

The Hydrocarbon Solvents producers Association (HSPA) welcomes the opportunity to comment to the proposed Harmonized Classification and Labelling for n-Hexane. Please find below our comments which we are happy to further exchange on.

CLP classification of n-hexane

HSPA agrees with the proposed STOT classification and labelling harmonization for n-hexane.

From the reviewed human case studies, exposure of individuals to n-hexane at air concentrations that are $> 140 \text{ mg/m}^3$ may lead to polyneuropathy and therefore the substance should be classified and labelled as STOT RE Category 1 – H372.

n-Hexane may be present as a constituent in light hydrocarbon solvents (e.g. technical hexane) at varying concentrations depending on the boiling range of the solvent, but also in solvent based formulations.

In the past decades, the industry has built a legacy of solvents, formulations and industrial processes on the basis of the current 5% cut off for classification.

HSPA would like to propose a pragmatic approach for the classification cut-off for n-hexane as a marker for hazard following CLP mixture rules to protect human health while safeguarding the European industry technical legacy; this compromise will allow to mitigate the impact of the classification and labeling harmonization of n-hexane on European industrial processes, products and ultimately on consumers and society.

Classification cut off limits

The key study by Wang et al. (1986) indicates a relationship between frequency of effect (polyneuropathy and abnormal motor nerve conduction velocity (MVC)) and the concentration of n-hexane in the solvent used (Tables II and III). In line with the other studies listed in the CLP report, use of solvents containing n-hexane $> 10\%$ may result in neurotoxicity. Because under CLP rules, hazard is communicated according to the concentration of a component in a mixture, the concentration of 10% established by Wang et al. (1986) is in alignment with the 10% cut off for mixtures containing a STOT cat.1 substance. The same study also indicates that use of solvents containing $< 10\%$ n-hexane did not result in neurotoxicity. This shows practical difficulties because under CLP, substances with STOT RE cat.1 classification should carry a lower classification (STOT RE. cat.2 – H373) when found at concentrations between 1.0 and 10%.

A pragmatic solution for this issue is to maintain the current specific concentration limit of 5% applying the STOT RE cat.2 at concentrations of $\geq 5\%$ but $< 10\%$, so that consequently solvents with $< 5\%$ are not classified and resulting in the following scheme:

$\geq 10\%$ n-hexane – STOT RE cat.1 (H372)
 $< 10\%$ but $\geq 5\%$ - n-hexane – STOT RE cat.2 (H373)
 $< 5\%$ n-hexane – no classification



This pragmatic solution has the following considerations to minimize disruption:

- a) Is based on human evidence for neurotoxicity supporting STOT RE cat.1 (H372)
- b) Insures safe use as evidence shows no neurotoxicity at concentrations <10%
- c) Classification is based on data of n-hexane concentrations in the solvent and not in the air which are managed e.g. via occupational exposure limits (OELs) and DNELs.
- d) Maintains the status quo of a 5% n-hexane cut-off to classify substances for STOT RE related effects that has been in place for decades allowing industry to tailor solvents and applications to this technical requirement.
- e) Has minimal consequences for the downstream sector where solvents with >5% n-hexane are already classified as STOT RE cat.2 – H373, whereas only solvents with >10% n-hexane would be re-classified.
- f) Has no impact on OECD 230 nomenclature guidance for hydrocarbon solvents.
- g) Avoids substantial significant REACH related re-work with no added value.
- h) Has limited impact on the REACH naming convention and registered substances which use 5% n-hexane in their name. Removing the 5% n-hexane (as a classification cut-off) would result in a meaningless registered name with no added value for safety.
- i) Has no impact on the ongoing REACH read-across and testing strategy.

Under the CLH proposal for n-hexane classification, the current 5% cut-off is questioned because it is higher than what would be a default of 1% for n-hexane containing mixtures and complex substances following n-hexane classification as STOT RE cat.1 (H372).

However, the consequences of its elimination are disproportionate when considering that the scientific basis for its elimination are not supported by the data in the cited references and particularly in the key study selected for the lowest effect level. The use of reductions in motor nerve conduction velocity (MCV) as an indication of lowest effective dose of 80 mg/m³ quoted from Wang's paper is questionable.

