WEITERENTWICKLUNG DER RCP-METHODE ZUR BEWERTUNG VON LÖSEMITTELKOHLENWASSERSTOFF-GEMISCHEN AM ARBEITSPLATZ (VORHABEN 617.0-FP372)

erstellt im Auftrag von:
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ZUSAMMENFASSUNG

Zur toxikologischen Charakterisierung von Lösemittelkohlenwasserstoffgemischen bei der Exposition am Arbeitsplatz gibt es die RCP-Methode (RCP = reciprocal calculation based procedure), die auch in Deutschland seit 2007 angewandt wird. Die derzeit angewandten konkreten Gruppenleitwerte und Gruppengrenzen bei der Anwendung des RCP-Verfahrens waren zu überprüfen.

Bestehende regulatorische Werte zu Einzelstoffen aus dem Bereich von C5-C15 aliphatischen und C6-C15 aromatischen Kohlenwasserstoffen und neuere Daten wurden dokumentiert und die Datenhintergründe (Originalstudien) ermittelt. Aus dem toxikologischen Profil der Einzelstoffdaten wurde Gruppen (nach Kohlenstoff-Kettenlänge segmentierte Bereiche) mit ähnlichen Arbeitsplatzgrenzwerten („Gruppenleitwerte"; GGV) gebildet. Einzelne Substanzen mit deutlich abweichendem Wirkungsprofil oder abweichender Wirkstärke wurden von den in sich homogeneren Gruppen ausgenommen. Toxikologische Erkenntnisse zu definierten Lösemittelkohlenwasserstoffgemischen oder UVCB (substances of unknown or variable composition, complex reaction products or biological materials) wurden zum Vergleich herangezogen. Es wurden zwei Optionen als Projektergebnis erarbeitet und begründet:

Option A:

Gruppenbildung C6-C15 Aliphaten mit Gruppenleitwert (GGV) von 300 mg/m³
Gruppenbildung C9-C15 Aromaten mit Gruppenleitwert (GGV) von 50 mg/m³

Option B:

Gruppenbildung C6-C8 Aliphaten mit Gruppenleitwert (GGV) von 700 mg/m³
Gruppenbildung C9-C15 Aliphaten mit Gruppenleitwert (GGV) von 300 mg/m³
Gruppenbildung C9-C15 Aromaten mit Gruppenleitwert (GGV) von 50 mg/m³

Folgende Einzelstoffe wurden ermittelt, für die die jeweiligen GGV nicht gelten sollen:

Pentane (alle Isomere, einschließlich Cyclopentan), n-Hexan, Decalin, Benzol, Toluol, Xylol (alle Isomere), Ethylbenzol, Naphthalin, Tetralin, Diethylbenzol (alle Isomere), n-Butylbenzol, Methylnaphthalin (alle Isomere), Acenaphthen, Acenaphthylen, Biphenyl, 1,2,4-Triethylbenzol, Fluoren.

Die entsprechenden einzelstoffbezogenen Arbeitsplatzgrenzwerte (hier auch als „substance specific value" (SSV) bezeichnet) und/oder tolerierte Maximalmengen wurden im Rahmen des vorliegenden Projekts nicht geprüft oder ermittelt.

Bei dem gewählten Ansatz bedeutete es eine relevante Unsicherheit, dass häufig die höchste getestete Konzentration mit der „no observed adverse effect concentration" (NOAEC) gleichgesetzt wurde, obwohl möglicherweise dieser NOAEC höher gelegen haben könnte. Die Vorgehensweise (meist) mit Anwendung von Standardextrapolationsfaktoren stellt ebenfalls eine gewisse Unsicherheit dar. Andererseits wurde nicht immer der niedrigste sich ergebende vorläufige Arbeitsplatzgrenzwert (AGW) als Gruppenleitwert (GGV) herangezogen. Ferner bedeutet die Variabilität in der Wirkstärke, wie sie sich aus Einzelstoff- und Gemischestudien ableitet, auch eine relevante Unsicherheit hinsichtlich der postulierten Gleichartigkeit im Wirkprinzip der Einzelstoffe in der Stoffgruppe.

SUMMARY

Hydrodrocarbon solvents may be toxicologically assessed using the reciprocal calculation based procedure (RCP) in order to derive occupational exposure limits (OEL). This procedure is also established in Germany since 2007. Current specific group guidance values (GGV) and grouping ranges within RCP were reassessed in this project.

Therefore, existing regulatory values for single substances in the range of C5-C15 aliphatic and C6-C15 aromatic hydrocarbons and additional recent data were documented and the original background information was retrieved. Toxicological profiles from similar substances were clustered to groups with segmentation according to carbon-chain length to derive group guidance values (GGV). Single substances with identified distinct mode of action or with clearly deviating toxic potency were exempted from the more homogeneous groups. Toxicological findings on defined mixtures or UVCB (substances of unknown or variable composition, complex reaction products or biological materials) were used for comparison. As result, two options (option A, B) for grouping and GGVs are proposed:

Option A:
Single group: C6-C15 aliphatics with GGV of 300 mg/m³
Single group: C9-C15 aromatics with GGV of 50 mg/m³

Option B:
Single group: C6-C8 aliphatics with GGV of 700 mg/m³
Single group: C9-C15 aliphatics with GGV of 300 mg/m³
Single group: C9-C15 aromatics with GGV of 50 mg/m³

The following single substances should be exempted from the respective groups and GGV:
Pentanes (all isomers, including cyclopentane), n-hexane, decalin, benzene, toluene, xylenes (all isomers), ethylbenzene, naphthalene, tetralin, diethylbenzenes (all isomers), n-butylbenzenes, methylnaphthalene (all isomers), acenaphthene, acenaphthylene, biphenyl, 1,2,4-triethylbenzene, fluorene.

Single substance OELs (SSVs) and/or maximum tolerable amounts (cut offs for irrelevance) for these exempted single substances were not determined within this project.
With the given experimental data it caused considerable uncertainty, that in many cases the highest concentration tested had to be assumed to be equal to the „no observed adverse effect concentration“ (NOAEC), though the “real” NOAEC could have been higher. Also, the use of default assessment factors may be regarded as an uncertain screening procedure. However, not always the lowest resulting OEL was used for GGV. It should be noted that sometimes very deviating study results between the various single substance’s or mixture’s NOAECs also may reflect a significant heterogeneity in mode of action and potency, which does not support a highly homogeneous toxicity profile within the respective hydrocarbon solvent groupings. This makes it necessary to apply default factors and take conservative starting points for the assessments.

Inhaltsverzeichnis - Content

1 TECHNISCHER BERICHTSTEIL

1.1 Titel und Laufzeit des Vorhabens

Titel: Weiterentwicklung der RCP-Methode zur Bewertung von Lösemittelkohlenwasserstoff-Gemischen am Arbeitsplatz

Kurztitel: RCP Lösemittelkohlenwasserstoffe

Vorhabenskennzeichen: 617.0-FP372

Laufzeit: 1.6.2014 bis 31.12.2014

1.2 Problemstellung

Bei Lösemittelkohlenwasserstoffgemischen handelt es sich um benzinähnliche Stoffgemische, die in zahlreichen Industriebranchen, z.B. bei der Entfettung von Metallteilen oder als Verdünner für Farben und Lacken, eine wichtige Bedeutung haben. Eine Exposition von Beschäftigten ist nahezu an allen Arbeitsplätzen im Verantwortungsbereich aller Unfallversicherungsträger möglich.

Die Zusammensetzung von Lösemittelkohlenwasserstoffgemischen ist sehr unterschiedlich und oft sind die vielen enthaltenen Einzelverbindungen nicht genau charakterisiert und toxikologisch kaum untersucht. Trotzdem ist es im Sinne eines angemessenen Arbeitsschutzes erforderlich, einen Arbeitsplatzgrenzwert (AGW) nach der Technischen Regel für Gefahrstoffe (TRGS) 900 für diese Gemische zu etablieren. Hierfür gibt es ein spezielles Verfahren, die RCP-Methode (RCP = reciprocal calculation based procedure), das auch in Deutschland seit 2007 angewandt wird. Dabei werden Stoffgruppen chemisch ähnlicher Kohlenwasserstoffe gebildet, bei denen unterstellt wird, dass sie eine ähnliche toxikologische Wirkstärke besitzen wie einzelne ausgewiesene Gruppenvertreter. Die Methodik erlaubt, mit Hilfe von groben Angaben aus dem Sicherheitsdatenblatt einen AGW für ein so definiertes Lösemittelkohlenwasserstoffgemisch zu berechnen. Allerdings hat sich bei der Anwendung dieser Methode gezeigt, dass bei den derzeit gewählten Gruppenleitwerten nach TRGS 900 Widersprüche zu toxikologischen Erkenntnissen über Einzelverbindungen und spezifische Gemische auftreten, so dass der erforderliche Arbeitsschutz nicht sicher gewährleistet ist. Vor diesem Hintergrund ist es erforderlich, die RCP-Methode, die sich grundsätzlich bewährt hat, zu verbessern, um qualifiziertere Arbeitsplatzgrenzwerte für Lösemittelkohlenwasserstoffgemische ableiten zu können.

1.3 Forschungszweck/-ziel

Ziel des Projektes war es, die bestehende Methodik zur Ableitung von Arbeitsplatzgrenzwerten für Lösemittelkohlenwasserstoffgemische (RCP-Methode) unter Berücksichtigung neuerer toxikologischer Daten zu überarbeiten und dabei die (in jüngster Zeit etablierte) Systematik der Stoffidentifizierung für Kohlenwasserstofffraktionen unter REACH zu beachten.

1.4 Methodik und Darstellung der Zeitabläufe; Kooperation

Das Vorhaben wurde in einem „6-Schritte“-Verfahren (teilweise mit iterativer Bearbeitung) durchgeführt:

- Arbeitsschritt 1: Identifizierung und Ableitung von orientierenden Arbeitsplatzgrenzwerten für einzelne Lösemittelkohlenwasserstoffe (Screening)
- Arbeitsschritt 2: Identifizierung und Ableitung von Arbeitsplatzgrenzwerten für Lösemittelkohlenwasserstoffgemische
- Arbeitsschritt 3: Gruppenbildung für Lösemittelkohlenwasserstofffraktionen
- Arbeitsschritt 4: Ausklammerung von Einzelstoffen aufgrund von Relevanz in Lösemittelkohlenwasserstoffgemischen und/oder von abweichendem Toxizitätsprofil
- Arbeitsschritt 5: Differenzierte Überprüfung der Kandidaten für Gruppenleitwerte
- Arbeitsschritt 6: Vorschlag von aktualisierten Gruppenleitwerten und Zuordnungs-regeln einschließlich Diskussion

Das Projekt wurde durch eine koordinierende Arbeitsgruppe begleitet, die zur Diskussion von Zwischenergebnissen und Konzepten zur Verfügung stand. Darin waren neben den Projektnehmern vertreten

(1. Sitzung vor Projektbeginn; 14.11.2013):

Dr. Csomor, RP Kassel,

Dr. Jacobi, DHC Solvent Chemie, Mülheim,

Dr. Breuer, IFA, Sankt Augustin,

Dr. Nies, IFA, Sankt Augustin,

Dr. Pflaumbaum, IFA, Sankt Augustin

(2.Sitzung; 20.10.2014):

Dr. Csomor, RP Kassel,

Dr. Greim, DFG-Arbeitsstoffkommission,

Dr. Jacobi, HSPA/DHC Solvent Chemie,

Frau Werner, IFA,

Dr. Breuer, IFA,

Dr. Nies, IFA

Zusätzlich wurden Zwischenergebnisse mit der Herstellerindustrie und der diese vertretenden Toxikologen (Drs. Richard McKee, Juan Carlos Carillo) kommuniziert. Über diese Kontakte konnten zusätzliche Materialien beschafft und bewertet und Anregungen zur Verbesserung des Konzepts diskutiert werden. Aus diesem Grunde (internationaler Diskurs) wurde der Hauptteil dieses Projektberichts in englischer Sprache formuliert.

Aufgrund von Verzögerung in der Bereitstellung von Materialien und erforderlichen Diskussionen der koordinierenden Arbeitsgruppe wurde das ursprünglich vorgesehene Projektende vom 31.10.2014 auf den 31.12.2014 kostenneutral verschoben.

1.5 Ergebnisse des Vorhabens

Es wurden zwei Optionen als Projektergebnis erarbeitet und begründet:

Option A:

Gruppenbildung C6-C15 Aliphaten mit Gruppenleitwert (GGV) von 300 mg/m³

Gruppenbildung C9-C15 Aromaten mit Gruppenleitwert (GGV) von 50 mg/m³

Zusätzlich Arbeitsplatzgrenzwerte für definierte Einzelstoffe, wenn deren jeweilige Maximalmenge im Gemisch/UVCB überschritten. Bei eingehaltener Maximalmenge sind die jeweiligen Stoffe im Gemisch nicht zu berücksichtigen (ihre Menge der dann der jeweiligen Gruppe zuzuordnen).

Option B:

Gruppenbildung C6-C8 Aliphaten mit Gruppenleitwert (GGV) von 700 mg/m³

Gruppenbildung C9-C15 Aliphaten mit Gruppenleitwert (GGV) von 300 mg/m³

Gruppenbildung C9-C15 Aromaten mit Gruppenleitwert (GGV) von 50 mg/m³

Zusätzlich Arbeitsplatzgrenzwerte für definierte Einzelstoffe, wenn deren jeweilige Maximalmenge im Gemisch/UVCB überschritten. Bei eingehaltener Maximalmenge sind die jeweiligen Stoffe im Gemisch nicht zu berücksichtigen (ihre Menge der dann der jeweiligen Gruppe zuzuordnen).

Einzelstoffwerte (bei beiden Optionen A,B):

Zusätzlich sind Arbeitsplatzgrenzwerte für folgende Einzelstoffe festzulegen (sofern je zu definierende Maximalmenge im Gemisch überschritten) oder bestehende Arbeitsplatzgrenzwerte sind zu bestätigen:

Pentane (alle Isomere, einschließlich Cyclopentan)

n-Hexan

Decalin

Benzol

Toluol

Xylole

Ethylbenzol

Naphthalin

Tetralin

Diethylbenzol (alle Isomere)

n-Butylbenzol

Methylnaphthalin (alle Isomere)

Acenaphthen

Acenaphthylen

Biphenyl

1,2,4-Triethylbenzol

Fluoren

Die entsprechenden einzelstoffbezogenen Arbeitsplatzgrenzwerte und/oder tolerierte Maximalmengen wurden im Rahmen des vorliegenden Projekts nicht geprüft oder ermittelt.

Die vorgeschlagenen Gruppenbildung/ Gruppengrenzen ergeben sich entsprechend den unterschiedlichen Gruppengrenzen der oben beschriebenen Optionen und decken sich somit nicht vollständig mit den HSPA- Grenzen.

1.6 Auflistung der für das Vorhaben relevanten Ergebnisse von nicht am Vorhaben beteiligten Forschungsstellen

entfällt

1.7 Bewertung der Ergebnisse hinsichtlich des Forschungszwecks/-ziels

Die Ergebnisse stellen eine relevante Veränderung gegenüber dem Ist-Zustand (Gegenwärtige Gruppenaufteilung nach TRGS 900) dar und erscheinen gut begründet. Option A (Ergebnis nach Besprechung am 20.10. 2014) bietet die einfachste Lösung, die auch von der Umsetzung her (Berechnung des OEL im Einzelfall, Analytik, Kontrolle) hilfreich wäre. Option B (mit etwas stärkerer Differenzierung) scheint für Expositionen gegenüber Lösemittelgemischen mit hohem Aliphatengehalt (< C9-Faktion) unter Berücksichtigung realistischer Expositionshöhen möglicherweise leichter umsetzbar und ist nach Überprüfung durch Bewertung entsprechender Lösemittelgemische dennoch ausreichend protektiv. Für beide Optionen (A,B) ist es unerfreulich, dass für zahlreiche Einzelstoffe (insbesondere Aromaten) Sonderregelungen erforderlich werden, die die Festlegung von Einzelstoffgrenzwerten und Maximalmengen erfordern und im Einzelfall den Berechnungs- und Kontrollaufwand erhöhen. Eine abschließende Beurteilung ist unter Berücksichtigung der Relevanz dieser Stoffe in Lösemittelkohlenwasserstoffgemischen möglich (im Rahmen des Projekts nicht erfolgt).

1.8 Aktueller Umsetzungs- und Verwertungsplan

Es ist insbesondere geplant:

- Weitere Diskussion der Ergebnisse (z.B. in Gremien des Ausschusses für Gefahrstoffe, AGS) mit dem Ziel der Festlegung auf eine der vorgestellten Optionen (A,B) und Verankerung der Ergebnisse im Regelungswerk (TRGS 900), dazu im Einzelnen:
- Diskussion zu Einzelstoffen mit Lösemittelherstellerindustrie, Fachleuten in der Analytik zu vorliegenden Messergebnissen (Gehalts- und Raumluftmessungen) zur Festlegung von Maximalmengen/ Irrelevanzmengen für ausgewiesene Einzelstoffe
- Diskussion mit bewertenden Toxikologen und Fachgremien zur Zuweisung/ Bestätigung von Arbeitsplatzgrenzwerten (AGW) oder Maßzahlen aus Expositions-Risiko-Beziehungen (ERB) für ausgewiesene Einzelstoffe, die nicht in Gruppenleitwerten nach RCP Konzept enthalten sind

- Ggf. Reintegration von derzeit ausgenommenen Einzelstoffen in RCP-Gruppen, wenn sich die in diesem Projekt ausgewiesenen niedrigeren regulatorischen Werte für diese Stoffe nicht (nicht mit genügender Wahrscheinlichkeit) bestätigen würden
- Publikation der Ergebnisse in maßgeblichen Fachzeitschriften mit dem Ziel der Umsetzung und Erläuterung der Ergebnisse
- Präsentation der Ergebnisse auf geeigneten Fachforen
- Vornahme von Messungen und Dokumentation zur weiteren Absicherung der Machbarkeit/ Umsetzung der Ergebnisse durch Einrichtungen der DGUV.

2 ERWEITERTE ZUSAMMENFASSUNG

Zur toxikologischen Charakterisierung von Lösemittelkohlenwasserstoffgemischen bei der Exposition am Arbeitsplatz gibt es die RCP-Methode (RCP = reciprocal calculation based procedure), die auch in Deutschland seit 2007 angewandt wird. Die derzeit angewandten konkreten Werte und Gruppengrenzen bei der Anwendung des RCP-Verfahrens waren zu überprüfen.

Bestehende regulatorische Werte zu Einzelstoffen aus dem Bereich von C5-C15 aliphatischen und C6-C15 aromatischen Kohlenwasserstoffen wurden dokumentiert und die Datenhintergründe (Originalstudien) ermittelt. Zusätzlich wurde nach neueren experimentellen tierexperimentellen Arbeiten und Humanstudien zu den vielen Einzelstoffen aus dem genannten Spektrum von Lösemittelkohlenwasserstoffen gesucht. Auf alle diese Daten wurde der Standardansatz des AGW-Konzepts (Methodik für Arbeitsplatzgrenzwertableitungen in Deutschland) angewandt und so ein vorläufiger möglicher Einzelstoff-AGW für möglichst viele Stoffe ermittelt. Toxikologische Erkenntnisse zu definierten Lösemittelkohlenwasserstoffgemischen wurden zum Vergleich herangezogen, um a) für das definierte Gemisch eine direkte Ableitung eines vorläufigen AGW vorzunehmen, b) die gewählten GGV zu überprüfen, c) die Gruppengrenzen (Bereiche) zu überprüfen.
Angesichts einer derzeit kontroversen Bewertung der Adversität von Veränderungen in der Leber aufgrund von Exposition gegenüber Lösemittelkohlenwasserstoffen wurden vor allem Befunde zur neurotoxischen Wirkung ins Zentrum der Bewertung gestellt (wobei auch lokale Wirkungen wie Reizungen oder allgemeine systemische Wirkungen wie signifikant verringerte Gewichtszunahme die kritische Toxizität eines Stoffes oder eines Gemischs ergeben konnten). Es wurde vorausgesetzt, dass ein Grenzwert für chronische Exposition nicht höher sein dürfte als ein Grenzwert, der sich aus der Kurzzeitexposition ergibt.

Aus dem toxikologischen Profil der Einzelstoffdaten wurde Gruppen (nach Kohlenstoff-Kettenlänge segmentierte Bereiche) mit ähnlichen AGW („Gruppenleitwert“; GGV) gebildet. Einzelne Substanzen mit deutlich abweichendem Wirkungsprofil oder abweichender Wirkstärke wurden von den in sich homogeneren Gruppen ausgenommen. Toxikologische Erkenntnisse zu definierten Lösemittelkohlenwasserstoffgemischen oder UVCB (substances of unknown or variable composition, complex reaction products or biological materials) wurden zum Vergleich herangezogen.

