treated as a group. Generally we strongly support such approach, but in this specific case we would like to see more information (justification) in the report why we can use this approach method to the classification of all type of White Spirit. (ECHA: transferred from general comments)	harmonized classification. Data from poisoning centers mainly pertain to acute toxicity and thus are less relevant for effects in relation to repeated low level exposure. However, with regard to other clinical data these have been included in the CLH-report under ´Case studies` in section 5.6.2.2.2.1.1 and 5.6.2.2.2.1.2 where data from neurophysiological studies (section 5.6.2.2.2.1.1) and neuropsychological studies (5.6.2.2.2.1.2) on patients that have been exposed to white spirit are included. As indicated in the introductory text in section 5 in the CLH-report our classification proposals for the different types of white spirit are based on the grouping approach used by WHO/IPCS (covering the same five white spirits included in the CLH-report) and SCOEL. (covering data on white spirit type 1, white spirit type 3 and Stoddard solvent). This approach is consistent with the earlier grouping of white spirit made by CEFIC in 1989 and 1991 (covering the same five white spirits included in this CLH-report) in relation to the classifications in the 21 ATP. However, we will consider whether more explanation or some adjustments in the	

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			CLH-report could increase the clarity on this point.	
02/03/2010	**France / MSCA**	Repeated toxicity: The multi-exposure of painters is one of the major limitations of the epidemiological studies. Indeed, painters may be exposed in considerable amounts to additional paint solvents other than white spirit. They may be also exposed to dust from old paint layers which main contain lead. However, the major solvent exposure is due to white spirit in few epidemiological studies. In accordance with section 3.2.2 and 3.2.4 of the directive 67/548/EC (annex VI), white spirit may be considered as toxic and classified R48/20 based on epidemiological studies which reported serious damages to the central nervous system as a consequence of prolonged inhalation exposure. Dizziness, headache and altered performances in neuropsychological tests are symptoms which have been frequently reported. The chronic encephalopathy is the most serious pathology observed: patients with this syndrome suffer from loss of intellectual abilities which interfere with social or occupational life (e.g. memory impairment, impaired judgement, personality change…). The difficulty to identify to what type of white spirit the painters were exposed to (not specified in the reports) is another limitation of the epidemiological studies. Since available human data are mainly concerning white spirit with high levels of aromatic compounds rather than de-aromatised white spirit, no conclusion can be drawn with respect to possible differences in the neurotoxic profiles.	We acknowledge your support to our classification proposal.	No additional comment

Date	Country/ Person/Organisation/ MSCA	Comment	Response	Rapporteur's comment
		Available studies investigating the neurotoxic potential of white spirit in rats following inhalation have been carried out from 3 weeks to 6 months. These studies are not sufficient to support differences in the adverse neurological long-term effects between the various types of white spirit. Moreover biological relevant effects were observed although at exposure levels higher than those which are recommended to classify a substance as harmful in the section 3.2.3 of the directive 67/548/EC annex VI. However, the data from animal studies include irreversible effects in the central nervous system and are therefore considered supportive of the findings observed in epidemiological studies. So, the proposal for a classification which covers the various types of white spirit is relevant. Due to the danger of serious damages to health by prolonged exposure by inhalation reported by human data in this CLH report, the classification "Xn; R48/20" and "STOT RE 1, H372 » (according to Regulation 1272/2008/EC) for the five types of white spirit is justified. In the light of the seriousness of the effect, the high potential for human exposure and the absence of classification inventory giving access to the classification currently applied for non-harmonised endpoints for white spirit, the classification proposal for harmonisation of repeated toxicity is supported.		
03/03/2010	**Sweden / Swedish Chemicals Agency (KEMI)**	White spirits: Being aware of common drawback with epidemiologic studies (e.g. although most exposures originate from white spirit; the solvents are generally not specified in different reports), we agree to the proposed classification (Xn; R48/20 or STOT RE 1, H372) based on information in the two reviews IPCS	We acknowledge your support to our classification proposal. RCOM to COM1: As indicated in the introductory text in section 5 in the CLH-report our classification proposals for the different	No additional comment