Comparison with data from other sources used in the CLH report suggests that the relationship between small differences in MCV and n-hexane are not sufficiently robust to justify the use of these data to draw the conclusions presented in the CLH document. A review of the information provided in all the papers indicates that the no effect level for neurological effects, including reductions in MCV, is in the range of 140-300 mg/m³

Whilst we understand the desire for a harmonization/standardization of cut-off concentrations limits for classification, the consequences of eliminating the status quo of 5% cut off are disproportionate to any evidence of health benefits.

Our proposal is a pragmatic solution that acknowledges the need to reflect the human hazard of n-hexane, but at the same time considers the practical consequences of such a change.

Our arguments are supported by the following observations.



Estimation of No Effect and Low Effect levels for Toxicologically-Relevant Changes in Motor Nerve Conduction Velocity^{1,2}

The CLH document (2021) includes an analysis that was conducted to determine whether a specific concentration limit was needed as a basis to classify n-hexane-containing solvents. Ultimately it was concluded that a specific (lower) concentration limit was not required. Although the conclusion is correct, the calculation itself is questionable. More specifically, the calculation is based on data from Table IV of Wang et al. (1986) which provides data from motor nerve conduction velocity (MCV) studies of n-hexane-exposed workers, and even more specifically the data in the column associated with the group that is claimed to have been the least exposed (80 mg/m³). As shown in the data from the most exposed workers in the same table, reductions in MCV are associated with n-hexane neuropathy, but it is less clear that small changes in MCV are biologically meaningful, or that they can be used as sensitive indicators of potential nerve damage which is the underlying assumption of this analysis provided in the CLH document.

According to Governa et al. (1981), one of the studies listed in the CLP report, “The values of conduction velocities...are considered borderline if they are from 2-3 standard deviations (SD) relative to the mean normal value, and pathological when they are over 3 standard deviations.” Using those criteria and referring to the motor nerve conduction velocity (MCV) data in Table IV of Wang et al. (1986), the difference in the lowest exposure group (0-80 mg/m³) is statistically significant and > 1 SD from control, but the difference is less than 2 standard deviations, so it is not even borderline pathological. Of course, that does not rule out the possibility that the difference is still toxicologically relevant; however, it is important to note that these specific data were taken out of context, without regard to other results in the same table or similar data from other authors (table 1).

If reductions in MCV were directly related to the degree of n-hexane intoxication, one would expect to see a dose-response relationship, i.e., the differences should increase with increasing exposure, but that is not the case. Rather as shown in table 1, the difference in the group exposed to hexane at levels between 39 and 327 mg/m³ (medium) was significant but less than 1 SD from control, and the difference in the group exposed to n-hexane at levels between 120-144 mg/m³ (high) was also significant but less than 1 SD from control. In both cases, the most likely explanation is that these differences, although statistically significant, were a reflection in normal variability. Workers in these groups were without clinical cases of neurotoxicity. In contrast, the difference in the 80 - 660 mg/m³ (very high) exposed group was significant, almost 3 SD from control, and close to a pathological state. Workers in this group were reported to develop neurotoxicity.

¹ The assessment focused on median nerve data since it was provided in all studies that included MCV data. It was assumed that conclusions for other nerves would be similar.

² All exposure information converted to mg/m³



Table 1. Motor Nerve Conduction Velocity (MCV) Information from papers cited in the CLH document to relative air concentrations. Comparison of control values of Key study (in gray) to studies of clinically asymptomatic workers. The levels “Low to very high” are arbitrary to represent data from the key study.

Reference	Control	Low	Medium	High	Very high
Wang et al. (1986) ¹	61.2 ± 5.8	54.3 ± 2.8 (p < 0.001)	58.3 ± 3.6 (p < 0.05)	55.0 ± 2.1 (p < 0.01)	44.3 ± 8.3 (p < 0.001)
Neghab et al. (2012)	57.4 ± 4.4		58.6 ± 3.2 (not significantly different)		
Sanagi et al. (1980)	57.5 ± 3.2		57.3 ± 3.4 (not significantly different)		
Pastore et al. (1994)	57.4 ± 6.2		59.3 ± 5.1 (not significantly different)		

Therefore, among the possible explanations for the MCV data in the low exposure group are (i) that the MCV values were not an indication of n-hexane-induced effects but rather simply normal variations; (ii) that the MCV values were an indication of n-hexane-induced effects but the exposures were substantially underestimated; or (iii) that the differences were real but influenced by exposure to other substances such as toluene.