C5 Aliphaten: Der bisherige Gruppenleitwert für C5 Aliphaten (1500 mg/m³) könnte aufrechterhalten werden, war aber vor allem wegen der Gruppenbildung mit den toxischeren >C5 Verbindungen erforderlich. Die Daten zu C5 Stoffen (Pentane, alle Isomeren einschließlich Cyclopentan) rechtfertigen, für sich genommen, überwiegend den bestehenden AGW von 3000 mg/m³. Wenn Pentane von der Gruppenzuordnung ausgeklammert werden, ist jedoch keine abschließende Festlegung eines Einzelstoffgrenzwerts für Pentane im vorliegenden Rahmen erforderlich. Es kann ein gesonderter Einzelstoffgrenzwert ermittelt werden (SSV).

C6 Aliphaten: Bisher gab es einen Gruppenleitwert von 1500 mg/m³, der auch für C6 Verbindungen gültig war. Allerdings musste aus der gruppe (neben n-Hexan) auch Cyclohexan ausgeklammert werden, u.a. weil der deutsche AGW für Cyclohexan mit 700 mg/m³ unter dem Gruppenleitwert für C5-C8 Aliphaten lag. Es zeigt sich jedoch, dass auch wegen weiterer Stoffe und weiterer Studien der bestehende GGV abgesenkt werden sollte. Je nach gewünschter Sicherheit im Ergebnis können Werte zwischen 300 und 700 mg/m³ für C6 Aliphaten vorgesehen werden. Dementsprechend ergäbe sich die Möglichkeit zur Reintegration von Cyclohexan in die Gruppe.

C7 Aliphaten: Der bestehende Gruppenleitwert von 1500 mg/m³, der auch für diese C7 Gruppe bisher bestand, wird insbesondere auf Basis von experimentellen Befunden zu Methylcyclohexan in Frage gestellt. Aber auch Studien zur (akuten) Neurotoxizität von C6/C7 Cycloparaffinen sprechen für einen niedrigeren GGV. Je nach gewünschter Datensicherheit und Annahmen zur Repräsentativität von Methylcyclohexan könnten GGV zwischen 700 und 300 mg/m³ gerechtfertigt werden.

C8 Aliphaten: Die Datenlage zu C8 Aliphaten (bisher ebenfalls in der Gruppe C5-C8 Aliphaten mit einem GGV von 1500 mg/m³) ist sehr limitiert. Grundsätzlich ist mit einem Absinken der Wirkschwelle für Neurotoxizität gegenüber C6/C7 Verbindungen zu rechnen, was sich jedoch nicht in den beschränkten Daten zu diesem Endpunkt niederschlägt. Bisher wurden Trimethylpentane wegen einer möglichen tumorpromovierenden Wirkung von dieser Gruppe ausgeschlossen. Es bestehen jedoch weiterhin relevante Unsicherheiten bei dieser Einstufung und es kann toleriert werden, die Verbindungen vorläufig (bei gleichzeitiger Prüfung durch andere Gremien) in der C8-Gruppe zu belassen. Entsprechend dem allgemeinen Trend zur zunehmenden Toxizität mit steigender Kettenlänge wird auch für diese Gruppe ein GGV zwischen 700 und 300 mg/m³ vorgeschlagen.

C9 Aliphaten: Auch für C9 Aliphaten erweist sich die Datenlage als schlecht. Der vormalige GGV lag bei 600 mg/m³ nach RCP Konzept in Deutschland. Es kommt jedoch eine Neurotoxizitätsstudie mit C9-C11 Isoparaffinen (Gemisch) zum Tragen, die einen GGV von 300 mg/m³ stützt. Die Höhe eines solchen Werts wird durch weitere Gemischedaten und durch eine ältere Studie zu n-Nonan gestützt. Die entsprechend deutliche Wirkungsverstärkung gegenüber kürzer kettigen Aliphaten bestätigt den allgemein anerkannten Trend zum Anstieg der Toxizität.

C10 Aliphaten: Neurotoxizitätsstudien mit n-Decan und mit C9-C11 Isoparaffinen stützen die Beibehaltung eines GGV von 300 mg/m³ für diese Gruppe (vormaliger Wert 600 mg/m³ nach RCP Konzept in Deutschland). Bei dieser Gruppe sollte Decalin ausgenommen werden, das derzeit einen sehr viel niedrigeren MAK-Wert (und DNEL) aufweist. Zur Bestätigung des Decalin OEL als Einzelwert (SSV) sind zusätzliche Diskussionen erforderlich.

≥C11 Aliphaten: Für C11 Aliphaten gelten die Befunde aus den Neurotoxizitätsstudien mit C9-C11 Isoparaffinen. Für >C11 Verbindungen ist zu erwarten, dass die Aufnahme in das

Gehirn sehr gering ist, so dass die Neurotoxizität eine geringere Rolle spielt. Begrenzte Daten (vor allem zu Gemischen) sprechen jedoch für eine Beibehaltung des GGV, wie er für C11 Aliphaten als begründet eingeordnet wurde.

C6-C8 Aromaten: Die vorläufig bereits vorgesehene Ausklammerung von C6, C7-C8 Aromaten aus einem Gruppenleitwert wurde ohne differenzierte Datenanalyse bestätigt. Es scheint flexibler, die aktuelle Datenlage zu verfolgen, um ggf. Einzelstoffgrenzwerte für die wenigen, eindeutig identifizierbaren Verbindungen dieser Gruppen zu etablieren, statt auf einen zwangsläufig ungenaueren Gruppenleitwert zu verweisen.

C9 Aromaten: Der bestehende GGV für C9 Aromaten liegt bei 100 mg/m³ und steht nicht im Einklang zum neu abgeleiteten Wert für iso-Propylbenzol (Cumol), der in Deutschland bei 50 mg/m³ liegt. Auch die Daten zu Trimethylbenzol sprechen teilweise für eine Absenkung des Gruppenleitwerts. Eine Neurotoxizitätsstudie mit einem C9 Aromaten Gemisch unterstützt die Absenkung des GGV.

C10 Aromaten: In der Gruppe der C10 Aromaten befinden sich einige Stoffe, die aufgrund eines abweichenden Toxizitätsprofils oder einer auffällig abweichenden Wirkstärke (in Richtung auf stärkere Toxizität) von der Gruppe ausgenommen werden sollten. Dazu zählen Tatralin, Diethylbenzole, Naphthalin und n-Butylbenzol. Es ist unbefriedigend, dass bei Diethylbenzolen (außer 1,2-Diethylbenzole) kein spezifischer Wirkungsmechanismus ausgemacht wurde, der die Abtrennung für diese Substanzen rechtfertigt, so dass die niedrigen OELs für diese Stoffe eine umfassendere Unsicherheit für das RCP-Verfahren bedeutet.

≥C11 Aromaten: Wiederum, wie bereits bei C10 Aromaten, sind einzelne Stoffe aufgrund von Hinweisen auf eine besonders ausgeprägte Toxizität oder einen entsprechenden Wirkmechanismus aus der Gruppe der C9-C15 Aromaten mit einem Gruppenleitwert von 50 mg/m³ (vormals 100 mg/m³) auszunehmen. Dazu zählen Methylnaphthalin, Biphenyl, Acenaphthen, Acenaphthylen, 1,2,4-Triethylbenzol und Fluoren. Über die Relevanz dieser Verbindungen in Lösemittelkohlenwasserstoffgemischen konnte keine Information im vorliegenden Rahmen eingeholt werden. Weitere Daten bestätigen überwiegend, dass der gewählte GGV von 50 mg/m³ auch für >C9 Aromaten beibehalten werden sollte.

Eine zentrale Bedeutung für die Gesamtbewertung (Gruppenaufteilung und Zuordnung von GGV) hatten Daten zu Gemischen. Eine neuere Studie von Juran et al. (2014) erbrachte einen NOAEC von 300 mg/m³ für „white spirit“ („Standard“ und „dearomatisiert“) nach akuter Exposition auf Basis von einer Testung von Freiwilligen. Aufgrund dieser Studie, die durch mehrere Vorläuferstudien und durch Befunde aus dem Tierexperiment gestützt wird, scheint ein AGW von ≤ 100 mg/m³ für ähnliche Gemische gerechtfertigt. Dies bedeutet, dass nach den Erkenntnissen aus Akutdaten kein höherer OEL bei Langzeitexposition gegenüber ähnlichen Gemischen festgelegt werden sollte. Mit Hilfe von Vergleichskalkulationen aus direkten OEL Berechnungen mit Gemischestudien und paralleler Berechnung des Gesamt-

OEL über RCP mit verschiedenen Setzungen für GGV wurde die Qualität von 2 solcher Optionen bestätigt und zur Grundlage des hier vorgestellten Vorschlags gemacht.

Es wurden demnach zwei Optionen als Projektergebnis erarbeitet und begründet:

Option A:

Gruppenbildung C6-C15 Aliphaten mit Gruppenleitwert (GGV) von 300 mg/m³

Gruppenbildung C9-C15 Aromaten mit Gruppenleitwert (GGV) von 50 mg/m³

Option B:

Gruppenbildung C6-C8 Aliphaten mit Gruppenleitwert (GGV) von 700 mg/m³

Gruppenbildung C9-C15 Aliphaten mit Gruppenleitwert (GGV) von 300 mg/m³

Gruppenbildung C9-C15 Aromaten mit Gruppenleitwert (GGV) von 50 mg/m³

Zusätzlich sind bei beiden Optionen Arbeitsplatzgrenzwerte für definierte Einzelstoffe auszuweisen, wenn deren jeweilige Maximalmenge im Gemisch/UVCB überschritten. Bei eingehaltener Maximalmenge sind die jeweiligen Stoffe im Gemisch nicht zu berücksichtigen (ihre Menge ist dann der jeweiligen Gruppe zuzuordnen). Folgende Einzelstoffe wurden ermittelt, für die die jeweiligen GGV nicht gelten sollen:

Pentane (alle Isomere, einschließlich Cyclopentan), n-Hexan, Decalin, Benzol, Toluol, Xylol (alle Isomere), Ethylbenzol, Naphthalin, Tetralin, Diethylbenzol (alle Isomere), n-Butylbenzol, Methylnaphthalin (alle Isomere), Acenaphthen, Acenaphthylen, Biphenyl, 1,2,4-Triethylbenzol, Fluoren.

Die entsprechenden einzelstoffbezogenen Arbeitsplatzgrenzwerte und/oder tolerierte Maximalmengen wurden im Rahmen des vorliegenden Projekts nicht geprüft oder ermittelt.

Als Vorteil von Option A erweist sich die gute Übereinstimmung mit den direkt aus Gemischedaten abgeleiteten OEL und die einfache Struktur, die die Berechnung, analytische Erfassung und Kontrolle des Konzepts in der Praxis begünstigt. Allerdings ist auch bei Option B eine sehr gute Übereinstimmung mit den direkten Gemischedaten gegeben mit noch geringerer Abweichung im Vergleich zu Option A. Die Wahl dieser etwas differenzierten Gruppenbildung kann insbesondere dann gerechtfertigt sein, wenn in der Praxis <C8 Aliphaten eine relevante Bedeutung haben und für diese <C8 Stoffe eine relevante Exposition angenommen werden muss.

Die vorgeschlagenen Gruppenbildung/ Gruppengrenzen ergeben sich entsprechend den unterschiedlichen Gruppengrenzen der oben beschriebenen Optionen und decken sich somit nicht vollständig mit den Grenzen, wie sie kürzlich durch Gremien der Lösemittelherstellerindustrie (HSPA) ermittelt und u.a. für Registrierungszwecke im Rahmen von REACH etabliert wurden. Die Unterschiede erscheinen in Bezug auf die Umsetzung keine relevanten Probleme zu bedeuten.

Bei dem gewählten Ansatz bedeutete es eine relevante Unsicherheit, dass häufig die höchste getestete Konzentration mit der „no observed adverse effect concentration“ (NOAEC) gleichgesetzt wurde, obwohl möglicherweise dieser NOAEC höher gelegen haben könnte. Die Vorgehensweise (meist) mit Anwendung von Standardextrapolationsfaktoren stellt

ebenfalls eine gewisse Unsicherheit dar. Andererseits wurde nicht immer der niedrigste sich ergebende vorläufige AGW als Gruppenleitwert herangezogen. Ferner bedeutet die Variabilität in der Wirkstärke, wie sie sich aus Einzelstoff- und Gemischestudien ableitet, auch eine relevante Unsicherheit hinsichtlich der postulierten Gleichartigkeit im Wirkprinzip der Einzelstoffe in der Stoffgruppe. Um der Heterogenität von Einzelbefunden Rechnung zu tragen, ist es erforderlich, mit Standardextrapolationen und konservativen Startpunkten bei der jeweiligen Extrapolation zu arbeiten.

3 BACKGROUND

Hydrocarbon solvents are gasoline type of mixtures of chemical substances with no complex additives, which are in use at many workplaces in different industries. Occupational exposure to hydrocarbon solvents is frequent and may occur almost everywhere.

Ingredient hydrocarbons are contained in mixtures in different and varying percentages. Many of the single contained substances have not been toxicologically assessed and are not precisely characterised. In order to provide sufficient worker's health protection, a procedure has been established, called RCP (RCP = reciprocal calculation based procedure), which is also the background for occupational exposure limits (OEL) on hydrocarbon solvent mixtures in Germany since 2007 (Pflaumbaum et al., 2008a; b). With this procedure, structurally similar hydrocarbons are combined to groups. It is assumed that structurally similar compounds also exert similar toxicological effects with similar effect potency and mode of action. The groups are represented by group guidance values (GGV) and ranges of carbon chain lengths for which the GGVs are selected as reference.

However, as has been demonstrated recently, that some single substance's and mixture assessments for hydrocarbon solvents are not in agreement with those GGV. Therefore the current project was initiated in order to reassess GGV for the respective groups, in order to redefine or reconfirm group ranges, and to adapt to systematics provided by the international hydrocarbon solvent product association (HSPA) for hydrocarbon grouping recently established within the REACH registration process. RCP in its initial form already has arranged the possible exclusion of some single substances, which definitely are not similar to "typical" representatives of the respective group. Hence, the project should also select such substances as possible candidates for single substance assessments with single substance reference values (SSV) to be determined.

4 METHOD

4.1 Single substance and mixture data retrieval

Single hydrocarbons belonging to a carbon chain length were identified by structural search and listed. Respective international OELs were retrieved and documented. Where possible, background documents were analysed, which were the critical studies and endpoints for the selected OEL. It was discussed whether current GGVs were compatible with the single substance OEL.

An exhaustive and systematic data search was performed using CAS numbers of single substances and key terms relevant to inhalation and toxicity, hydrocarbons, solvents, white spirit or similar terms. Recent reviews or assessments (like SIDS documents from OECD) were analysed for background data. Important publications were analysed, if they were cited by other authors, to find updated discussions or extensions of the reported data. More than 300 studies and publications were selected for further analysis.

4.2 Assessment factors

To back the RCP procedure, experimental and epidemiological data on many single substances and mixtures had to be reviewed arranged with respect to their effect potency. This should be done after calibration to the envisaged scenario (workplace, daily chronic exposure). For the workplace, an eight hour daily exposure for 5 days per week was assumed. Existing data had to be transformed by assessment factors (or extrapolation factors). In Germany, for the derivation of OEL (Arbeitsplatzgrenzwert; AGW) there exists a methodology with the following default values:

4.2.1 Species extrapolation

In case of inhalation data, for systemic effects usually 1 ppm (animal exposure) is taken as 1 ppm (human exposure) as starting point. This implicitly includes an allometric scaling approach and is consistent to what is derived from typical PBPK modelling. This is in accordance to the procedure under REACH guidance (ECHA, 2012).

For locally acting substances with sensory irritation as key endpoint the “respiratory depression” in mice as RD50 was used as starting point, with a total extrapolation factor of 30 as conventional estimate of an OEL without further modifications. It was acknowledged that this starting point and size of the extrapolation factor are only weakly supported by specific data and therefore are only used as supportive evidence (Bos et al., 2002).

4.2.2 Time extrapolation (from subacute to chronic)

The usual default is to extrapolate from subacute to subchronic by a factor of 3, from subchronic to chronic by a factor of 2, with a total time extrapolation factor of 6 from subacute to chronic duration. This is in accordance to the procedure under REACH (ECHA, 2012). However, these factors should not be used to extrapolate from single acute exposure.

4.2.3 Time extrapolation (from hours to full workday exposure)

To extrapolate from, e.g., 4 hours exposure to 8 hours exposure, Haber's law was used without modification (Gaylor, 2000), if the same species was the starting point. However, for extrapolation from animal exposure to human exposure, in addition, it has to be considered that humans have a higher physical activity at the workplace than rats in experimental testing scenarios. Therefore, according to ECHA default procedures, a factor of 2 is used from a 6 hour animal exposure to eight hour daily exposure duration at the workplace.

4.2.4 Time extrapolation (from acute to chronic exposure)

As was demonstrated by comparison of results after acute or chronic exposure in human experimental studies (usually with volunteers) in neurobehavioral tests (acute) and other signs of neurotoxicity after chronic exposure, there is apparently no increase of effect size with duration from adequate effect threshold determined by high quality acute testing to chronic exposure. Therefore, a time extrapolation factor of 1 is justified in those cases. However, it is not clear, whether a 4 hour test already is sufficient to cover eight hour exposure. Therefore, extrapolations according to section 4.2.3 are still included, if applicable. Similarly, for acute high quality animal studies no separate time extrapolation factor from single acute exposure to chronic exposure may be warranted. Note, that we do not account for potential reversibility or adaption on acute effects after long term exposure in case of neurotoxic effects.

4.2.5 Variability factor

This factor relates to interspecies and intraspecies variability. By application of the scaling factor (see chapter 4.2.1) we extrapolate from the average animal to the average worker. In order to cover species with a higher sensitivity than the tested species or strain and in order to address the more sensitive human at the workplace this variability factor is applied. There may be toxicokinetic or toxicodynamic reasons which are all combined within this factor of 5. However, if three or more animal species are tested and the most sensitive one is used as 'point of departure' for the assessment, the default factor of 5 may be lowered to 3 because of this precautious starting point.

4.2.6 Effect level (LOAEC) to No Adverse Effect Level (NAEC)

The conventional extrapolation factor of 3 is used for extrapolation from LOAEL to NOAEL, even though there are no adequate data to support this factor and the slope of the dose response relationship may vary substantially for different compounds.

4.2.7 Route-to-route extrapolation

Allometric scaling (with a scaling factor of, e.g., four for rat to human extrapolation) is used according to international guideline methodology.

4.2.8 Conclusions

In general, we used default assessment factors (extrapolation factors) as outlined above. Because of the large amount of data and the screening type of assessment, we hesitated to deviate from default for specific studies. If, however, such deviations appeared to be

obvious from the data analysis, we modified the assessment factors accordingly. It should be noted, that, even though deviations from default may be justified for the single substance in question, this modification may not be supported for similar substances with slightly other properties. In case of hydrocarbon solvents data the specific OEL always needs be represent not only the single substance with sound data, but also other substances, with potentially slightly different properties and less data. This background supports the use of default assessment factors as an overall strategy in this project.

As a starting point for extrapolation, usually the NOAEC should be used as "point of departure" (POD). However, as often the highest concentration tested was without observed adverse effects, this concentration had to be used as POD and therefore is regarded as NOAEC. This implies relevant uncertainties for cases, where this type of POD was used for assessment.

4.3 Grouping

4.3.1 Existing RCP approach in Germany

A default approach to address health effects after exposure to mixtures is the additivity assumption as proposed by ACGIH (Ogata et al., 1993) in the USA or Technical Rule (TRGS) 402 in Germany (TRGS 402, 1997; Bartsch et al., 1998). This approach is used for hydrocarbon solvents, with:

$$\frac{1}{OEL_{mixture}} = \frac{fraction_a}{GGV_a} + \frac{fraction_b}{GGV_b} + \cdots \frac{fraction_n}{GGV_n}$$

, where the various fractions a, b, …, n are characterized by similar chemical structure and similar toxicological properties. The fractions are given in numerical values adding up to 1 for the entire mixture and the fractional OELs (GGVs) are given in mg/m^3. A single substance x with unique toxicological properties may be included into this formula by identifying the amount of this specific substance as a separate fraction ($fraction_x$) and by assigning a specific OEL (SSV_x) to this compound.