Date	Country/ Person/Organisation/ MSCA	Comment	Response	Rapporteur's comment
		1996 (40 ppm for >13 years) and SCOEL 2007 (40 - 90 ppm; long term exposure). An association between long-term exposure to different types of white spirit and chronic central nervous system effects has been demonstrated by many different investigators. The observed effects (impaired memory, concentration, performing ability, cognitive functions) are considered serious; the effects have been demonstrated in humans at exposure levels in work places after long-term exposure. In addition the neurotoxicological effects have also been measured in animal studies although at higher concentrations. The data presented in the CLH report may still be used for the white spirits types currently on the market although the content of white spirits has changed throughout the years (i.e. lower content of aromatics). This is based on the overall conclusion from the studies that the content of white spirits (especially concentration of aromatics) has not shown significant differences in the adverse effects observed. Specific comments: 1. What is the rationale behind the selection of the white spirits types proposed for the classification? According to our Product Register there are other products currently on the market that, based on their physico-chemical properties, could be included into the category. 2. The ranges of the boiling points presented in the table 5 do not correspond to the descriptions of the different types of white spirits according to EC name and IUPAC name. 3. There are different units used in table 1 and table 2 to compare North Europe white spirit's with USA	types of white spirit are based on the grouping approach used by IPCS (covering the same five white spirits included in the CLH-report) and SCOEL. (covering data on white spirit type 1, white spirit type 3 and Stoddard solvent). This approach is consistent with the earlier grouping of white spirit made by CEFIC in 1989 and 1991 (covering the same five white spirits included in this CLH-report) in relation to the classifications in the 21 ATP. However, we will consider whether more explanation or some adjustments in the CLH-report could increase the clarity on this point. To our knowledge no further substances are termed white spirit, although you may be right that other petrochemical solvents may have a content of hydrocarbons that to some extent may overlap the hydrocarbon composition of white spirit. However, in order not to make the read-across too broad our grouping was narrowed to the solvents termed as white spirit and our documentation relates to the assessments of this group of substances made by IPCS and SCOEL. RCOM to COM 2: The EC and IUPAC definitions on the substances is based on the refinery stream and the following treatment of this and	SCOEL conclude on animal electrophysiological studies, that there is no difference in neurotoxicity between aromatized and de-aromatized white spirits.

Date	Country/ Person/Organisation/ MSCA	Comment	Response	Rapporteur's comment
		white spirit. It should be corrected.	further gives ranges in relation to the carbon number and boiling range. The data in table 5 is industry data from specific commercial substances that lie within these ranges, so overall they are covered by the EC- IUPAC definition although the intervals for the single specific substances are not as wide as in the overall EC/ IUPAC definitions. RCOM to COM 3: The data in the CLH report is presented as they are presented in the WHO/IPCS document.	
03/03/2010	**Belgium / Jacques Warnon / CEPE**	PAGE 62: Referring to the classification requirements for target organ toxicity via inhalation either given by CLP Regulation (EC) N° 1272/2008 or by Dangerous Substances Directive 67/548/EEC, CEPE is in the opinion that white spirit types – as used in the European market – do not match the criteria as given in the above mentioned legislation. The publications of Lam et al. show clearly that the aromatic content (especially benzene) has an impact on the CNS effects (see references in the CLH report). Furthermore additional references do not support the classification proposal. Therefore CEPE recommend, not to follow the Danish proposal with R48/20 or STOT RE1, or at minimum refer to the nota H and P as well for the CNS effects. Additional references:		

Date	Country/ Person/Organisation/ MSCA	Comment	Response	Rapporteur's comment
		White spirit (CAS 8052-41-3) Groups of rats were exposed to 100, 400, or 800 ppm of white spirit 8 hours a day for 3 consecutive days. FOB testing indicated changes in gait and body temperature for the 800 ppm group. Motor activity was reduced in a dose-responsive manner. Additionally, dose-responsive psychomotor slowing was seen in the visual discrimination test. The NOEL for neurobehavioral effects was 100 ppm. [Lammers JH, Kulig BM, McKee RH, Owen D. and Nessel CS Lammers, The Toxicologist, 54(1):361-362 (Abstract No. 1696)] White spirit (CAS 64742-48-9) Concentration-dependent increases in locomotor activity were observed in male mice exposed via inhalation to 4000 and 6000 ppm for 30 minutes. Increases were observed within 6 minutes of the initiation of exposure and lasted the duration of the exposure. The locomotor effects were reversible. The hydrocarbon mixture did not reliably affect the rates of responding in an operant behaviour test during exposure to 500, 1000, 2000, or 4000 ppm. [Bowen, S. E. and R. L. Balster (1998). Pharmacol. Biochem. Behav., 61(3):271-280]		References not relevant for classification (short-term exposure setting, animal studies)
03/03/2010	**Belgium / CEPE**	Refering to the classification requirements for target organ toxicity via inhalation - either given by CLP regulation 1272/2008 or by dangerous substance directive 67/548/EEC - CEPE is in the opinion that white spirit types - as used in the European market - does not match the criteria as given in the above mentioned legislation. The information in SDSs of the	From the CLH-dossier it is clear that the classification for damage to the central nervous system through prolonged exposure first of all is based on the human data. It is acknowledged that data from experimental animal studies may look inconsistent and not in itself warrant	No additional comment

