

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 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.

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 statistically 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) 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.

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 neurotoxicity 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 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 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 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 assess 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.

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. 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 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.”

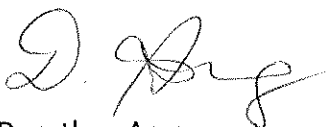
In short, whether or not white spirit causes neurological effects other than those associated with acute central nervous system effects is not supported by the available data in humans.

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 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 “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.



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