Currently, the RCP method as proposed by CEFIC/HSPA contains 4 plus 6 fractions, 4 fractions of molecules with similar structure and similar toxicological properties and 6 single substances with unique toxicological properties:

- C5-C8 aliphatics (GGV: 1500 mg/m³)
- C9-C15 aliphatics (GGV: 600 mg/m³)
- C7-C8 aromatics (GGV: 200 mg/m³)
- C9-C15 aromatics (GGV: 100 mg/m³)

The single substances with SSV are:

- n-hexane (CASNR: 110-54-3)
- Cyclohexane (110-82-7)
- Trimethylpentanes: (564-02-3, 540-84-1, 560-21-4, 565-75-3)
- Naphthalene (91-20-3)

- 1,2 Diethylbenzene (135-01-3)
- n-Butylbenzene (104-51-8)

According to more recent discussions in Germany, also the following substances are discussed for exclusion from GGVs:

- Benzene (71-43-2)
- Toluene (108-88-3)
- Ethylbenzene (100-41-4)
- Xylenes (1330-20-7)

The respective fractions are quantified according to the amount (percentage) given for the liquid.

4.3.2 HSPA-proposal for nomenclature of hydrocarbon solvents for purposes of REACH registration

Below, we report on the concept by HSPA for renaming hydrocarbon solvent mixtures (UVCB) with respect to the demands by REACH[1] (see Table 4-1).

[1] http://www.reachcentrum.eu/Consortia%20Documents/P-I163/Other/P-I163_HSPA_Naming_convention_2011.03.pdf

Table 4-1 Categories and subcategories for mixtures of hydrocarbon solvents nomenclature under REACH by HSPA

Category	Subcategory (associated HSPA Substance name)	DNEL [mg/m³]
C9 Aromatics	-	150
C10-12 Aromatics	H., C10, aromatics, >1% naphthalene	151
	H., C10, aromatics, <1% naphthalene	151
	H., C10-C13, aromatics, <1% naphthalene	151
	H., C10-C13, aromatics, >1% naphthalene	151
C9-14 Aliphatics (2-25% aromatics)	H., C9-C10, n-alkanes, isoalkanes, cyclics, aromatics (2-25%)	Not reg.
	H., C10-C13, n-alkanes, isoalkanes, cyclics, aromatics (2-25%)	No DNEL
	H., C8-12, n-alkanes, isoalkanes, cyclics, aromatics (2-25%)	330
	H., C9-12, n-alkanes, isoalkanes, cyclics, aromatics (2-25%)	330
	H., C11-C14, n-alkanes, isoalkanes, cyclics, aromatics (2-25%)	No DNEL
C14-20 Aliphatics (2-30% aromatic)	H., C14-C18, n-alkanes, isoalkanes, cyclics, aromatics (2-30 %)	No DNEL
	H., C16-C20, n-alkanes, isoalkanes, cyclics, aromatics (2-30 %)	No DNEL
C5 Aliphatics	Normal-Pentane	No DNEL
	ISO-Pentane	3000
	Cyclopentane	3000
	Hydrocarbons, C5, n-alkanes, isoalkanes	3000
C6 Aliphatics	Normal-Hexane	Not reg.
	H., C6, isoalkanes, <5% n-hexane	5306
	H., C6, n-alkanes, isoalkanes, cyclics, n-hexane rich	93
	H., C6-C7, n-alkanes, isoalkanes, cyclics, <5% n-hexane	5306
	H., C5-C7, n-alkanes, isoalkanes, n-hexane rich	93
C7-C9 Aliphatics	H., C7, n-alkanes, isoalkanes, cyclics	2085
	H., C6-C7, n-alkanes, isoalkanes, cyclics, > 5% n-hexane	145
	H., C6-C7, n-alkanes, isoalkanes, cyclics, < 5% n-hexane	2035
	H., C7-C9, n-alkanes, isoalkanes, cyclics	2035
	H., C6-C10, n-alkanes, isoalkanes, > 5% n-hexane	230
	H., C7-C9, isoalkanes	2035
	H., C7-C8, cyclics	2035
	Methyl cyclohexane	64.3
	Normal-Heptane	2085
	Iso-Heptane	2085
	Normal-Octane	2035
	Iso-Octane	2035
	Nonane	2035
C9-14 Aliphatics (<=2% aromatic)	H., C9-C11, n-alkanes, isoalkanes, cyclics, < 2% aromatics	1500
	H., C9-C10, n-alkanes, isoalkanes, cyclics, < 2% aromatics	1500
	H., C9-C11, isoalkanes, cyclics, < 2% aromatics	871
	H., C10-C13, n-alkanes, isoalkanes, cyclics, < 2% aromatics	No DNEL
	H., C10-C13, isoalkanes, cyclics, < 2% aromatics	No DNEL
	H., C11-C14, n-alkanes, isoalkanes, cyclics, < 2% aromatics	No DNEL
	H., C13-C15, n-alkanes, isoalkanes, cyclics, < 2% aromatics	No DNEL
	H., C12-C16, isoalkanes, cyclics, < 2% aromatics	No DNEL
	H., C12-C15, n-alkanes, isoalkanes, cyclics, < 2% aromatics	No DNEL

	H., C11-C14, isoalkanes, cyclics, < 2% aromatics	No DNEL
	H., C10-C12, isoalkanes, < 2% aromatics	No DNEL
	H., C11-C12, isoalkanes, < 2% aromatics	No DNEL
	H., C11-C13, isoalkanes, < 2% aromatics	No DNEL
	H., C10-C13, n-alkanes, < 2% aromatics	No DNEL
	H., C11-C14, n-alkanes, < 2% aromatics	No DNEL
	H., C9-C11, cyclics, < 2% aromatics	1500
	Decane	No DNEL
	Undecane	No DNEL
	Dodecane	No DNEL
	Tridecane	No DNEL
	Tetradecane	No DNEL
	Isododecane	No DNEL
	H., C10-C14, n-alkanes, isoalkanes, <2% aromatic	No DNEL
C14-20 Aliphatics (<=2% aromatic)	H., C13-C18, n-alkanes, isoalkanes, cyclics, < 2% aromatics	No DNEL
	H., C14-C18, n-alkanes, isoalkanes, cyclics, < 2% aromatics	No DNEL
	H., C16-C20, n-alkanes, isoalkanes, cyclics, < 2% aromatics	No DNEL
	H., C13-C16, isoalkanes, cyclics, < 2% aromatics	No DNEL
	H., C14-C19, isoalkanes, cyclics, < 2% aromatics	No DNEL
	H., C14-C17, n-alkanes, < 2% aromatics	No DNEL
	H., C14-C20, n-alkanes, < 2% aromatics	No DNEL
	Pentadecane	No DNEL
	Hexadecane (n-Hexadecane)	No DNEL
	Hexadecane (iso-hexadecane)	871
	Heptadecane	Not reg.
	Octadecane	No DNEL
	Icosane (isoicosane)	No DNEL
	Icosane (n-icosane)	No DNEL
	H., C14-C20, n-alkanes, isoalkanes, <2% aromatics	No DNEL

H. = Hydrocarbons

These categories may be visualised by the schematic presentation in Figure 4-1.

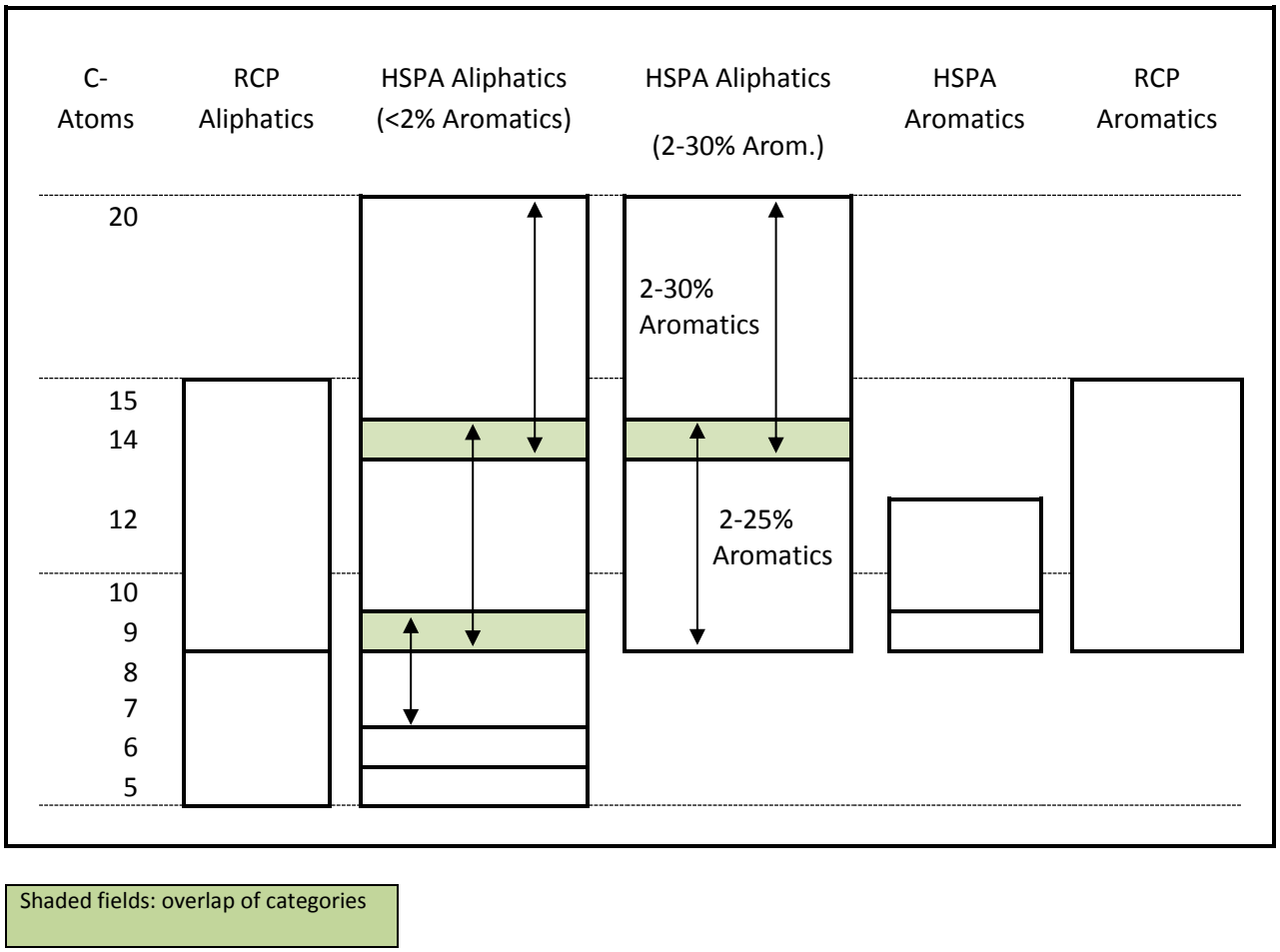

Figure 4-1: **Schematic overview on HSPA grouping of hydrocarbon solvents in comparison to current RCP approach (C6-C8 aromatics already excluded from RCP presentation)**

4.3.3 OECD HPV Categories

Assessment of hydrocarbon solvents by OECD was performed lately and yielded the following categorisation:

- C5 Aliphatics Hydrocarbon solvents category (OECD, 2008)
- C6 Aliphatics Hydrocarbon solvents category
- C7-C9 Aliphatics Hydrocarbon solvents category (OECD, 2010a)
- C9-C14 Aliphatics (<2 % aromatics) Hydrocarbon solvents category (OECD, 2012b)
- C9-C14 Aliphatics (2-25 % aromatics) Aliphatics Hydrocarbon solvents category (OECD, 2012a)
- C14-C20 Aliphatics (<2 % aromatics) Hydrocarbon solvents category (OECD, 2011)
- C9 Aromatics Hydrocarbon solvents category (OECD, 2012c)

- C10-C13 Aromatics Hydrocarbon solvents category (OECD, 2012d)

4.3.4 Differences and demarcation

The definition of solvents according to HSPA and McKee et al. (2005) is restricted to carbon chain length C5-C15. This deviates from other definitions with broader ranges. In this report, we do not address hydrocarbons with > C15.

4.4 Presentation of assessments

For each group of substances we first reported the existing group guidance value (GGV), which is currently linked to this C_x – group.

Then we list specific single substances, for which the data search was performed (however, also some additional information was considered, without reference to single defined substance, if available).

Within the third subsection we report the most relevant existing OELs reported for substances belonging to this C_x – group.

The forth subsection contains information from recent studies not yet covered in existing OEL assessments or background study data, which were found that they have been used in existing OEL assessments.

The fifth subsection on each C_x – group covers the data assessment, the discussion and the conclusion, where we derive a preliminary representative reference value for this C_x – group (or we confirm the existing reference value). However, as GGV may contain more than one C_x – group, this conclusion may only be preliminary, because an integrated view will only be possible after all C_x – groups have been analysed (sections 5.1-5.12,5.13-5.22) and moreover data on mixtures have been addressed (section 6) to finally provide all GGVs in an overall approach (section 7).

To illustrate the overall potential OEL profile for a C_x – group in this fifth subsection, a graphical presentation of the assessment is shown. The legend for these graphical presentations is given below (Figure 4-2). We are aware, that some of the assessments include relevant uncertainties, because the “point of departure” (POD) for extrapolation had been the highest concentration tested. This implies, that the “no observed adverse effect level” (NOAEC) may have been higher (or much higher) than the POD. In this case the extrapolation is performed with the appropriate default assessment factors, but the extrapolated OEL is regarded to be equal or higher (≥) than the calculated value. In this case the extrapolation is illustrated by a dashed line with an arrow at the lower end. If, however, the NOAEC is better qualified (because a LOAEC is experimentally supported), the extrapolation dashed line ends with a stop bar at the lower end. As will be demonstrated, for many single substances or mixtures neurotoxicity may be a key toxicological endpoint. If a study addressed neurotoxicity by detailed testing, such extrapolated potential OELs will be marked with an “N” (for **N**eurotoxicity).

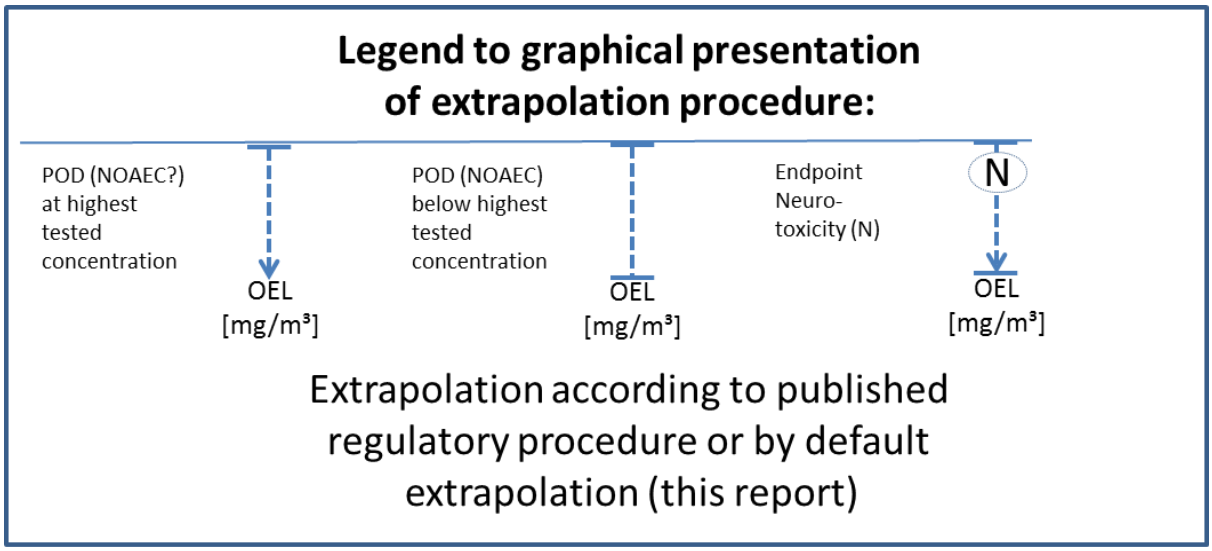

Figure 4-2: **Legend for the graphical presentations in the following subsections (see text for further explanation)**

5 SINGLE SUBSTANCES

5.1 C5- Aliphatic Hydrocarbon Solvents

5.1.1 Assigned group guidance value (RCP, German approach, TRGS 900)

For the group of C5-C8 aliphatics currently in Germany the group guidance value is 1500 mg/m³ (AGS, 2012).

5.1.2 Substance Search

We searched for experimental or epidemiological data on the substances

- Cyclopentane (CASRN: 287-92-3)
- N-Pentane (CASRN: 109-66-0)
- Iso-Pentane, 2-Methylbutane (CASRN: 78-78-4)
- Neopentane (CASRN: 463-82-1)

and for the group in general (C5 aliphatic hydrocarbons).

5.1.3 Existing OEL or equivalent derived reference values (workers)

Substance	Type reference value	mg/m³	Source
All pentane isomers	AGW (Germany)	3000	(AGS, 2006; BMAS, 2014)
All pentane isomers	MAK (Germany)	3000	(DFG, 2014)
n-pentane, iso-pentane	OEL (Europe)	3000	(SCOEL, 1997)
All pentane isomers	DNEL (Europe)	3000	(ECHA, 2014)
Cyclopentane	OEL (Denmark)	850	(IFA, 2014) (lowest)
n-pentane	OEL (USA/NIOSH; Canada)	350	(IFA, 2014) (lowest)
iso-pentane	OEL (Denmark)	1500	(IFA, 2014) (lowest)
All pentane isomers	OEL (other countries)	1800	(IFA, 2014)
All pentane isomers	TLV	1770	(ACGIH, 2011)

5.1.4 Recent Data

- Lammers et al. (2011) report that n-pentane did not produce CNS effects in rats tested up to 20000 mg/m³ (8 h/d on 3 consecutive days; highest concentration tested).
- Similarly, McKee et al. (2011) found no neurobehavioral effects after acute exposure to cyclopentane at and below 20000 mg/m³ (8 h/d on 3 consecutive days; highest concentration tested).

- Yu et al. (2011) report a one generation reproductive toxicity study on iso-pentane in rats, with a general NOAEL of 300 mg/kg x d (and a NOAEL of 1000 mg/kg x d for reproductive toxicity and developmental effects, highest dose tested).
- Kim et al. (2012) performed a subchronic inhalation study according to OECD-guideline 413 with rats exposed to 0, 340, 1530 and 6885 ppm (1020, 4590, 20655 mg/m³). The NOAEC was at the highest dose tests (i.e. 20700 mg/m³).

No further relevant studies were found.

5.1.5 Assessment, discussion and conclusions

OEL and DNEL for C5-aliphatic hydrocarbon solvents were derived based on subchronic studies (POD 20000 – 30000 mg/m³; Cyclopentane and n-Pentane (McKee et al., 1998)). If assessed by default AGW method, this would result in an OEL of 1000 – 1500 mg/m³ (AF20 = $5_{variability}*2_{6\text{-}8h}*2_{sc\text{-}c}$). However, as the NOAEC may be higher than the POD, the potential OEL would probably be > 1000 mg/m³.

The background document for the 1770 mg/m³ (600 ppm) TLV by ACGIH states that 600 ppm 'should provide a substantial margin of safety against narcotic and irritative effects', for which a NOAEC of 5000 ppm (10 minutes human controlled exposure) is reported.

An OECD assessment from 2008 provided no relevant further data (OECD, 2008).

The USA-NIOSH assessment was based on a study with possible contribution of other hydrocarbons to effect concentrations. A comment by OSHA indicated that identical concentrations were proposed for n-hexane and C5-C8 aliphatics. Therefore this reference value is not regarded adequate for C5 aliphatic hydrocarbon solvents without n-hexane. The background for the Danish assessment was not elucidated and was, therefore, not considered.

If the one-generation reproductive study on iso-pentane by Yu et al. (2011) is used with path-to-path extrapolation (assumptions: 4: allometric scaling rat; 70 kg body weight, 10 m³ respiratory volume during light activity of worker in 8 h shift), this would result in a considerable lower general threshold (NOAEC = 525 mg/m³; extrapolated ≈ 50 mg/m³ with AF10= $5_{variability}*2_{sc\text{-}c}$). However, the general threshold may have been influenced by species specific effects (kidney, male rat) and was not confirmed by appropriate inhalation studies. Reproductive effects were not detected at the highest dose tested and therefore no extrapolation on an OEL analogue reference value was performed.