Date	Country/ Person/Organisation/ MSCA	Comment	Response	Rapporteur's comment
		European suppliers of white spirit does not support the proposed classification, too. References were given to the ECETOC technical report no. 70 (1996). The publication of Lam et. al. shows clearly that some aromatic ingredients (especially toluene and as well benzene) has an impact on the CNS effects (see references in the CLH report). Furthermore addtional references do not support the Danish classification proposal [1,2]. Therefore CEPE recommend, not to follow the Danish proposal with STOT RE1 vs R48/20 generally. The classification should refer to the nota H and P as well for the effects on CNS. additional references: [1] white spirit (CAS 8052-41-3) Groups of rats were exposed to 100, 400, or 800 ppm of white spirit 8 hours a day for 3 consecutive days. FOB testing indicated changes in gait and body temperature for the 800 ppm group. Motor activity was reduced in a dose-responsive manner. Additionally, dose-responsive psychomotor slowing was seen in the visual discrimination test. The NOEL for neurobehavioral effects was 100 ppm [Lammers JH, Kulig BM, McKee RH, Owen D, and Nessel CS Lammers, The Toxicologist, 54(1):361-362 (Abstract No. 1696)] [2] white spirit (CAS 64742-48-9) Concentration-dependent increases in locomotor activity were observed in male mice exposed via inhalation to 4000 and 6000 ppm for 30 minutes.	classification for reaped exposure. Nevertheless experimental animal studies with positive findings in relation to the CNS (as shown in table 9 & 10 in the CLH dossier) should not be dismissed but considered together with the findings from the human data, and in this regard we find the animal data as supportive for the classification. Our classification proposal relies on the conclusions of the experts groups of the IPCS and SCOEL, and both groups concluded based on the human epidemiological studies and using a WoE approach a causal association between long term exposure and chronic toxic encephalopathy at concentration levels which are below acute neurotoxic effect levels.	No additional comment

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		Increases were observed within 6 minutes of the initiation of exposure and lasted the duration of the exposure. The locomotor effects were reversible. The hydrocarbon mixture did not reliably effect the rates of responding in an operant behavior test during exposure to 500, 1000, 2000, or 4000 ppm. [Bowen, S. E. and R. L. Balster (1998). Pharmacol. Biochem. Behav., 61(3):271-280] (ECHA: transferred from general comments)		
03/03/2010	**Belgium / Sylvie Lemoine / A.I.S.E.**	A.I.S.E. comments on the proposal for harmonised classification of "white spirits" A.I.S.E. is the representative body of the Soaps, Detergents and Maintenance Products Industry in Europe. Many company members of A.I.S.E. use "white spirits" in different types of products such as solvent-based products for industrial cleaning, maintenance products for consumers and professionals (e.g. waxes, polishes), insect-control products, some laundry pre-wash products and other types of cleaning products. A.I.S.E. fully supports the comments from the Hydrocarbon Solvent Producers Association, both the scientific reasoning and the conclusion that the proposed classification is not warranted based on existing animal and human data.	Please see RCOM to the comments from HSPA/CEFIC	No additional comment

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		A STOT RE1 classification would have significant impact on downstream users of "white spirits". Some of A.I.S.E. members' products contain levels of white spirits that are at or above the 10% concentration limit for classification of mixtures. These mixtures would have to be classified as STOT RE1 and mixtures containing between 1 and 10% of "white spirits" would have to be classified STOT RE2 (human health pictogram in both cases). Further, products sold to the general public would have to be equipped with child-resistant closures and tactile warnings of danger. So many downstream user mixtures would be impacted by such detrimental classification and major unnecessary reformulation work would likely be needed. The level of exposure to this group of substances in our sector is low because of workplace legislation already in place for professional/industrial uses and because of the very small amounts of this substance used by consumers. We call on the Risk Assessment Committee and ECHA to critically and thoroughly review all available information, taking due account of the SCOEL review (August 2007, full reference in the HSPA paper) and of the well-known uncertainties associated with human studies cited by the Danish EPA, in line with the CLP criteria and corresponding guidance, before disproportionate classification decision is further considered. As all existing data are currently being reviewed by industry for the purpose of the REACH registration data, it would seem appropriate, as a minimum, to wait until the registration data are available before		

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		further consideration of this Annex XV dossier. (ECHA: transferred from general comments)		