Importantly, in contrast to the study by Wang et al. (1986) where air concentrations between groups overlap, there are the results of the studies by Senagi et al. (1980) and Neghab et al. (2012) which show that nerve conduction velocities are not affected by exposure levels of n-hexane which are in the 140 – 200 mg/m³ range (medium-high range in Table 1). This conclusion appears to be supported by the data from Pastore et al. (1994) who found no effects on MCV among workers with end of shift urinary levels of 2,5-hexanedione to be more than twice the recommended BEI for n-hexane.

Studies of workers with polyneuropathy indicate substantial reductions in MCV with low effect levels in the range of 300 mg/m³. In conclusion, the data in Wang et al. (1986) are not strong enough to support the conclusion that 80 mg/m³ is a low effect level for n-hexane-induced neurological effects based on the small reductions in MCV. The totality of the data indicate that the no effect level is > 140 mg/m³ but less than 300 mg/m³.



Given the difficulties to associate an air concentration to neurological effects, the data by Wang et al. (1986) provides evidence that solvents with n-hexane concentrations below <10% are not neurotoxic. For practical considerations of classification and labeling this is in alignment with the CLP cut off of 10% for substances classified as STOT RE cat.1 (H372). This is not in contradiction to the proposal to apply a concentration limit of 5% as discussed above which is supported by evidence that low concentrations of n-hexane do not cause neurotoxic effects.

The data, provided in more detail include:

(a) Studies of clinically asymptomatic workers

Neghab et al. (2012) – This study evaluated 27 asymptomatic workers exposed to n-hexane through their work in shoe making. There were no reduction in median MCV among workers exposed to n-hexane (9 h/d, 6d/w) at levels of 115 mg/m³ (according to the authors, this is equivalent to approximately 141 mg/m³ according to the calculation from Scala and Brief). No correlation was found between nerve conduction and n-hexane levels in the air. There was however a correlation between decreased nerve conduction and urinary concentrations of 2,5 hexanedione.

Sanagi et al. (1980). This study examined workers from two specific tasks in the plant in which exposure to n-hexane had taken place. These included 14 currently exposed and 5 previously exposed and compared them to 14 workers from other parts of the plant who had not been exposed to n-hexane. Exposure monitoring indicated an average exposure of 58 ppm (204 mg/m³). Nerve conduction velocities were not reduced by exposure.

Pastore, C. et al. (1994) examined a group of 20, asymptomatic workers who used solvents containing n-hexane. Exposure information was not provided, but the authors did determine that end of shift urinary concentrations of 2,5-hexanedione averaged 11 mg/l versus a recommended BEI of 5 mg/l (note the BEI is 5 mg/l per g creatinine. There was no indication in Pastore et al. that the creatinine correction had been done). The MCV values were not different from controls. This indicates that nerve conduction velocities are not affected at exposure levels exceeding the recommended BEI values.

(b) Studies of workers with polyneuropathy

Huang et al. (1991). In one group of 5 workers exposed to n-hexane at levels estimated to have been 303 – 387 mg/m³, all developed polyneuropathy. The median nerve conduction velocity (39.8 m/sec) was significant and more than 3 SD from control. In a second group exposed at 264 mg/m³, there were 2 cases of polyneuropathy among 8 workers. The average MCV was 52.2 m/s, which was significant and about 2 SD from control. The exposure period was not stipulated. It should be noted



that the authors remarked that ventilation had been improved between the time the cases were identified and the exposure sampling was completed.

Huang and Chu (1989). In this study measurements were done on 5 individuals who had been diagnosed with polyneuropathy. The median MCV among this group was 39.5 ± 11.8 m/s versus a control value of 60.3 ± 3.8 , a difference of more than 3 SD. The measured n-hexane exposure was 194 mg/m^3 , but the measurements were taken a month after the factory had been ordered to take mitigation measures.

Öge et al. (1994). This study evaluated 27 patients who had been diagnosed with polyneuropathy following exposure to n-hexane. Air concentrations ranged from 211 – 2850 mg/m^3 . Nerve conduction velocity studies revealed substantial differences between the patients and an unexposed control group.

Scelsi et al. (1980) documents polyneuropathy in 3 patients following use of a solvent containing 80% n-hexane. Motor nerve conduction velocity studies suggested substantial reductions, but control data were not provided. Further there was no exposure information.

References

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The Hydrocarbon Solvents Producers Association is a Cefic Sector group representing the EU manufacturers of those solvents.

Cepca, DHC Solvents, ExxonMobil, Haltermann
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EU Transparency Register n° 64879142323-90

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