The recent study by Lammers et al. (2011) (AF5 = $5_{variability}$) and by McKee et al. (2011) (AF5 = $5_{variability}$; both neurotoxicity as toxicological endpoint; potential OEL ≥ 4000 mg/m³) confirmed the existing assessments. The same is true for the subchronic OECD-study by Kim et al. (2012) with a NOAEC of 20700 mg/m³, i.e., a potential OEL of ≥1015 mg/m³ (AF20 = $5_{variability}*2_{6\text{-}8h}*2_{sc\text{-}c}$).

In summary, there is no reason to deviate from current substance-specific, C5-group specific or RCP-GGV value because of recent data or because of relevant concerns about existing assessments methodology. The assigned value in Germany of 3000 mg/m³ (or the current GGV for C5-C8 aliphatics of 1500 mg/m³) would still be appropriate. But as for all group members specific substance guidance values (SSV) exist, it is proposed to exclude C5 aliphatics from the RCP grouping approach and use the SSV instead. The profile on potential OEL derived from existing assessments and recent data is shown in Figure 5-1.

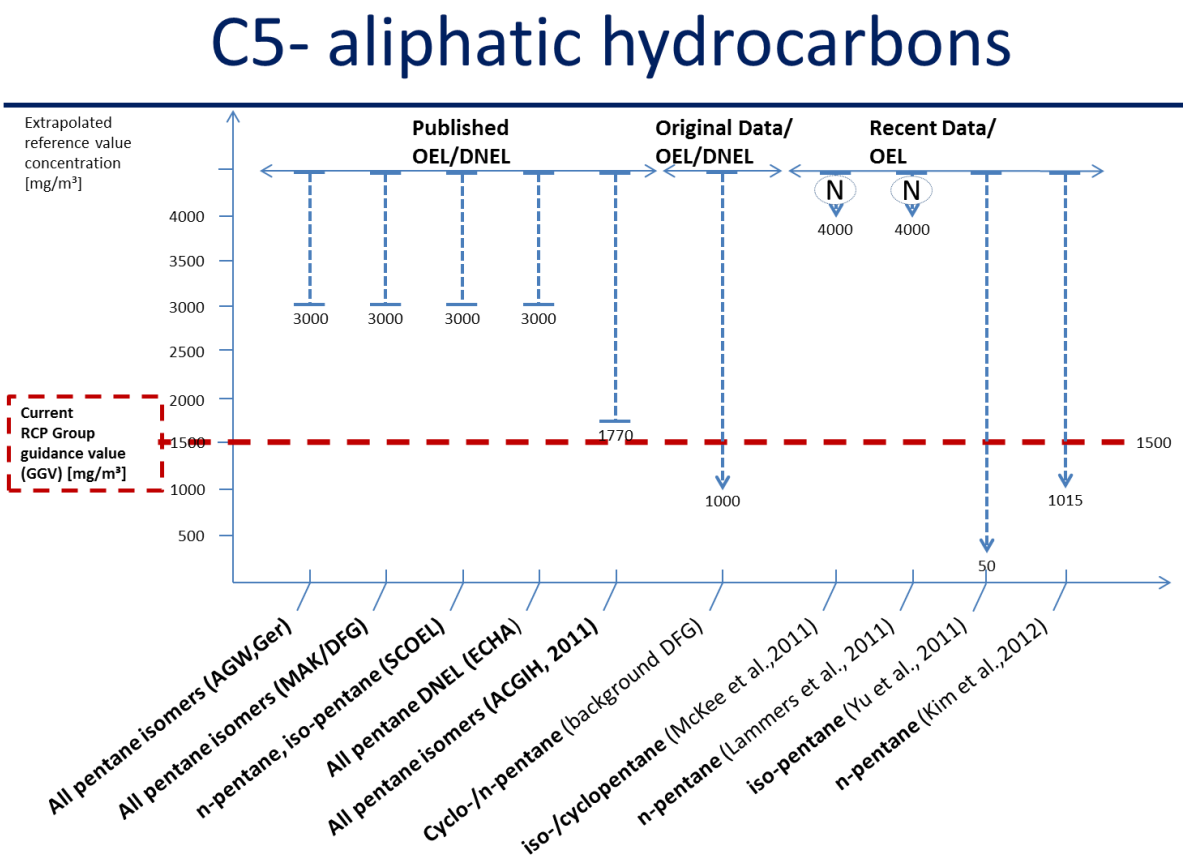

Figure 5-1: **Schematic illustration of potential OELs for C5 aliphatic hydrocarbon solvents (see Figure 4-2 for legend and comments in text)**

5.2 C6- Aliphatic Hydrocarbon Solvents

5.2.1 Assigned group guidance value (RCP, German approach, TRGS 900)

For the group of C5-C8 aliphatics currently in Germany the group guidance value is 1500 mg/m³ (AGS, 2012).

5.2.2 Substance Search

We searched for experimental or epidemiological data on the substances:

- 2-Methylpentane (CASRN: 107-83-5)
- 3-Methylpentane (CASRN: 96-14-0)
- 2,2-Dimethylbutane, Neohexane (CASRN: 75-83-2)
- 2,3-Dimethylbutane (CASRN: 79-29-8)
- Methylcyclopentane (CASRN: 96-37-7)
- Cyclohexane (CASRN: 110-82-7)

and for the group in general (C6 aliphatic hydrocarbons).

Further assessments on n-hexane (CASRN: 110-54-3) were not discussed as this C6-compound has been separated from the C5-C8 aliphatics group within the RCP procedure in Germany (assignment of SSV). Also, Cyclohexane has been excluded from the group guidance value within the RCP procedure in Germany. However, if the overall GGV would be lowered, it should be reconsidered whether cyclohexane still has to be eliminated. Therefore, assessment data on cyclohexane were also documented.

5.2.3 Existing OEL or equivalent derived reference values (workers)

Substance	Type reference value	mg/m³	Source
All hexane isomers (but without n-hexane) and 2-methylcylopentane	AGW (Germany)	1800	(AGS, 2006; BMAS, 2014)
	MAK (Germany)	1800	(DFG, 2014)
2-methylpentane	DNEL (Europe)	5306	(ECHA, 2014)
	OEL (Sweden and others)	700	(IFA, 2014)
All hexane isomers (but without n-hexane)	OEL (NIOSH/)	350	(IFA, 2014)
Acyclic hexane isomers (but without n-hexane)	OEL Poland	400	(IFA, 2014) / (Szymańska and Bruchajzer, 2008)
cyclohexane	AGW (Germany)	700	(AGS, 2006; BMAS, 2014)
	ACGIH-TLV-TWA	350	(ACGIH, 2012)

5.2.4 Recent Data

- A subchronic inhalation study in rats on methylcyclopentane by Yang et al. (2014) provided a NOAEC of 4550 mg/m³ (rats exposed 6 h/d, 5 d/week, 13 weeks; effects at highest concentration tested (5870 ppm): salivation and rubbing, ↑liver weight, ↑ kidney weight in females only).
- Another, very similar, subchronic inhalation study in rats was performed according to OECD guideline 413. Animals were exposed to 0, 290, 1160 and 4650 ppm (0, 1015, 4060, 16240 mg/m³) of 2-methylpentane. There were nephrotoxic effects in male rats with a LOAEC of 1015 mg/m³ (dose dependent increase, but irrelevant effect in humans). For females the NOAEC was 16240 mg/m³ (Chung et al., 2014).
- Lammers et al. (2009) performed an experimental study on neurobehavioral effects in rats. Animals were exposed for 8 h/d for 3 consecutive days to a test atmosphere cyclohexane with concentrations of 0, 1400, 8000, 28000 mg/m³. In rats, even in high concentration group only small effects on gait and a statistically significant reduction in psychomotor speed in visual discrimination tests was noted. A NOAEC of 8000 mg/m³ was identified. The authors concluded that cyclohexane produced minimal acute effects on the CNS in rats and humans (Lammers et al., 2009). Based on the

data by Lammers et al. and PBPK-modelling Hissink et al. (2009) concluded that 'exposure of volunteers to cyclohexane at levels of 4100 mg/m³ will result in brain levels similar to those in rats exposed to 8000 mg/m³ (NOAEC).

- In the parallel study with 12 human volunteers these persons were exposed for 4 hours twice to 86 or 860 mg cyclohexane/m³ (with test sessions spaced 7 days apart). No significant changes in neurobehavioral test results were observed (Lammers et al., 2009). Based on the animal data and on the PBPK- modelling the authors discuss that the human NOAEC may be higher than the highest concentration used in this study.
- Data on a C6/C7 cycloparaffinic solvent is discussed in the section on mixtures (McKee et al., 2011). The authors observed no adverse effects with 4200 mg/m³ exposure in a neurotoxicity study with rats (see 6.1.1).

No further relevant studies were found.

5.2.5 Assessment, discussion and conclusions

a) Background to OELs on C6 aliphatic hydrocarbons (except cyclohexane and n-hexane)

The German MAK value for C6-aliphatic hydrocarbon solvents except n-hexane was derived based on a study by Frontali et al. (1981) on 2-methylpentane (purity > 98 %, 90d inhalation toxicity study, 9 to 10 h/d, 5 to 6 d/week). The NOAEC in that subchronic study was 5370 mg/m³ (single concentration tested with no effects observed). According to default extrapolation procedure an OEL of 537 mg/m³ would result (AF10= $5_{variability}$*$2_{sc\text{-}c}$). The weight gain was significantly reduced in exposed animals. Therefore, we assume that the POD was not chosen well below the NOAEC.

Another inhalation study by Spencer (1982) with male rats (inhalation exposure on 22 h/d, 7 d/week, 6 months) to n-hexane plus hexane-isomers mixture (5% Cyclohexane, 30% Methylcyclopentane, 30% 3-Methylpentane, 30% 2-Methylpentane and 5% 2,3-Dimethylbutane and less than 1% n-hexane) is also used as key study for German OEL derivation. The study showed no adverse effects at 5250 mg/m³. After default assessment with AGW methodology this would result in an OEL of about 4000 mg/m³ (correction of NOAEC experimental conditions to worker exposure: *7d/5d and *22 h/8 h AF5= $5_{variability}$; no further time extrapolation).

The background for the DNEL of 5306 mg/m³ was not fully elucidated. However, three key studies were provided:

- A NOAEC of 10504 mg/m³ from a 90 d inhalation study with rats with commercial hexane (40-55 % n-hexane, > 10 % methylcyclopentane; exposure for 6 h/d, 5d/week for 13 weeks) would result in an OEL of 525 mg/m³ with AGW assessment factors applied (AF20 = $5_{variability}$*$2_{sc\text{-}c}$ *$2_{6h\text{-}8h}$).
- A subchronic inhalation toxicity study with mice was documented for commercial hexane as second key study with a NOAEC of 31652 mg/m³ (40-55 % n-hexane, > 10 % methylcyclopentane; exposure for 6 h/d, 5d/week for 13 weeks to 0, 3182, 10504, 31652 mg/m³). Based on this study an OEL of 1580 mg/m³ would be established with default AGW assessment factors (AF20 = $5_{variability}$*$2_{sc\text{-}c}$*$2_{6h\text{-}8h}$). However, the NOAEC was at the highest dose group tested, thus an OEL might be higher.
- Finally, a comparable subchronic neurotoxicity study with rats revealed a NOAEC of 31680 mg/m³, which corresponds to an identical OEL as from the former study.

An OECD assessment on C6 aliphatics (SIDS) has not been completed yet and no results are reported[2].

The USA-NIOSH assessment was based on a study with possible contribution of other hydrocarbons to effect concentrations. A comment by OSHA indicated that identical concentrations were proposed for n-hexane and C5-C8 aliphatics. Therefore this reference value is not regarded adequate for C6 aliphatic hydrocarbon solvents without n-hexane.

We found no background document for the OEL of 700 mg/m³, as established in some European countries, which are reported in IFA (2014). In a comment to the Polish MAC value of 400 mg/m³ the authors state 'experimental data suggest that there is no basis for a verification of the MAC value for hexane isomers' (Szymańska and Bruchajzer, 2008).

b) Background to OELs on cyclohexane

The OEL for cyclohexane from SCOEL, AGS and from DFG (700 mg/m³) was derived from a NOAEC of 500 ppm (1750 mg/m³) in a subchronic experimental study with rats and mice (Malley et al., 2000; exposure for 6 h/day, 5 days/week for 14 weeks to 0, 500, 2000, or 7000 ppm concentrations of cyclohexane; acute, transient effects - diminished/absent response to an auditory alerting stimulus). A (close to) default procedure assessment based on the experimental NOAEC in the animals of 1750 mg/m³ would result in an OEL of 175 mg/m³ (AF10 = $5_{variability}$ *2_{6h-8h}; because of the "transient type of effects" we did not consider time extrapolation from subchronic to chronic exposure duration; the authors).

Minor subjective neurobehavioral effects in humans at 250 ppm (880 mg/m³) exposure to cyclohexane (4 hours exposure) (Hoogendijk and Emmen, 1998) were not regarded as adverse by SCOEL (but were taken into account by ACGIH). Therefore the resulting TLV (ACGIH) was lower 100 ppm (350 mg/m³) compared to 200 ppm (700 mg/m³) by SCOEL and AGS/DFG. Using a default AGW approach (AF6 = $3_{variability}$ *2_{4h-8h}) based on 880 mg/m³ as a NOAC an OEL of 150 mg/m³ would result (because of the subjective symptoms observed, we assume that the NOAEC will not be higher than the highest concentration applied in this testing).

c) Recent studies on C6 aliphatic hydrocarbons (except cyclohexane and n-hexane)

The recent study on methylcyclopentane by Yang et al. (2014) would result in an OEL of 230 mg/m³ (AF20 = $5_{variability}$*2_{sc-c}*2_{6h-8h}); basis: liver weight effects in both male and female rats; kidney weight increase in females), but is not confirmed by a very similar parallel study by Chung et al., (2014) with 2-methylpentane, which would result in an OEL of 800 mg/m³ (AF20 = $5_{variability}$*2_{sc-c}*2_{6h-8h}).

d) Recent studies on cyclohexane

For cyclohexane, the recent study by Lammers et al. (2009) demonstrated no adverse effects in neurobehavioral testing at 860 mg/m³ (two exposures for 4 hours; 12 volunteers). Applying an extrapolation factor of 3 for sensitive subjects (intraspecies variability) leads to an OEL of 290 mg/m³. In addition some factor for time extrapolation (4 hours to 8 hours) should have been considered, but was neglected as the OEL is based on the highest concentration tested and thus the real NOAEC could potentially be higher. However, if the study by Hoogendijk and Emmen(1998) is considered (see above) with first subjective symptoms at 880 mg/m³ (4 hours exposure), this does not indicate that the POD was chosen

[2] date of access: 01-12-2014: http://webnet.oecd.org/Hpv/UI/ChemGroup.aspx

too low. Using the NOAEC for subtle neurobehavioural effects in rats of 8000 mg/m³ would result in an OEL of 1600 mg/m³ (AF5 = $5_{variability}$). Note, however, that the NOAEC for rats (and mice) was considerably lower (1750 mg/m³) in the study by Malley et al. (2000).

Although not strictly assignable just to cyclohexane (as methylcyclopentane may also be included), we also consider the recent study by McKee et al. (2011) on C6/C7 cycloparaffinic hydrocarbons, from which an OEL of 840 mg/m³ (neurotoxic effects) would be derived (see section 4.3).

e) conclusions

In summary, the current OEL in Germany of 1800 mg/m³ (C6 compounds) or 1500 mg/m³ (current group value C5-C8 according to RCP) is mainly based on the study by Spencer (1982), which, however, leads to a higher OEL compared to the assessment from Frontali et al. (1981) with an OEL of 531 mg/m³. The NOAEC in the study from Frontali et al. may be higher than indicated, as the POD was the highest concentration tested. From the reported key studies in the DNEL-assessment (ECHA) an OEL of 525-1580 mg/m³ could be derived. More recent studies provide conflicting results with a provisionally derived OEL of ≤ 800 mg/m³ (except cyclohexane).

Based on the human data by Lammers et al. (2009) for cyclohexane an OEL of ≤ 290 mg/m³ could be justified. This is close to the TLV from ACGIH of 350 mg/m³. Subchronic animal data with rats and mice support the size of this OEL, where 175 mg/m³ was derived from the data by Mally et al. However, other animal data provide much higher extrapolated OELs for cyclohexane, including the data from a C6/C7 cycloparaffinic mixture (potential OEL 840 mg/m³) or the extrapolated OEL from rats (1600 mg/m³) in the study by Lammers et al. (2009).

There are reasons to reintegrate cyclohexane into the group of C6 aliphatics:

- Some animal studies did not find significant differences in toxic potency between other C6 aliphatics or cyclohexane or C6/C7 cycloparaffinic mixtures.
- There is no distinct mode of action (MoA) identified for cyclohexane apart from other C6 hydrocarbons (except the excluded n-hexane).

If a common OEL for C6 aliphatic hydrocarbons is derived, the value could either be selected as 700 mg/m³ or as 300 mg/m³:

- 700 mg/m³ is consistent with the lower end of most reference values to be derived from C6 hydrocarbons (without cyclohexane) and an average concentration from animal and human studies for cyclohexane. Moreover, the value is in agreement with the current German AGW for cyclohexane. Even if the toxicity of cyclohexane were somewhat underestimated, this would not lead to serious consequences as, according to manufacturer's information (Carrillo et al., 2014b), the content of cyclohexane in hydrocarbon solvent mixtures is limited.
- 300 mg/m³ is a more conservative estimate and mainly focusses on cyclohexane as reference substance for C6 aliphatic hydrocarbons. The distance to the lower end for other C6 hydrocarbon potential OELs but cyclohexane is less than a factor of 2.

An any case, we propose to reconsider the guidance value for C6 aliphatics and set a value clearly lower than the current value of 1500 mg/m³, despite somewhat conflicting data. Figure 5-2 and Figure 5-3 show derived potential OELs for C6 aliphatic compounds as an

overview. Final assignments may only be decided on after integrating of data also for other aliphatic hydrocarbons.

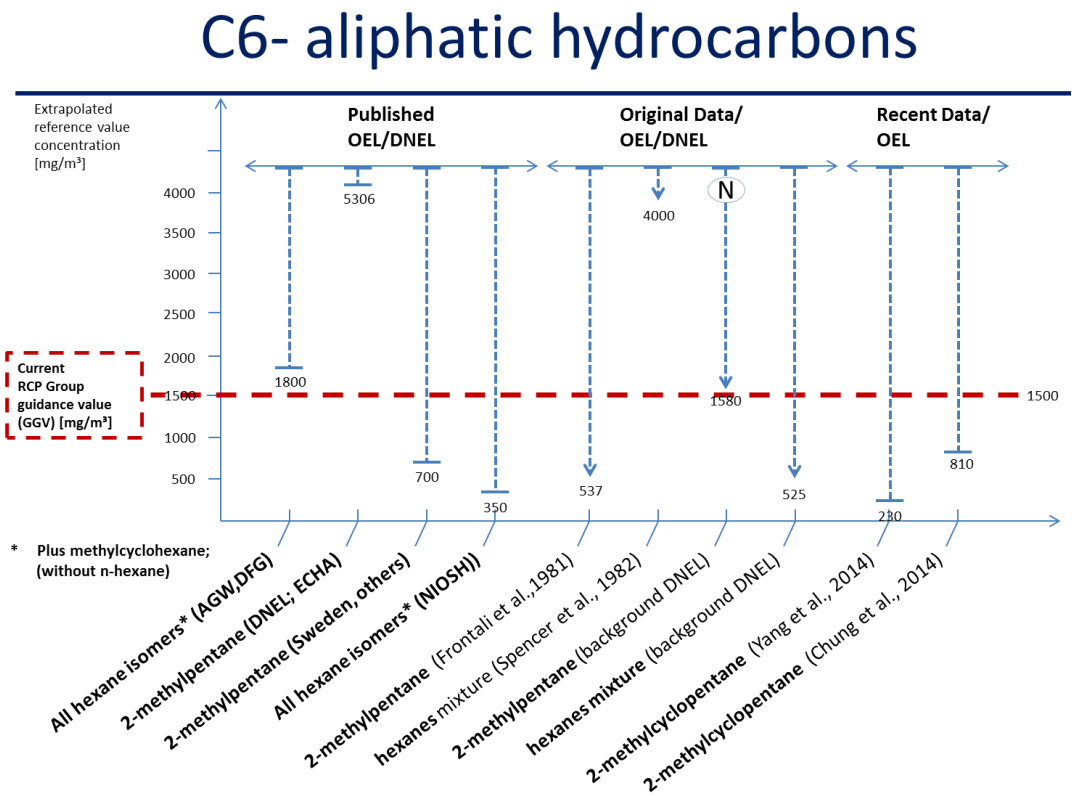

Figure 5-2: **Schematic illustration of potential OELs for C6 aliphatic hydrocarbon solvents without cyclohexane and n-hexane (see Figure 4-2 for legend and comments in text)**

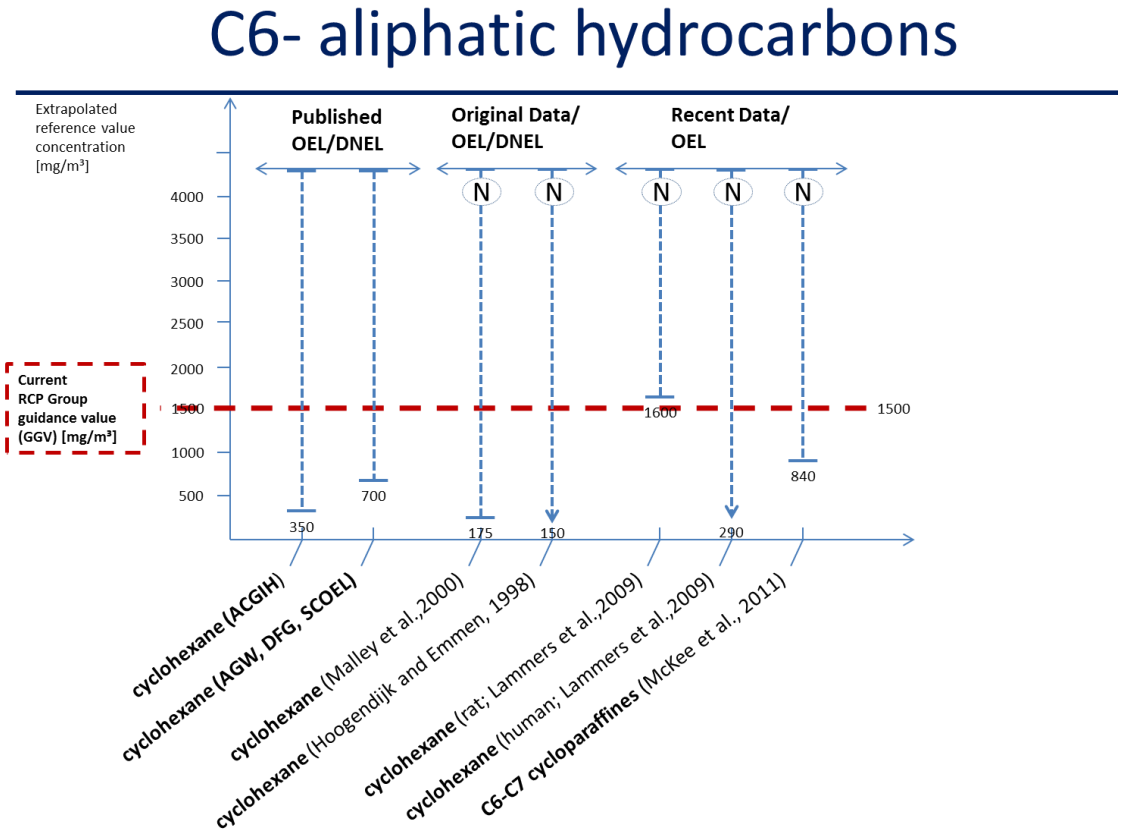

Figure 5-3: **Schematic illustration of potential OELs for cyclohexane (see Figure 4-2 for legend and comments in text)**

5.3 C7- Aliphatic Hydrocarbon Solvents

5.3.1 Assigned group guidance value (RCP, German approach, TRGS 900)

For the group of C5-C8 aliphatics currently in Germany the group guidance value is 1500 mg/m³ (AGS, 2012).

5.3.2 Substance Search

We searched for experimental or epidemiological data on the substances:

- 1,3-Dimethylcyclopentane (CASRN: 1759-58-6)
- Ethylcyclopentane (CASRN: 1640-89-7)
- Methylcyclohexane (CASRN: 108-87-2)
- n-heptane (CASRN: 142-82-5)
- Isoheptane (CASRN: 31394-54-4)
- Bicyclo[2.2.1]heptane (Norbornane) (CASRN: 279-23-2)

and for the group in general (C7 aliphatic hydrocarbons).

5.3.3 Existing OEL or equivalent derived reference values (workers)

Substance	Type reference value	mg/m³	Source
methylcyclohexane	AGW (Germany)	810	(AGS, 2006; BMAS, 2014)
	MAK (Germany)	810	(DFG, 2014)
	DNEL (Europe)	64.3	(ECHA, 2014)
	HBROEL	200	(HCN, 2005a)
heptane (all Isomers)	AGW (Germany)	2100	(AGS, 2006; BMAS, 2014)
	MAK (Germany)	2100	(DFG, 2014)
	TLV	1640	ACGIH, 2014
n-heptane, isohepatane	DNEL (Europe)	2085	(ECHA, 2014)
n-heptane	NIOSH-REL	350	(IFA, 2014) (lowest)
n-heptane	OEL Sweden / Denmark	800 / 820	(IFA, 2014)

5.3.4 Recent Data

- In a study on neurobehavioral effects in rats after acute exposure (8 h/d for 3 consecutive days) to isoparaffinic and cycloparaffinic hydrocarbons, McKee et al. (2011) tested iso-heptane and a mixed C6/C7 cycloparaffinic solvent. For iso-heptane no CNS effects were found up to the highest concentration tested (i.e. 20000 mg/m³). For the mixed C6/C7 cycloparaffinic solvent reversible changes in latency to response in visual discrimination testing were detected and a NOAEC of 4200 mg/m³ was established (minor, reversible changes in latency to response in visual discrimination testing at 14 000 mg/m³; C6/C7 cycloparaffinic solvent is also further discussed in the section on mixtures, see 6.1.1).
- A recent study with rats addressed general toxicity and reproductive toxicity of methylcyclohexane after subcutaneous injection. The LOAEC was 100 mg/kg bw x d (Kim et al., 2011).

No further relevant studies were found.

5.3.5 Assessment, discussion and conclusions

n-heptane

The OEL (Germany, AGW) of 2100 mg/m³ for n-heptane was derived by DFG.

No neurotoxic effects were observed in rats exposed to 3000 ppm via inhalation up to 26 weeks, (potentially neurotoxic) gamma-diketones concentration after exposure to 500 ppm n-heptane was 4-times lower than after 50 ppm n-hexane exposure. Sensory irritation would result in higher OEL. The DNEL for n-heptane and iso-heptane were derived from a

subchronic NOAEC of 3000 ppm (12470 mg/m³) in a rat study with 12 hours exposure per day and 7 days exposure per week for 16 weeks (Takeuchi et al., 1980; 1981). Similarly, the SCOEL assessment based on this study and resulted in an OEL of 2085 mg/m³ (500 ppm = preferred value approach). Using the AGW default procedure after correction for exposure (5 days/week instead of 7days/week) would result in an OEL of 1745 mg/m³ (AF10 = $5_{variability}*2_{sc-c}$).

The USA-NIOSH assessment was based on a study with possible contribution of other hydrocarbons to effect concentrations. A comment by OSHA indicated that identical concentrations were proposed for n-hexane and C5-C8 aliphatics. Therefore this reference value is not regarded adequate for C7 aliphatic hydrocarbon solvents without n-hexane.

methylcyclohexane

The OEL (Germany, AGW) of 810 mg/m³ for methylcyclohexane was derived by DFG. The MAK value was established in 2000 for methylcyclohexane and identified as critical effect nephrotoxicity in male rats from a one year study the NOAEC = 1600 mg/m³ (exposure for 6 h/d, 5 days/week) (Kinkead et al., 1985). In 2007 a re-evaluation of nephrotoxic effects was performed – MAK states that effect is most probably due to species and sex specific alpha-2u-globulin mechanism, but due to missing experimental verification (e.g. analysis of hyaline droplets) the earlier AGW-value/ MAK value is still in place. A default assessment based on the 1-year rat study (as used by DFG and AGS) with a NOAEC of 8000 mg/m³ disregarding the nephrotoxic effects in male animals (Kinkead et al., 1985) supports the derived OEL of ≈ 800 mg/m³ (AF10 = $5_{variability}*2_{6h-8h}$).

The background study NOAEC used for DNEL derivation was not found in the disseminated dossier on methylcyclohexane (DNEL workers inhalation, 64.3 mg/m³, repeated dose toxicity, total AF12.5 on NOAEC = 804 mg/m³).

The Health Council of the Netherlands (HCN, 2005a) derived an OEL of 200 mg/m³ based on a study by MacEwen et al.,1980 (original study not available, thus cited from secondary source). In this study a NOAEC for kidney effects in rats at 1636 mg/m³ methylcyclohexane was established (Exposure: 0, 1636, 8180 mg/m³; 6h/d; 5d/w; 1 year); they used an extrapolation factor of 9. At 8180 mg/m³ several effects including nephrotoxicity and haematological changes were observed. According to the German assessment procedure for AGW study results (POD: 1636 mg/m³ NOAEL) would lead to an OEL of 270 mg/m³ (AF6 = $3_{variability}*2_{6h-8h}$; variability factor of 5 reduced to 3 because of parallel testing of mice, dogs, and hamsters in addition to the rats, with rats as the most sensitive species).

An OECD assessment on C7-C9 aliphatics SIDS profile (OECD, 2010a) reported an NOAEC of 4570 mg/m³ (1162 ppm) for methylcyclohexane. This study (Treon et al., 1943) is also referred to by DFG (Greim, 2000) as a 10 week rabbit study with methylcyclohexane (inhalation exposure for 6 h/d and 5 d/week at concentrations of 950 or 4570 mg/m³). Higher concentrations (11350 – 59950 mg/m³) led to body weight loss, respiratory effects, light narcosis and convulsion prior to death. With a default assessment derivation this NOAEC of 4570 mg/m³ corresponds to an OEL of 230 mg/m³ (AF20 = $5_{variability}*2_{sc-c}*2_{6h-8h}$). However, as there were only slight effects observed at 11350 mg/m³, it may possibly be justified to apply reduced extrapolation factors for this assessment.

The reported behavioural effects after acute exposure in rats with a NOAEC of 4200 mg/m³ for the C6/C7 cycloparaffinic solvent (McKee et al., 2011) would yield an OEL of 840 mg/m³

(AF5 = $5_{variability}$), whereas the results on iso-heptane would lead to an OEL of (>) 4000 mg/m³ (AF5 = $5_{variability}$).

A recent publication after subcutaneous injection of this substance to rats provided a LOAEL of 100 mg/kg x d (Kim et al., 2011). Because of the type of application, no OEL can be derived from this study.

In summary, there is little evidence for n-heptane or iso-heptane to deviate from the current extrapolated OEL of 2085 -2100 mg/m³. Application of updated assessment factors may lead to minor reductions in OEL for these compounds.

For methylcyclohexane, the background (nephrotoxicity in male rats) for the current OEL by DFG and AGW (810 mg/m³) is not well supported, because of possible species specific effects. However,

- a default assessment based on a subchronic rabbit study (Treon et al., 1943 as cited from OECD assessment on C7-C9 alipathics) and
- the chronic inhalation study from MacEwen et al. (1980 cited from HCN, 2005a) and
- the acute inhalation study with rats on a C6/C7 cycloparaffinic mixture (McKee et al., 2011)

also support a similar OEL for methylcyclohexane, which is lower than the current OEL for heptanes (all isomers) of 2100 mg/m³. Therefore, if all C7 are left as a group without exempting methylcyclohexane, a value of about 270 - 840 mg/m³ should be discussed:

- An OEL of ≈ 270 mg/m³ would mean a conservative assessment supported by the HBROEL approach and by a default extrapolation based on the study by Treon et al. (1943). It largely takes account of the very low DNEL, for which no background studies could be traced.
- An OEL of ≈ 840 mg/m³ would be supported by a number of existing OEL for n-heptane or methylcyclohexane and by the mixture assessment by McKee et al. (McKee et al., 2011).

There is insufficient support to exclude Methylcyclohexane from the GGV and to assign a SSV, which is proposed by manufacturers (Carrillo et al., 2014b). However, there is insufficient evidence for a distinct mode of action to justify such exclusion. Moreover, technical feasibility of separate analysis of methylcyclohexane was not reported.

Figure 5-4 below provides a graphical presentation on potential OELs to be derived from the data on C7 aliphatic hydrocarbons.

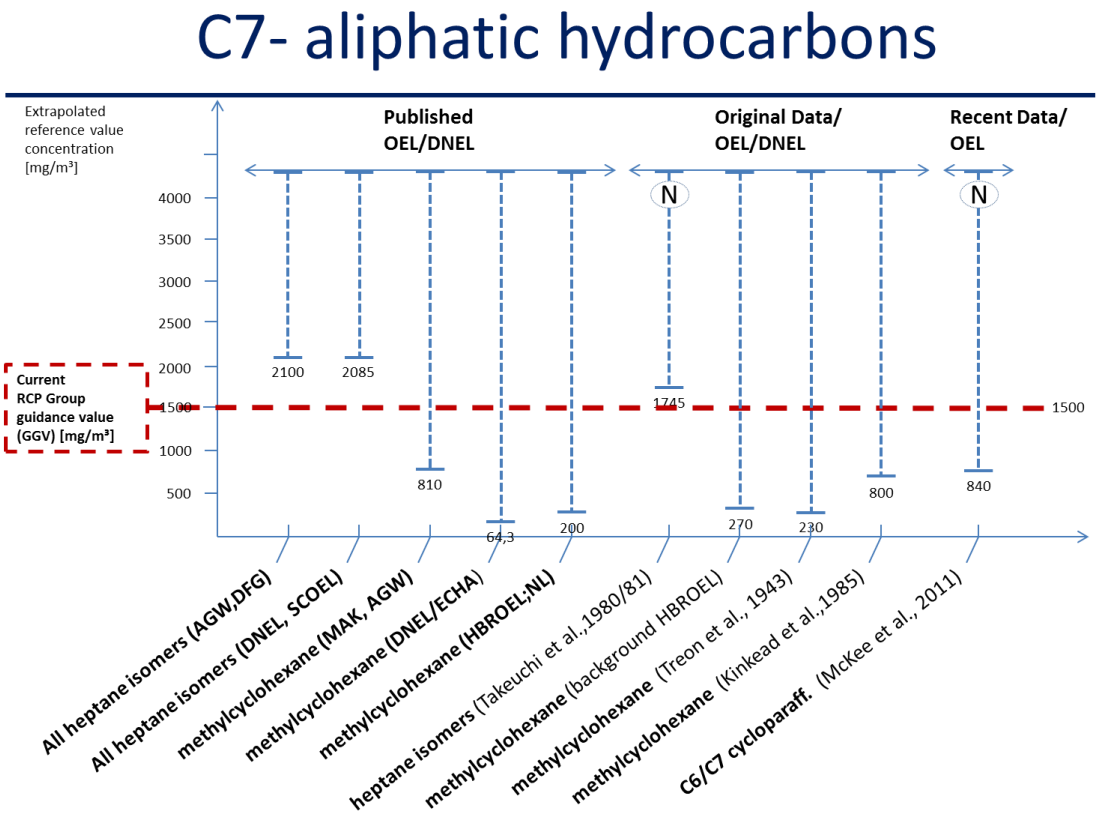

Figure 5-4: **Schematic illustration of potential OELs for C7 aliphatic hydrocarbon solvents (see Figure 4-2 for legend and comments in text)**

5.4 C8- Aliphatic Compounds

5.4.1 Assigned group guidance value (RCP, German approach, TRGS 900)

For the group of C5-C8 aliphatics currently in Germany the group guidance value is 1500 mg/m³ (AGS, 2012).

5.4.2 Substance Search

We searched for experimental or epidemiological data on the substances:

- 1,2,3-Trimethylcyclopentane (CASRN: 2613-69-6)
- 1,2,4-Trimethylcyclopentane (CASRN: 2613-72-1)
- 1,4-Dimethylcyclohexane (CASRN: 589-90-2)
- 1,2-Dimethylcyclohexane (CASRN: 583-57-3)
- Isopropylcyclopentane (CASRN: 3875-51-2)
- cis-1-ethyl-2-methylcyclopentane (CASRN: 930-89-2)
- 1-ethyl-3-methylcyclopentane (CASRN: 2613-65-2)
- 1,3-Dimethylcyclohexane (CASRN: 591-21-9)
- n-Propylcyclopentane (CASRN: 2040-96-2)
- 3-Methylheptane (CASRN: 589-81-1)
- 2-Methylheptane (CASRN: 592-27-8)
- Ethylcyclohexane (CASRN: 1678-91-7)
- 2,2,3-Trimethylpentane (CASRN: 564-02-3)
- 2,2,4-Trimethylpentane (CASRN: 540-84-1)
- 2,3,3-Trimethylpentane (CASRN: 560-21-4)
- 2,3,4-Trimethylpentane (CASRN: 565-75-3)
- Isooctane (CASRN: 540-84-1)
- n-Octane (CASRN: 111-65-9)
- Dicyclopentane (CASRN: 694-72-4),

and for the group in general (C8 aliphatic hydrocarbons).

Potential tumour promoting activity of trimethylpentanes (Greim, 2006) is not further assessed here. As discussed in the meeting on 20th October 2014 the respective assessment by DFG (MAK-Commission) will be reconsidered elsewhere (due to technical reasons separation of trimethylpentanes is not feasible).

5.4.3 Existing OEL or equivalent derived reference values (workers)

Substance	Type reference value	mg/m³	source
n-octane and isomers (without trimethylpentanes –isomers)	AGW (Germany)	2350	(AGS, 2006; BMAS, 2014)
	MAK (Germany)	2350	(DFG, 2014)
n-octane	DNEL (Europe)	2035	(ECHA, 2014)
	MAC (Netherlands)	1450	(HCN, 2005c)
	OEL (most countries)	1400	(IFA, 2014)
	NIOSH-OEL	350	(IFA, 2014) (lowest)
	Denmark-OEL	935	(IFA, 2014)
n-octane, isooctane	TLV (TWA)	1400	(ACGIH, 2011)

5.4.4 Recent Data

- Lammers et al. (2011) demonstrated that n-octane did not produce CNS effects in rats tested up to 14000 mg/m³ (8h/d for 3 consecutive days); this result was confirmed by McKee et al. (2011) for iso-octane.
- Sung et al. (2010) examined effects of n-octane after inhalation in a subchronic study (OECD TG 403; 6h/d, 5d/w, 13 weeks; 0,930, 2620, 7480 mg/m³), which provided a NOAEC of 7480 mg/m³ (highest tested concentration).
- Chalansonnet et al. (2013) identified no increased ROS (i.e. free MDA) in the cortex of rats exposed for 10 days via inhalation to six solvents including n-octane (5400 mg/m³).
- Boyes et al. (2010) found that inhalation of 2,2,4-trimethylpentane alters visual evoked potentials and signal detection behaviour in rats after acute exposure (single exposure for 62 Minutes). The NOAEC was 2000 ppm (9500 mg/m³) and the LOAEC was 2500 ppm.
- In a publication by Carrillo et al. (2013) on C10-C12-isoparaffinic hydrocarbon solvents the results of a study using C8 aliphatics (100% assumed) as test material were reported. Rats were exposed via inhalation for 6 h/d on 5d/week for 12 weeks to 0, 400 or 1200 ppm (approx. 5500 mg/m³) of this test material. Study assessment is limited, since study focused on kidney effects. As no adverse effects were reported the NOAEC of this study is (≥) 5500 mg/m³.

No further relevant studies were found.

5.4.5 Assessment, discussion and conclusions

MAK- value for n-octane and the respective AGW in Germany of 2350 mg/m³ (Greim, 2004) were derived from n-heptane and n-nonane due to insufficient substance specific data. Similarly, the TLV in USA of 1400 mg/m³ (300 ppm) was derived ‘by analogy to other

paraffinic hydrocarbons' (ACGIH, 2012) and from some acute screening data in the high dose range.

In the ECHA registration document for n-octane (ECHA, 2014), where a DNEL of 2035 mg/m³ was derived, three key studies were reported:

- one rat study with a NOAEC =24300 mg/m³ (6646 ppm) after subchronic inhalation of light alkylate naphtha distillate (CASRN 64741-66-8, i.e. C4 - 3.25; C5 - 33.30; C6 - 18.91; C7 - 9.81; C8 - 31.14; C9 - 3.21; C10 - 0.39.; composition (vol %): n-Paraffins: 3.47, total paraffins: 99.97, total olefins: 0.03) where highest dose tested revealed no adverse health effects (investigation of motor activity, FOB and neuropathological investigations included), besides adaptive response of liver weight. Based on this NOAEC of 24300 mg/m³ an OEL of (≥) 1215 mg/m³ would be established using default AGW extrapolation factors (AF20 = $5_{variability}$*$2_{6\text{-}8h}$*$2_{sc\text{-}c}$); further details see section 0) (Schreiner et al., 1998).
- Carpenter et al. (1978) examined the effects from n-nonane after subchronic exposure for 6 h/d on 5 days per week to 0, 1900, 3100 and 8400 mg/m³ (n-nonane, 98.4% purity). A NOAEC at the highest concentration of 8400 mg/m³ is reported in the ECHA-dossier. However, body weight was lowered significantly at this concentration and the authors propose a NOAEC of 3100 mg/m³. With this NOAEC and a default extrapolation an OEL of 155 mg/m³ (AF20 = $5_{variability}$*$2_{6\text{-}8h}$*$2_{sc\text{-}c}$) would be derived. Note that this assessment refers to n-nonane and not to n-octane (but was used as a read across assessment).
- Finally, ECHA reports a NOAEC of 14000 mg/m³ (3000 ppm) or above for neurotoxicity of n-octane in rats based on a short term neurotoxicity study (99.3% n-octane; exposure once daily (8h) for 3 consecutive days). Functional observational battery (FOB) and locomotor activity investigation showed no effects at the highest tested concentration. Presumably the study by Lammers et al. (2011) is referred to. With the default German extrapolation procedure an OEL of 2800 mg/m³ or above would result (AF5 = $5_{variability}$).

Therefore, the data reported in the REACH dossier provide a wide range of background data, some of which may lead to significantly lower OELs than the one used for DNEL derivation.

Besides n-octane we only found reference values for Trimethylpentanes (TMP) for the group of C8 aliphatic hydrocarbon solvents. The DNEL (workers, chronic exposure) for TMP is identical to the one for n-octane (2035 mg/m³). This DNEL is based on the same studies as reported above for n-octane.

However, DFG (Greim, 2004; 2006; Henschler, 1989) excludes TMP from the assessment on other C8 compounds.

The authors of this assessment report significant irritation effects after exposure to isooctane (single exposure of mice for 5 minutes). The exposure range was 1000-128000 ppm and the substance was said to be 'very irritating even at the lower concentrations'. 16000 ppm induced respiratory arrest after 5.5 minutes in 1 of 4 animals (Swann et al., 1974). Effect size and NOAEC or LOAEC are not precisely provided. Assuming, that irritation was restricted to sensory irritation and that 4000 ppm (19200 mg/m³) was close to RD50 (Alarie, 1973) this supports an OEL of about 640 mg/m³ (AF30 = as conventional procedure for RD50/30= OEL, not sufficiently validated). However, the report is regarded as not

sufficiently detailed to be used as a starting point for OEL derivation (not included in Figure 5-5).

The USA-NIOSH assessment was based on a study with possible contribution of other hydrocarbons to effect concentrations. A comment by OSHA indicated that identical concentrations were proposed for n-hexane and C5-C8 aliphatics. Therefore this reference value is not regarded adequate for C8 aliphatic hydrocarbon solvents without n-hexane.

The health council of the Netherlands (2005) reports the MAC (OEL) of 1450 mg/m³ for n-octane, which apparently was already derived earlier, but finds data insufficient to comment on this existing MAC-value.

There exists a toxicological review by EPA (2007) on 2,2,4-trimethylpentane. The committee summarized that existing studies were not suitable to derive a long term reference value.

An OECD assessment on C7-C9 aliphatics (OECD, 2010a) provided no additional relevant studies apart from those already referred to in chapter 3.3.5.

Recent data included the study by Sung et al. (2010), in which a NOAEC of 7480 mg/m³ after subchronic exposure of rats was proposed. Extrapolation according to methodology would yield an OEL of 375 mg/m³ (AF20 = $5_{variability}$*$2_{sc\text{-}c}$*$2_{6\text{-}8h}$). However, the NOAEC may be higher than the value given in that study (highest concentration tested). The studies by Lammers et al. (2011) and McKee et al. (2011) showed a NOAEC of (≥) 14000 mg/m³ for n-octane and isooctane. Using the default assessment procedure this provides an OEL of ≥ 2800 mg/m³ (AF5= $5_{variability}$). Based on the publication by Carrillo et al. (2013) the NOAEC of (≥) 5500 mg/m³ from this somewhat limited study (assessment limited since study focused on kidney effects) an OEL of (≥) 275 mg/m³ would be derived (AF20 = $5_{variability}$*$2_{6\text{-}8h}$*$2_{sc\text{-}c}$).

The assessment of ROS-production in brain after inhalation exposure to C8 aliphatic hydrocarbons by Chalansonnet et al. (2013) showed no effects, but is too specific to be used for an OEL assessment. There is no such extrapolation shown in Figure 5-5, below.

Acute inhalation of 2,2,4-trimethylpentane alters visual evoked potentials and signal detection behaviour in rats (Boyes et al., 2010). The NOAEC in this study was 2000 ppm (9500 mg/m³). However, as time extrapolation (from 1 hour exposure to chronic exposure) may not be performed, no such extrapolation shown in Figure 5-5, below. The testing scenario is different from the acute human volunteer studies, where a time extrapolation was regarded acceptable.

In summary, the data specific for C8 aliphatic hydrocarbon solvents, are too limited to directly quantify an OEL for this group. Similar, to the conclusions by others we propose to extrapolate from C7 compounds to C9 aliphatic hydrocarbon solvents and set an OEL within the range of those neighbourhood indicators:

For C7 aliphatic hydrocarbon solvents we proposed an OEL in the range between 270 and 840 mg/m³, for C9 aliphatic hydrocarbon solvents the weight of evidence shifts to the lower end of this range, i.e. 300 mg/m³ as an OEL. Extrapolated potential OELs from few single studies on C8 aliphatic hydrocarbon solvents are in agreement with this range. We propose to reintegrate trimethylpentanes for the time being despite their alleged tumour promoting activity, but reconfirmation is regarded necessary.

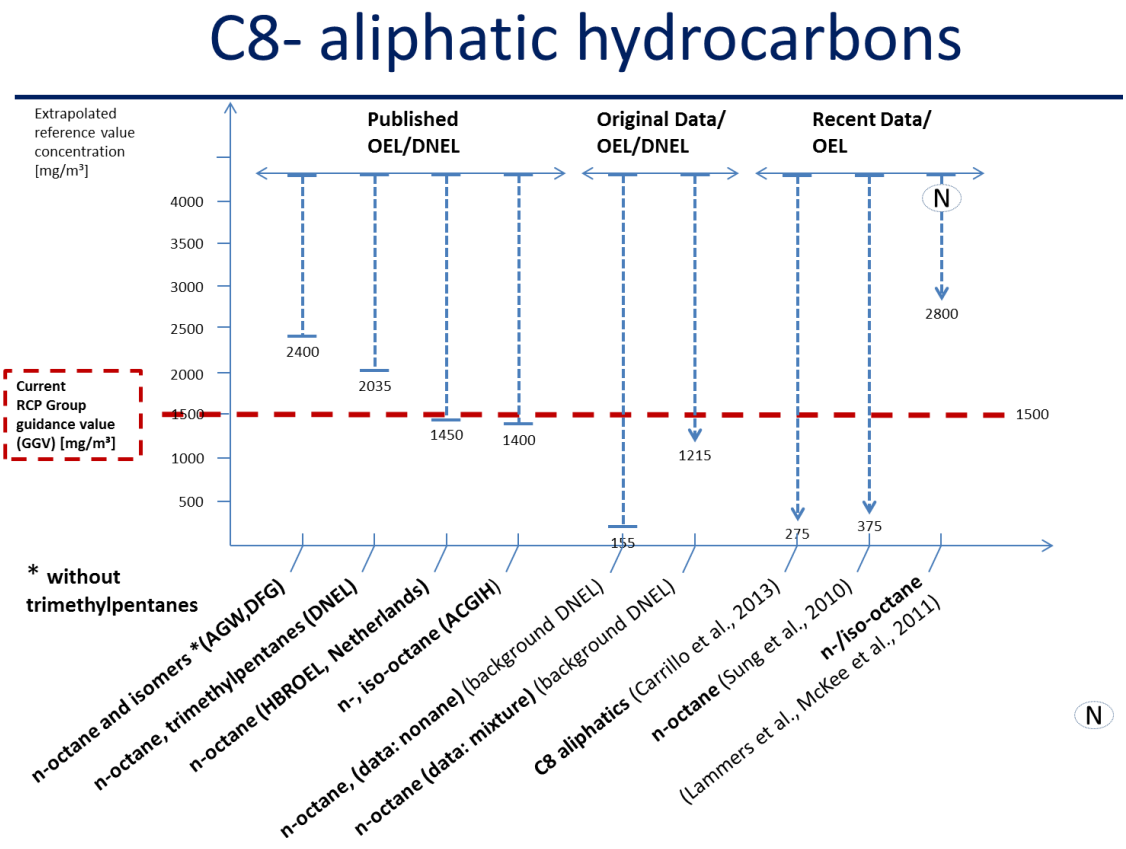

Figure 5-5: **Schematic illustration of potential OELs for C8 aliphatic hydrocarbon solvents (see Figure 4-2 for legend and comments in text)**

5.5 C9- Aliphatic Hydrocarbon Solvents

5.5.1 Assigned group guidance value (RCP, German approach, TRGS 900)

For the group of C9-C15 aliphatics currently in Germany the group guidance value is 600 mg/m³ (AGS, 2012).

5.5.2 Substance Search

We searched for experimental or epidemiological data on the substances:

- 1,2,3-Trimethylcyclohexane (CASRN: 1678-97-3)
- 1,2,4-Trimethylcyclohexane (CASRN:7667-60-9)
- iso-Butylcyclopentane (CASRN:3788-32-7)
- n-Butylcyclopentane (CASRN: 2040-95-1)
- n-Propylcyclohexane (CASRN:1678-92-8)
- iso-Propylcyclohexane (CASRN:696-29-7)
- 2,6-Dimethylheptane (CASRN:1072-05-5)
- 2,3-Dimethylheptane (CASRN:3074-71-3)
- 2,4-Dimethylheptane (CASRN:2213-23-2)
- 2-Methyloctane (CASRN:3221-61-2)
- 3-Methyloctane (CASRN:2216-33-3)
- 3-Ethylheptane (CASRN:15869-80-4)
- n-Nonane (CASRN:111-84-2)
- cis-Bicyclo[4.3.0]nonane (CASRN:4551-51-3)
- trans-Bicyclo[4.3.0]nonane (CASRN:3296-50-2)
- 2-Ethylbicyclo[2.2.1]heptane (CASRN:2146-41-0)

and for the group in general (C9 aliphatic hydrocarbons).

5.5.3 Existing OEL or equivalent derived reference values (workers)

Substance	Type reference value	mg/m³	source
n-nonane; nonanes	AGW (Germany)	not assigned	(AGS, 2006; BMAS, 2014)
	MAK (Germany)	not assigned	(DFG, 2014)
n-nonane	DNEL (Europe)	2035	(ECHA, 2014)
	OEL (China)	500	(IFA, 2014) (lowest)
	OEL	1050	(IFA, 2014) (most countries)
	HBROEL	500	(HCN, 2005b)
nonanes	OEL (Sweden)	800	(IFA, 2014)
n-nonane and neononane	TLV	1050	(ACGIH, 2012)

5.5.4 Recent Data

No further relevant studies on single substances were found. However, one experimental recent study on mixtures was available:

- Neurobehavioral effects of acute exposure to isoparaffinic and cycloparaffinic hydrocarbons were investigated by McKee et al. (2011). Rats were exposed for 8h/day for 3 consecutive days to 0, 500, 1500, 5000 mg/m³ of a C9-C11 isoparaffinic solvent (CASRN: 90622-57-4). Minor acute CNS effects were observed in the high dose group. A NOAEC of 1500 mg/m³ was established. For further details see section 6.1.1.

5.5.5 Assessment, discussion and conclusions

The TLV (TWA) in the United States is 200 ppm or 1050 mg/m³ (ACGIH, 2012). Probably, this value has been taken over in other countries, which report this concentration as an OEL (IFA, 2014). The ACGIH background document indicates that the value should be lower than that for octane (which is 300 ppm) because toxicity of aliphatics 'increases with carbon chain length'. The study by Carpenter et al. (1978, see below) is reported with a NOAEC of 3150 mg/m³, but not used directly for the assessment.

We did not find background documents for the OEL of 500 mg/m³ in China (IFA, 2014).

The DNEL as provided in the ECHA registration document is 2035 mg/m³. Two studies were referred to as key studies:

- Carpenter et al. (1978) examined the effects from n-nonane after subchronic exposure to 0, 1900, 3100 and 8400 mg/m³ (n-nonane, 98.4% purity). A NOAEC at the highest concentration of 8400 mg/m³ is reported in the ECHA-dossier. However, body weight was lowered significantly at this concentration and the authors propose a NOAEC of 3150 mg/m³. With this NOAEC and a default extrapolation a DNEL of 155 mg/m³ (AF20 = $5_{variability}$*$2_{6\text{-}8h}$*$2_{sc\text{-}c}$).

The Health Council of the Netherlands proposed a HBROEL of 500 mg/m³ for the Netherlands, based on the Carpenter study as reported above (Carpenter et al., 1978) with a reduced assessment factor of 9 based on a NOAEC of 3150 mg/m³ and a 'preferred value approach' (rounding up).

An OECD assessment on C7-C9 aliphatics (OECD, 2010a) does not formally derive on OEL, but refers to respective studies on n-nonane without exact citation. They mention a 13-weeks study for n-nonane (protocol similar to OECD TG413) with a LOAEC of 1600 ppm and a NOAEC of 590 ppm (3150 mg/m³). Probably, again the study by Carpenter et al. is referred to (Carpenter et al., 1978).

There were no relevant recent data on single C9 compounds found. However, neurobehavioural effects of acute exposure to isoparaffinic (and cycloparaffinic) hydrocarbons were investigated by McKee et al. (2011). Rats were exposed for 8h/day for 3 consecutive days to 0, 500, 1500, 5000 mg/m³ of a C9-C11 isoparaffinic solvent. Minor acute CNS effects were observed in the high dose group with a NOAEC of 1500 mg/m³. According to the default AGW methodology this would result in an OEL of 300 mg/m³ (AF5 = $5_{variability}$). For C9-C11 cycloparaffinic hydrocarbons, the REACH document on tetradecane reports a

NOAEC of 2500 mg/m³ in rats (original study not identified). According to the default AGW methodology this would result in an OEL of 500 mg/m³ (AF5 = $5_{variability}$).

In addition, in a study on a C10-C12 isoparaffinic solvent mixture, Carrillo et al. (2013) refer to an earlier experimental study by Phillips and Egan (1984). In this study, which was designed to examine kidney effects mostly, rats were exposed for 6 h/d on 5d/week for 12 weeks to 0, 300 or 900 ppm (nominal) of a C9-C11 isoparaffinic solvent. More details are provided in the section on mixtures (see section 6.1.1). This mixture contained 10% C9 aliphatic hydrocarbon solvents. If the default extrapolation procedure for AGW values is used, an OEL of ≥ 260 mg/m³ would be derived (AF20 = $5_{variability}$*$2_{6\text{-}8h}$*$2_{sc\text{-}c}$). However, as the highest concentration was used as POD, the NOAEC may be higher.

In summary, recent data on a C9-C11 isoparaffinic mixture (McKee et al., 2011) therefore call for an OEL of about 300 mg/m³ for ≥ C9 aliphatic hydrocarbon solvents. It is well known that neurotoxicity increases with carbon chain length for aliphatic hydrocarbon solvents. Using the results from cyclohexane and C6-/C7-cycloparaffinic hydrocarbons as a starting point, the result on the C9-C11 isoparaffinic mixture is in line with this increase of neurotoxicity with chain length, even though data on n- and iso-octane indicate a much lower neurotoxic potency for C8 compounds. A similar OEL of 300 mg/m³ is supported by earlier studies (Carpenter et al., 1978; Phillips and Egan, 1984). However, those supporting studies have relevant limitations.

Overall data base and resulting potential OELs are presented in Figure 5-6 below.

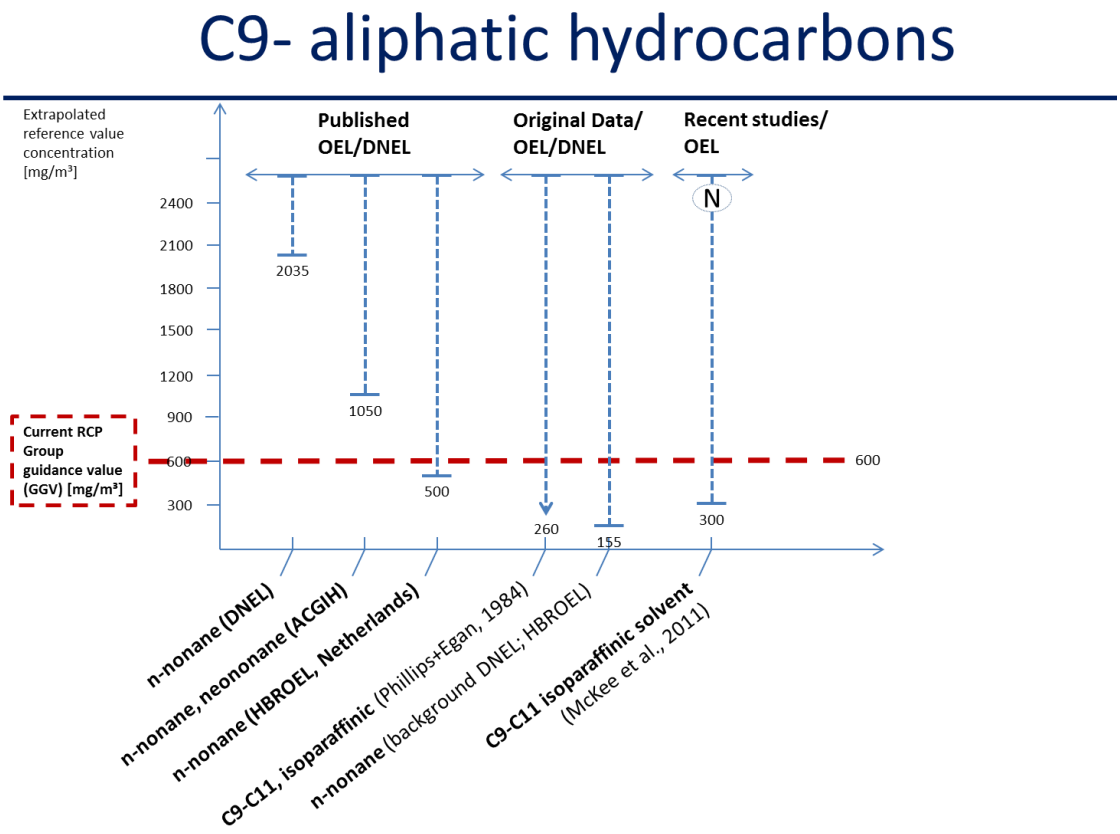

Figure 5-6: Schematic illustration of potential OELs for C9 aliphatic hydrocarbon solvents (see Figure 4-2 for legend and comments in text)

5.6 C10- Aliphatic Hydrocarbon Solvents

5.6.1 Assigned group guidance value (RCP, German approach, TRGS 900)

For the group of C9-C15 aliphatics currently in Germany the group guidance value is 600 mg/m³ (AGS, 2012).

5.6.2 Substance Search

We searched for experimental or epidemiological data on the substances:

- Decalin (CASRN: 91-17-8)
- iso-Butylcyclohexane (CASRN: 1678-98-4)
- n-Decane (CASRN: 124-18-5)
- n-Pentylcyclopentane (CASRN: 3741-00-2)
- n-Butylcyclohexane (CASRN: 1678-93-9)
- n-Pentylcyclohexane (CASRN: 4292-92-6)
- 2,6-Dimethyloctane (CASRN: 2051-30-1)
- 2,3-Dimethyloctane (CASRN: 7146-60-3)
- 2,4-Dimethyloctane (CASRN: 4032-94-4)
- 2-Methylnonane (CASRN: 871-83-0)
- 3-Methylnonane (CASRN: 5911-04-6)
- 3-Ethyloctane (CASRN: 5881-17-4)

and for the group in general (C10 aliphatic hydrocarbons).

5.6.3 Existing OEL or equivalent derived reference values (workers)

Substance	**Type reference value**	**mg/m³**	**source**
decalin	AGW (Germany)	No value	(AGS, 2006; BMAS, 2014)
	MAK (Germany)	29	(DFG, 2014)
	DNEL (Europe)	24	(ECHA, 2014)
	OEL	100	Poland (IFA, 2014)
n-decane	OEL	250	Denmark (IFA, 2014)
Other decanes, except n-decane	OEL	350	Denmark (IFA, 2014)

5.6.4 Recent Data

- An acute rat study (exposure for 3 consecutive days, 8h/d) analysed neurobehavioral effects of n-decane. At 5000 mg/m³ there were minimal reversible effects observed, with a NOAEC of 1500 mg/m³(Lammers et al., 2011).
- A C10 cycloparaffinic solvent tested under same conditions in rats provided a NOAEC of 5000 mg/m³ (McKee et al., 2011).
- Stuchal et al. (2013) derived a human equivalent concentration of 7.9 mg/m³ for decalin based on a benchmark extrapolation ($BMDL_{10}$ = 44 mg/m³) on liver toxicity (syncytial effects) from the data of the 2-year mouse study by NTP (NTP, 2005).

No further relevant studies on single tested substances were found.

5.6.5 Assessment, discussion and conclusions

The background for the OEL on n-decane and iso-decanes in Denmark (250-350 mg/m³) could not be retrieved.

No DNEL was derived within the registration document for n-decane, because: 'No-threshold effect and/or no dose-response information [was] available' (ECHA, 2014). However, the registration document refers to three key documents:

- data on iso-dodecane (read-across) with a NOAEC of 1160 mg/m³ (or above), based on a subchronic rat study (6 h/d, 5d/week, 13 weeks) with no adverse effects at the highest concentration. (Note default extrapolation according to German AGW procedure would result in an OEL of (≥) 58 mg/m³ (AF20 = $5_{variability}*2_{6\text{-}8h}*2_{sc\text{-}c}$)). Because this study is not sufficiently specific for C10 hydrocarbon solvents, it is not shown in Figure 5-7, below.
- In a subchronic inhalation toxicity study (OECD TG 413) or in combined chronic and carcinogenicity study (OECD TG 453) rats were exposed to 0, 138, 550, 1100, and 2200 mg/m³ of Stoddard solvent IIC (CASRN: 64742-88-7; C10-13 n-paraffins, 2-25% aromatics; 'high flash' and low aromatic grade; composition: mixture of n-paraffins, isoparaffins, or cycloparaffins with 10 to 13 carbons, e.g. 1.70 % decane, 19.3 % undecane, and 5.73 % dodecane (no further details), 0.56 % decalin; aromatics 0.93 % and 0.58 %, i.e. NTP, 2004). Within the registration dossier (ECHA, 2014): no adverse effects up to the highest concentration tested were identified in females. In males alpha 2u globulin related nephropathy starting already at 138 mg/m³ was observed but not accounted for as adverse as this is a species and sex specific effect not relevant for humans. Note that no haematological or neurotoxicological examination was performed (for study details see also section 6.1.1.). Based on these observations a NOAEC of 2200 mg/m³ was established, leading to an OEL of (≥) 220 mg/m³ (AF10 = $5_{variability}*2_{6\text{-}8h}$). Because this study is not sufficiently specific for C10 hydrocarbon solvents (low content C10), it is not shown inFigure 5-7, below.
- The test material SHELLSOL TC (C8: 0,12%; C9: 0,92%; C10: 15,94%; C11: 38,7%; C12: 44,4%) was administered by inhalation to albino rats for 6 hours/day, 5 days/week for 13 weeks at nominal vapour concentrations of 10400 mg/m^3, 5200 mg/m^3, and 2600 mg/m^3 to assess inhalation toxicity. Liver and kidney weights were increased in male rats at all exposure levels, male heart weights were increased at the highest exposure level and liver and kidney weights were increased in female rats at 10400 mg/m^3.Kidney effects in male rats may possibly be attributed to species specific

effects. Furthermore, haematological changes were observed in the highest exposure group, but interpretation is not clear (secondary to kidney effects in male rats?). Also, the interpretation of liver weight changes in rodents after exposure to hydrocarbon solvents is discussed controversially. The registrant assessed the highest concentration of 10400 mg/m³ to be the NOAEC (for study details see also section 6.1.1). With a NOAEC of 10400 mg/m³, according to current methodology an OEL of (≥) 520 mg/m³ would result (AF20 = $5_{variability}$*$2_{6\text{-}8h}$*$2_{sc\text{-}c}$). This study probably is identical to the study reported by Carrillo et al. (2013).

The background document for the OEL of decalin (100 mg/m³) in Poland and the German MAK value (29 mg/m³) (DFG, 2014) could not be traced. The DNEL on decalin was derived from the NTP study with mice and rat with a NOAEC of 25 ppm (144 mg/m³) for liver effects (NTP, 2005).

We did not address potential local carcinogenicity or cocarcinogenicity of n-decane, as discussed in the OECD document (2012b).

The OECD assessment on C9-C14 aliphatic hydrocarbon solvents (less than 2% aromatics) refers to 7 experimental inhalation studies with mixtures (C9-C14, different combinations and ranges within this group). In all of them the highest concentration tested was the NOAEC; just one study, which was contradicted by a similar other experiment, indicated reduced body weight gain in female Wistar rats at a mid-dose concentration. The highest concentration tested and therefore the highest NOAEC was 10400 mg/m³ (which, probably, is the SHELLSOL TC study, as described above). However, all mentioned NOAEC depend on the interpretation of the liver weight changes. "*The pathology report described the liver changes as indicative of liver enlargement (hypertrophy). Liver enzymes were not elevated and the liver weight changes were not observed in animals held for 28 days without treatment."* (OECD, 2012b).

In addition, Carrillo et al. (2013) refer to an earlier experimental study by Phillips and Egan (1984). In this study, which was designed to examine kidney effects mostly, rats were exposed for 6 h/d on 5d/week for 12 weeks to 0, 300 or 900 ppm (nominal) of a C9-C11 isoparaffinic solvent. More details are provided in the section on mixtures (section 6). This mixture contained (assumed) 45 % C10 aliphatic hydrocarbons. If the default extrapolation procedure for AGW values is used, an OEL of (≥) 260 mg/m³ would be derived (AF20 = $5_{variability}$*$2_{6\text{-}8h}$*$2_{sc\text{-}c}$). However, as the highest concentration was used as POD, the NOAEC may be higher.

From recent studies, an acute NOAEC (1500 mg/m³) for neurobehavioral effects of n-decane has been found by Lammers et al. (2011). According to the default assessment an OEL of 300 mg/m³ could be established (AF5 = $5_{variability}$).

Neurobehavioural effects of acute exposure to isoparaffinic (and cycloparaffinic) hydrocarbons were also investigated by McKee et al. (2011). Rats were exposed for 8h/day for 3 consecutive days to 0, 500, 1500, 5000 mg/m³ of a C9-C11 isoparaffinic solvent. Minor acute CNS effects were observed in the high dose group with a NOAEC of 1500 mg/m³. According to the default AGW methodology this would result in an OEL of 300 mg/m³ (AF5 = $5_{variability}$). For C9-C11 cycloparaffinic hydrocarbons, the REACH document on tetradecane reports a NOAEC of 2500 mg/m³ in rats (original study not identified). According to the default AGW methodology this would result in an OEL of 500 mg/m³ (AF5 = $5_{variability}$).

For the C10 cycloparaffinic solvent (NOAEC 5000 mg/m³) an OEL of 1000 mg/m³ would be derived (AF5 = $5_{variability}$) from the study by McKee et al. (McKee et al., 2011).

The study by Stuchal et al. (2013) found a human equivalent concentration of 7.9 mg/m³ for decalin for liver toxicity (syncytial effects) from the data of the 2-year mouse study by NTP (NTP, 2005). The authors applied an assessment factor of 100 to that study to extrapolate a reference concentration for general population.

In summary, the group guidance value for C9-C15 aliphatics is challenged a) by neurobehavioral effects after acute exposure duration, which lead to a lower OEL for n-decane and C9-C11 isoparaffinic solvents, b) by the controversial discussion on the relevance of liver weight changes due to liver hypertrophic effects as being adaptive or adverse, c) by the low benchmark ($BMDL_{10}$) for decalin.

Justification for the current DNEL on decalin is questioned (Carrillo et al., 2014b). Moreover, only low amounts of decalin are present in hydrocarbon solvent mixtures. However, some draft calculations with the RCP method indicate, that even low amount of decalin (e.g., 1 %) would significantly lower the overall calculated OEL for a hydrocarbon solvent mixture, if the current low OEL for decalin is confirmed (exempting decalin from the GGV, and applying the SSV instead). Therefore we propose

a) to revisit decalin in order to assign an updated OEL to the single substance also taking into account the arguments by chemical industry toxicologists (Carrillo et al., 2014b) and the recent study by Stuchal et al. (2013); this OEL derivation is not covered in the present report,
b) to exempt decalin from the GGV and,
c) to set a maximum amount of decalin permitted in a hydrocarbon solvent mixture, above which decalin has to be explicitly included in the OEL calculation and should not be neglected. This amount may only be finally concluded on, after the SSV for decalin has been determined.

The other studies on C10 hydrocarbons (from mixtures and n-decane) support an OEL of about 300 mg/m³ for these compounds, mainly based on neurotoxicity.

Overall data base and resulting potential OELs are presented in Figure 5-7, below. We excluded derived OELs for decalin, because the current OEL for this substance should be reconsidered elsewhere.

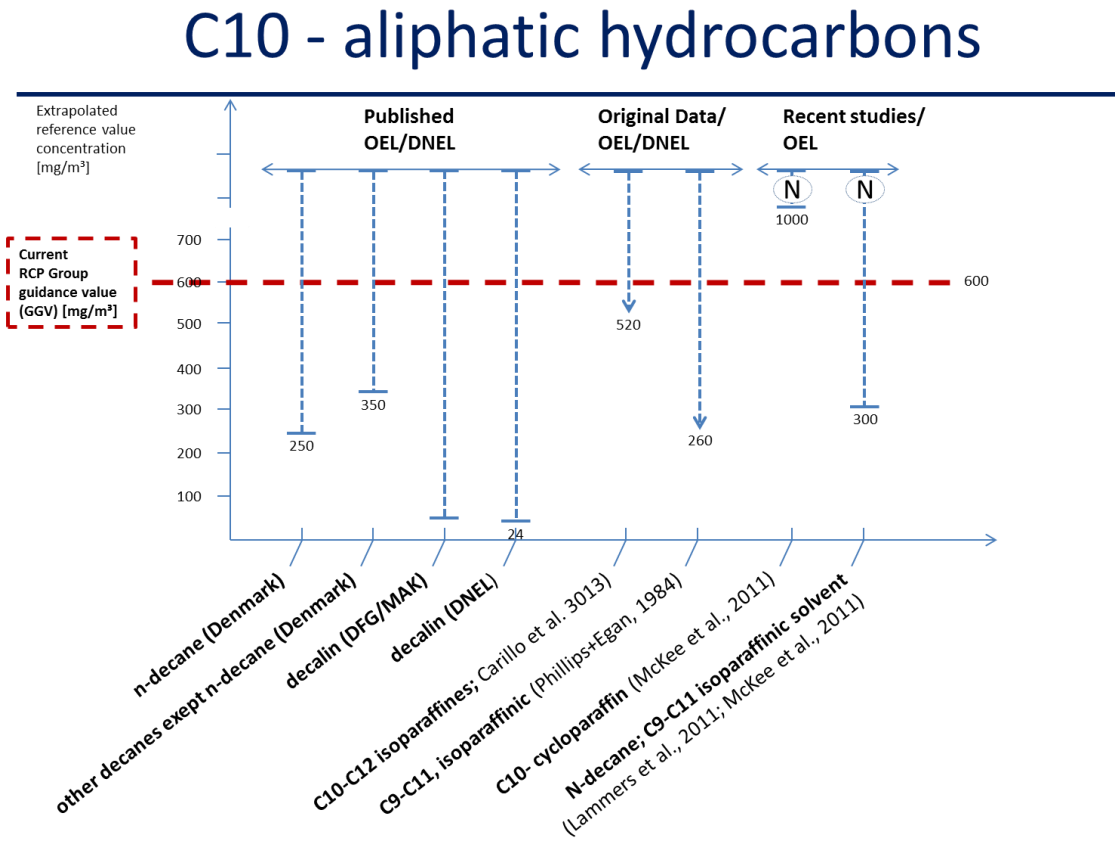

Figure 5-7: **Schematic illustration of potential OELs for C10 aliphatic hydrocarbon solvents (see Figure 4-2 for legend and comments in text)**

5.7 C11- Aliphatic Hydrocarbon Solvents

5.7.1 Assigned group guidance value (RCP, German approach, TRGS 900)

For the group of C9-C15 aliphatics currently in Germany the group guidance value is 600 mg/m³ (AGS, 2012).

5.7.2 Substance Search

We searched for experimental or epidemiological data on the substances:

- 2-Methyldecalin (CASRN: 2958-76-1)
- n-Hexylcyclopentane (CASRN: 4457-00-5)
- 2-Methyldecane (CASRN: 6975-98-0)
- 3-Methyldecane (CASRN: 13151-34-3)
- n-Undecane (CASRN: 1120-21-4)

5.7.3 Existing OEL or equivalent derived reference values (workers)

Substance	Type reference value	mg/m³	source
All single substances above	AGW (Germany)	No OEL values for specific substances derived	(AGS, 2006; BMAS, 2014)
	MAK (Germany)		(DFG, 2014)
	DNEL (Europe)		(ECHA, 2014)
	OEL		(IFA, 2014)

5.7.4 Recent Data

The C9-C14 Aliphatic [≤2% aromatic] Hydrocarbon Solvents Category was recently evaluated by OECD (OECD, 2012b), which contains Alkanes, C12-14 (CASRN: 129813-67-8), Alkanes C12-14-iso- (CASRN 68551-19-9) and Alkanes, C11-15-iso- (CASRN: 90622-58-5). But this review contained no relevant recent studies.

Neurobehavioural effects of acute exposure to isoparaffinic (and cycloparaffinic) hydrocarbons were investigated by McKee et al. (2011). Rats were exposed for 8h/day for 3 consecutive days to 0, 500, 1500, 5000 mg/m³ of a C9-C11 isoparaffinic solvent. Minor acute CNS effects were observed in the high dose group with a NOAEC of 1500 mg/m³.

N-undecane was evaluated by OECD (2010b). The only available study after repeated exposure was a combined repeat dose and reproduction/developmental toxicity study (OECD TG 422). Animals were treated via oral gavage with 0, 100, 300 and 1000 mg/kg bw x d for approximately 46-52 days. The NOAEL identified was 300 mg/kg bw x d.

No further relevant new studies were found.

5.7.5 Assessment, discussion and conclusions

There are no OELs existing for C11 aliphatics as a single substance. However, recently an OEL for destillates, (range: C9-C16) UVCB by DFG (Hartwig, 2012) of 140 mg/m³ was established.

No DNEL was derived within the registration document for n-undecane, because: 'No-threshold effect and/or no dose-response information [was] available' (ECHA, 2014). However, the registration document refers to the three key documents as already mentioned for n-decane in section 5.6.5:

- data on isododecane (read-across) with a NOAEC of 1160 mg/m³ (or above), based on a subchronic rat study (6 h/d, 5d/week, 13 weeks) with no adverse effects at the highest concentration. (Note default extrapolation according to German AGW procedure would result in an OEL of (≥) 58 mg/m³ (AF20 = $5_{variability}$*$2_{6\text{-}8h}$*$2_{sc\text{-}c}$)).
- In a subchronic inhalation toxicity study (OECD TG 413) or in combined chronic and carcinogenicity study (OECD TG 453) rats were exposed to 0, 138, 550, 1100, and 2200 mg/m³ of Stoddard solvent IIC (CASRN: 64742-88-7; C10-13 n-paraffins, 2-25% aromatics; 'high flash' and low aromatic grade; composition: mixture of n-paraffins, isoparaffins, or cycloparaffins with 10 to 13 carbons, e.g. 1.70 % decane, 19.3 % undecane, and 5.73 % dodecane (no further details), 0.56 % decalin; aromatics 0.93 % and 0.58 %, i.e. NTP, 2004). Within the registration dossier (ECHA, 2014): no

adverse effects up to the highest concentration tested were identified in females. In males alpha 2u globulin related nephropathy starting already at 138 mg/m³ was observed but not accounted for as adverse as this is a species and sex specific effect not relevant for humans. Note that no haematological or neurotoxicological examination was performed (for study details see also section 6.1.1.). Based on these observations a NOAEC of 2200 mg/m³ was established, leading to an OEL of (≥) 220 mg/m³ (AF10 = $5_{variability}$*$2_{6\text{-}8h}$).

- The test material SHELLSOL TC (C8: 0,12%; C9: 0,92%; C10: 15,94%; C11: 38,7%; C12: 44,4%) was administered by inhalation to albino rats for 6 hours/day, 5 days/week for 13 weeks at nominal vapour concentrations of 10400 mg/m^3, 5200 mg/m^3, and 2600 mg/m^3 to assess inhalation toxicity. Liver and kidney weights were increased in male rats at all exposure levels, male heart weights were increased at the highest exposure level and liver and kidney weights were increased in female rats at 10400 mg/m^3.Kidney effects in male rats may possibly be attributed to species specific effects. Furthermore, haematological changes were observed in the highest exposure group, but interpretation is not clear (secondary to kidney effects in male rats?). Also, the interpretation of liver weight changes in rodents after exposure to hydrocarbon solvents is discussed controversially. The registrant assessed the highest concentration of 10400 mg/m³ to be the NOAEC (for study details see also section 6.1.1.). With a NOAEC of 10400 mg/m³, according to current methodology an OEL of (≥) 520 mg/m³ would result (AF20 = $5_{variability}$*$2_{6\text{-}8h}$*$2_{sc\text{-}c}$). This study probably is identical to the study reported by Carrillo et al. (2013).

The NOAEC identified in the oral OECD TG 422 study (recent reproduction/developmental toxicity study) was 300 mg/kg bw x d (OECD, 2010b). As this was a gavage study and there were no effects observed in the highest tested concentration, there is considerable uncertainty about the quantitative interpretation of the results for inhalation exposure.

Carrillo et al. (2013) refer to an earlier experimental study by Phillips and Egan (1984). In this study, which was designed to examine kidney effects mostly, rats were exposed for 6 h/d on 5d/week for 12 weeks to 0, 300 or 900 ppm (nominal) of a C9-C11 isoparaffinic solvent. More details are provided in the section on mixtures (see section 6). This mixture contained (assumed) 45 % C11 aliphatic hydrocarbons. If the default extrapolation procedure for AGW values is used, an OEL of (≥) 260 mg/m³ would be derived (AF20 = $5_{variability}$*$2_{6\text{-}8h}$*$2_{sc\text{-}c}$). However, as the highest concentration was used as POD, the NOAEC may be higher.

Neurobehavioural effects of acute exposure to isoparaffinic (and cycloparaffinic) hydrocarbons were also investigated by McKee et al. (2011). Rats were exposed for 8h/day for 3 consecutive days to 0, 500, 1500, 5000 mg/m³ of a C9-C11 isoparaffinic solvent. Minor acute CNS effects were observed in the high dose group with a NOAEC of 1500 mg/m³. According to the default AGW methodology this would result in an OEL of 300 mg/m³ (AF5 = $5_{variability}$). For C9-C11 cycloparaffinic hydrocarbons, the REACH document on tetradecane reports a NOAEC of 2500 mg/m³ in rats (original study not identified). According to the default AGW methodology this would result in an OEL of 500 mg/m³ (AF5 = $5_{variability}$).

In summary, even though some potential reduction in neurotoxicity for >C10 hydrocarbon solvents due to lower uptake in brain is discussed in literature (Bowen and Balster, 1998; McKee et al., 2011), the extrapolated OELs based on neurotoxicity and other endpoints do not clearly permit to raise the GGV for C12 aliphatic hydrocarbon solvents above the OEL proposed for C10 compounds. In addition, sensory irritation potential increases for long

chained aliphatic hydrocarbon solvents (Kjaergaard and Molhave, 1987; Kristiansen and Nielsen, 1988). Because of the limited number of studies presented above, we do not show a schematic overview (figure) for derived potential OELs on C11 aliphatic hydrocarbon solvents or for > C11 hydrocarbons.

5.8 C12- Aliphatic Hydrocarbon Solvents

5.8.1 Assigned group guidance value (RCP, German approach, TRGS 900)

For the group of C9-C15 aliphatics currently in Germany the group guidance value is 600 mg/m³ (AGS, 2012).

5.8.2 Substance Search

We searched for experimental or epidemiological data on the substances:

- n-Heptylcyclopentane (CASRN: 5617-42-5)
- n-Hexylcyclohexane (CASRN: 4292-75-5)
- n-Dodecane (CASRN: 112-40-3)
- 3-Methylundecane (CASRN: 1002-43-3)
- Isododecane (CASRN: 31807-55-3)

5.8.3 Existing OEL or equivalent derived reference values (workers)

Substance	Type reference value	mg/m³	source
All single substances above	AGW (Germany)	No OEL values for specific substances derived	(AGS, 2006; BMAS, 2014)
	MAK (Germany)		(DFG, 2014)
	DNEL (Europe)		(ECHA, 2014)
	OEL		(IFA, 2014)

5.8.4 Recent Data

The C9-C14 Aliphatic [≤2% aromatic] Hydrocarbon Solvents Category was recently evaluated by OECD (OECD, 2012b), which contains Alkanes, C12-14 (CASRN: 129813-67-8), Alkanes C12-14 -iso (CASRN 68551-19-9) and Alkanes, C11-15-iso- (CASRN: 90622-58-5). But this review contained no relevant recent studies.

No further relevant studies were found.

5.8.5 Assessment, discussion and conclusions

No DNEL was derived within the registration document for n-dodecane, because: 'No-threshold effect and/or no dose-response information [was] available' (ECHA, 2014). However, the registration document refers to the three key documents as already mentioned for n-decane in section 5.6.5, and also mentions the neurotoxicity study by Bowen et al. (1998). However, this study is regarded as too brief in exposure duration (30 Minutes, acute exposure) to permit any interpretation for chronic CNS-effects.

For single substances starting from C11 only very little single substance data are available.

Assessments for grouped categories were mainly performed on basis of read-across from single well investigated substances or mixtures containing aliphatics in this range, e.g.:

- C9-C14 Aliphatic [≤2% aromatic] Hydrocarbon Solvents Category (OECD, 2012b)
- C9-C14 Aliphatic [2-25% aromatic] Hydrocarbon Solvents Category (OECD, 2012a)
- C14-C20 Aliphatic [≤2% aromatic] Hydrocarbon Solvents Category (OECD, 2011)
- Petroleum distillates, hydrotreated light (CASRN 64742-47-8, C9-C16 n-, iso-, and cyclicl alipathis, mainly C12)(Hartwig, 2012)

The study, which is most adequate for describing toxicity of higher aliphatics, is the Shellsol study (dearomatised white spirit, containing C11 = 38.7 % and C12 = 44.4 %) from 1980 as described by Carrillo et al. (2013). Based on the NOAEC identified (10400 mg/m³, i.e. the highest dose tested; only if liver effects are considered as adaptive and not adverse) an OEL of (≥) 520 mg/m³ (40 mg/m³, if liver effects are considered adverse) results (further details see section 6.1.1 on mixtures). However, this study did not specifically address neurotoxicity endpoints.

In the C9-C14 Aliphatic [≤2% aromatic] Hydrocarbon Solvents Category (OECD, 2012b), there are seven studies mentioned with test materials ready to fit the substance description. Three of these studies could be assigned to studies as mentioned in the section on mixtures (see 6; i.e. Shellsol Study, 1980 as cited by Carrillo et al.(2013) ; Phillips and Egan studies on C9-C11 isoparaffinic solvents and dearomatised white spirit (Phillips and Egan, 1984), but for four other studies the primary source could not be identified and thus are cited here from the secondary source, i.e.:

- C11-C14 n-paraffins, isoparaffins, cyclics (CAS RN 64742-47-8). Tested in a 90 day inhalation toxicity study (OECD TG 413) in albino rats. The NOAEC was 6000 mg/m³, the highest concentration tested. → OEL ≥ 300-600 (AF10-20 = $5_{variability}$*(2_{6-8h})*2_{sc-c}).
- C12 isoparaffins (<2% aromatics) (CAS RN 93685-81-5). Tested in a 90 day inhalation toxicity study (OECD TG 413) in Wistar rats. The NOAEC was 1390 mg/m³ (200 ppm) (based on reduced body weights in female rats, changes not significant). → OEL = 70-140 (AF10-20 = $5_{variability}$*(2_{6-8h})*2_{sc-c}).
- C12 isoparaffins (<2% aromatics) (CAS RN 93685-81-5). Tested in a 90 day inhalation toxicity study (OECD TG 413) in Wistar rats. The NOAEC was 6257 mg/m³ (900 ppm), the highest concentration tested. → OEL ≥ 313-616 (AF10-20 = $5_{variability}$*(2_{6-8h})*2_{sc-c}).
- C10-C13 n-alkanes, isoalkanes, cyclics (<2% aromatics) (CAS RN 64742-48-9). Tested in a 28 day inhalation toxicity study (OECD TG 412) in Rhesus monkeys. The NOAEC was 4200 mg/m³ (615 ppm), the highest concentration tested. → OEL ≥ 140 mg/m³ (AF30 = $5_{variability}$*6_{sc-c}).

Note: Changes in liver enzymes and liver weight were addressed but not accounted for as adverse (liver enzymes: small changes and not consistent over the studies; liver weight: no pathological changes and no elevated liver enzyme markers). However, most of these studies may be linked to a higher NOAEC, if the highest concentration used was below the NOAEC. Therefore, these studies do not permit firm conclusions.

We conclude that no sufficient data are available to derive a specific OEL for C12 aliphatic hydrocarbon solvents. However, results on mixtures including >C11 hydrocarbon fractions (see section 6.1.1) should be considered for the respective GGV.

5.9 C13- Aliphatic Hydrocarbon Solvents

5.9.1 Assigned group guidance value (RCP, German approach, TRGS 900)

For the group of C9-C15 aliphatics currently in Germany the group guidance value is 600 mg/m³ (AGS, 2012).

5.9.2 Substance Search

We searched for experimental or epidemiological data on the substances:

- n-Octylcyclopentane (CASRN: 1795-20-6)
- n-Heptylcyclohexane (CASRN: 5617-41-4)
- 2,6-Dimethylundecane (CASRN: 17301-23-4)
- 2-Methyldodecane (CASRN: 1560-97-0)
- n-Tridecane (CASRN: 629-50-5)

5.9.3 Existing OEL or equivalent derived reference values (workers)

Substance	Type reference value	mg/m³	source
All single substances above	AGW (Germany)	No OEL values for specific substances derived	(AGS, 2006; BMAS, 2014)
	MAK (Germany)		(DFG, 2014)
	DNEL (Europe)		(ECHA, 2014)
	OEL		(IFA, 2014)

5.9.4 Recent Data

The C9-C14 Aliphatic [≤2% aromatic] Hydrocarbon Solvents Category was recently evaluated by OECD (OECD, 2012b), which contains Alkanes, C12-14 (CASRN: 129813-67-8), Alkanes C12-14 -iso (CASRN 68551-19-9) and Alkanes, C11-15-iso- (CASRN: 90622-58-5). But this review contained no relevant recent studies.

No further relevant studies were found.

5.9.5 Assessment, discussion and conclusions

No DNEL was derived within the registration document for n-tridecane, because: 'No-threshold effect and/or no dose-response information [was] available' (ECHA, 2014). The REACH registration document refers to the three key documents as already mentioned for n-decane in section 5.6.5, and also mentions the neurotoxicity study by Bowen et al. (1998). However, this study is regarded as too brief in exposure duration (30 Minutes, acute exposure) to permit any interpretation for chronic CNS-effects.

For single substances starting from C11 only very little single substance data are available.

Assessments for grouped categories were mainly performed on basis of read-across from single well investigated substances or mixtures containing aliphatics in this range, e.g.:

- C9-C14 Aliphatic [≤2% aromatic] Hydrocarbon Solvents Category (OECD, 2012b)
- C9-C14 Aliphatic [2-25% aromatic] Hydrocarbon Solvents Category (OECD, 2012a)
- C14-C20 Aliphatic [≤2% aromatic] Hydrocarbon Solvents Category (OECD, 2011)
- Petroleum distillates, hydrotreated light (CASRN 64742-47-8, C9-C16 n-, iso-, and cyclic alipathis, mainly C12)(Hartwig, 2012)

The study, which is most adequate for describing toxicity of higher aliphatics, is the Shellsol study (dearomatised white spirit, containing C11 = 38.7 % and C12 = 44.4 %) from 1980 as described by Carrillo et al. (2013). Based on the NOAEC identified (10400 mg/m³, i.e. the highest dose tested; only if liver effects are considered as adaptive and not adverse) an OEL of (≥) 520 mg/m³ (40 mg/m³, if liver effects are considered adverse) results (further details see section 6.1.1 on mixtures). However, this study did not specifically address neurotoxicity endpoints.

In the C9-C14 Aliphatic [≤2% aromatic] Hydrocarbon Solvents Category (OECD, 2012b), there are seven studies mentioned with test materials ready to fit the substance description. Three of these studies could be assigned to studies as mentioned in the section on mixtures (see 6; i.e. Shellsol Study, 1980 as cited by Carrillo et al.(2013) ; Phillips and Egan studies on C9-C11 isoparaffinic solvents and dearomatised white spirit (Phillips and Egan, 1984), but for four other studies the primary source could not be identified and thus are cited here from the secondary source, i.e.:

- C11-C14 n-paraffins, isoparaffins, cyclics (CAS RN 64742-47-8). Tested in a 90 day inhalation toxicity study (OECD TG 413) in albino rats. The NOAEC was 6000 mg/m³, the highest concentration tested. → OEL ≥ 300-600 (AF10-20 = $5_{variability}$*(2_{6-8h})*2_{sc-c}).
- C12 isoparaffins (<2% aromatics) (CAS RN 93685-81-5). Tested in a 90 day inhalation toxicity study (OECD TG 413) in Wistar rats. The NOAEC was 1390 mg/m³ (200 ppm) (based on reduced body weights in female rats, changes not significant). → OEL = 70-140 (AF10-20 = $5_{variability}$*(2_{6-8h})*2_{sc-c}).
- C12 isoparaffins (<2% aromatics) (CAS RN 93685-81-5). Tested in a 90 day inhalation toxicity study (OECD TG 413) in Wistar rats. The NOAEC was 6257 mg/m³ (900 ppm), the highest concentration tested. → OEL ≥ 313-616 (AF10-20 = $5_{variability}$*(2_{6-8h})*2_{sc-c}).
- C10-C13 n-alkanes, isoalkanes, cyclics (<2% aromatics) (CAS RN 64742-48-9). Tested in a 28 day inhalation toxicity study (OECD TG 412) in Rhesus monkeys. The NOAEC was 4200 mg/m³ (615 ppm), the highest concentration tested. → OEL ≥ 140 mg/m³(AF30 = $5_{variability}$*6_{sc-c}).

Note: Changes in liver enzymes and liver weight were addressed but not accounted for as adverse (liver enzymes: small changes and not consistent over the studies; liver weight: no pathological changes and no elevated liver enzyme markers). However, most of these studies may be linked to a higher NOAEC, if the highest concentration used was below the NOAEC. Therefore, these studies do not permit firm conclusions.

We conclude that no sufficient data are available to derive a specific OEL for C13 aliphatic hydrocarbon solvents. However, results on mixtures including >C11 hydrocarbon fractions (see section 6.1.1) should be considered for the respective GGV.

5.10 C14- Aliphatic Hydrocarbon Solvents

5.10.1 Assigned group guidance value (RCP, German approach, TRGS 900)

For the group of C9-C15 aliphatics currently in Germany the group guidance value is 600 mg/m³ (AGS, 2012).

5.10.2 Substance Search

We searched for experimental or epidemiological data on the substances:

- n-Nonylcyclopentane (CASRN: 2882-98-6)
- n-Octylcyclohexane (CASRN: 1795-15-9)
- 3-Methyltridecane (CASRN: 6418-41-3)
- n-Tetradecane (CASRN: 629-59-4)

5.10.3 Existing OEL or equivalent derived reference values (workers)

Substance	Type reference value	mg/m³	source
All single substances above	AGW (Germany)	No OEL values for specific substances derived	(AGS, 2006; BMAS, 2014)
	MAK (Germany)		(DFG, 2014)
	DNEL (Europe)		(ECHA, 2014)
	OEL		(IFA, 2014)

5.10.4 Recent Data

- The C9-C14 Aliphatic [≤2% aromatic] Hydrocarbon Solvents Category was recently evaluated by OECD (OECD, 2012b), which contains Alkanes, C12-14 (CASRN: 129813-67-8), Alkanes C12-14 -iso (CASRN 68551-19-9) and Alkanes, C11-15-iso- (CASRN: 90622-58-5). But this review contained no relevant recent studies.
- A recent study reported about deposition of tetradecane vapours in models of the human respiratory system (Zhang and Kleinstreuer, 2011), but was not useful to derive an OEL.

No further relevant studies were found.

5.10.5 Assessment, discussion and conclusions

No DNEL was derived within the registration document for n-tetradecane, because: 'No-threshold effect and/or no dose-response information [was] available' (ECHA, 2014). However, the registration document refers to the three key documents as already mentioned for n-decane in section 5.6.5, and also mentions the neurotoxicity study by Bowen et al. (1998). However, this study is regarded as too brief in exposure duration (30 Minutes, acute exposure) to permit any interpretation for chronic CNS-effects.

For single substances starting from C11 only very little single substance data are available.

Assessments for grouped categories were mainly performed on basis of read-across from single well investigated substances or mixtures containing aliphatics in this range, e.g.:

- C9-C14 Aliphatic [≤2% aromatic] Hydrocarbon Solvents Category (OECD, 2012b)
- C9-C14 Aliphatic [2-25% aromatic] Hydrocarbon Solvents Category (OECD, 2012a)
- C14-C20 Aliphatic [≤2% aromatic] Hydrocarbon Solvents Category (OECD, 2011)
- Petroleum distillates, hydrotreated light (CASRN 64742-47-8, C9-C16 n-, iso-, and cyclicl alipathis, mainly C12)(Hartwig, 2012)

The study, which is most adequate for describing toxicity of higher aliphatics, is the Shellsol study (dearomatised white spirit, containing C11 = 38.7 % and C12 = 44.4 %) from 1980 as described by Carrillo et al. (2013). Based on the NOAEC identified (10400 mg/m³, i.e. the highest dose tested; only if liver effects are considered as adaptive and not adverse) an OEL of (≥) 520 mg/m³ (40 mg/m³, if liver effects are considered adverse) results (further details see section 6.1.1 on mixtures). However, this study did not specifically address neurotoxicity endpoints.

In the C9-C14 Aliphatic [≤2% aromatic] Hydrocarbon Solvents Category (OECD, 2012b), there are seven studies mentioned with test materials ready to fit the substance description. Three of these studies could be assigned to studies as mentioned in the section on mixtures (see 6; i.e. Shellsol Study, 1980 as cited by Carrillo et al.(2013) ; Phillips and Egan studies on C9-C11 isoparaffinic solvents and dearomatised white spirit (Phillips and Egan, 1984), but for four other studies the primary source could not be identified and thus are cited here from the secondary source, i.e.:

- C11-C14 n-paraffins, isoparaffins, cyclics (CAS RN 64742-47-8). Tested in a 90 day inhalation toxicity study (OECD TG 413) in albino rats. The NOAEC was 6000 mg/m³, the highest concentration tested. → OEL ≥ 300-600 mg/m³ (AF10-20 = $5_{variability}$*($2_{6\text{-}8h}$)*$2_{sc\text{-}c}$).
- C12 isoparaffins (<2% aromatics) (CAS RN 93685-81-5). Tested in a 90 day inhalation toxicity study (OECD TG 413) in Wistar rats. The NOAEC was 1390 mg/m³ (200 ppm) (based on reduced body weights in female rats, changes not significant). → OEL = 70-140 mg/m³ (AF10-20 = $5_{variability}$*($2_{6\text{-}8h}$)*$2_{sc\text{-}c}$).
- C12 isoparaffins (<2% aromatics) (CAS RN 93685-81-5). Tested in a 90 day inhalation toxicity study (OECD TG 413) in Wistar rats. The NOAEC was 6257 mg/m³ (900 ppm), the highest concentration tested. → OEL ≥ 313-616 mg/m³ (AF10-20 = $5_{variability}$*($2_{6\text{-}8h}$)*$2_{sc\text{-}c}$).

- C10-C13 n-alkanes, isoalkanes, cyclics (<2% aromatics) (CAS RN 64742-48-9). Tested in a 28 day inhalation toxicity study (OECD TG 412) in Rhesus monkeys. The NOAEC was 4200 mg/m³ (615 ppm), the highest concentration tested. → OEL ≥ 140 mg/m³ (AF30 = $5_{variability}$*6_{sc-c}).

Note: Changes in liver enzymes and liver weight were addressed but not accounted for as adverse (liver enzymes: small changes and not consistent over the studies; liver weight: no pathological changes and no elevated liver enzyme markers). However, most of these studies may be linked to a higher NOAEC, if the highest concentration used was below the NOAEC. Therefore, these studies do not permit firm conclusions.

We conclude that no sufficient data are available to derive a specific OEL for C14 aliphatic hydrocarbon solvents. However, results on mixtures including >C11 hydrocarbon fractions (see section 6.1.1) should be considered for the respective GGV.

5.11 C15- Aliphatic Hydrocarbon Solvents

5.11.1 Assigned group guidance value (RCP, German approach, TRGS 900)

For the group of C9-C15 aliphatics currently in Germany the group guidance value is 600 mg/m³ (AGS, 2012).

5.11.2 Substance Search

We searched for experimental or epidemiological data on the substances:

- 2,6,10-Trimethyldodecane (CASRN: 3891-98-3)
- n-Decylcyclopentane (CASRN: 1795-21-7)
- n-Nonylcyclohexane (CASRN: 2883-02-5)
- 2-Methyltetradecane (CASRN: 1560-95-8)
- n-Pentadecane (CASRN: 629-62-9)

5.11.3 Existing OEL or equivalent derived reference values (workers)

Substance	Type reference value	mg/m³	source
All single substances above	AGW (Germany)	No OEL values for specific substances derived	(AGS, 2006; BMAS, 2014)
	MAK (Germany)		(DFG, 2014)
	DNEL (Europe)		(ECHA, 2014)
	OEL		(IFA, 2014)

5.11.4 Recent Data

N-pentadecane is registered under REACH (ECHA, 2014) and included by OECD in the C14-C20 Aliphatic [≤2% aromatic] Hydrocarbon Solvents Category (OECD, 2011).

No further relevant studies were found.

5.11.5 Assessment, discussion and conclusions

No DNEL was derived within the registration document for n-tridecane, because: 'No-threshold effect and/or no dose-response information [was] available' (ECHA, 2014). Therefore we conclude that no sufficient data are available to derive a specific OEL for C15 aliphatic hydrocarbon solvents. However, results on mixtures including >C11 hydrocarbon fractions (see section 6.1.1) should be considered for the respective GGV.

5.12 Concluding Analysis from Single Substances' Data on Grouping of Aliphatic Hydrocarbon Solvents

The analysis of existing OELs and recent studies indicates a trend of increasing toxicity from C5 to C10 aliphatic hydrocarbon solvents. This trend is shown for acute neurotoxic effects for single substances. Above C10 we do not observe such further increased neurotoxicity, probably due to less absorption of the respective substances and lower uptake into brain.

However, the increase in neurotoxicity with carbon chain length is not demonstrated in all studies and for all compounds. There are remarkable deviations, for which no satisfactory explanation is available. For example, n- or iso-octane appear to be less neurotoxic than cyclohexane.

Due to these deviations, relevant uncertainties remain, but, based on the overall trend, the profile may be described as follows:

- For C5 aliphatic hydrocarbon solvents an OEL of 1500 to 3000 mg/m³ appears to be justified
- For C6-C8 aliphatic hydrocarbon solvents there remains relevant ambiguity to set an OEL at (or around) 700 mg/m³ or at 300 mg/m³
- For C9-C11 most qualified data (especially on acute neurotoxicity) support lowering of the OEL to 300 mg/m³
- Above C11, the substance specific data are not sufficiently qualified to decide whether the OEL should be increased or should maintain at 300 mg/m³.

Toxicological profiles of the single substances are less homogeneous than expected.

This could support the conclusion to exempt a number of single substances from the respective groups (e.g., cyclohexane or methylcyclohexane), but we propose to rather set the group guidance level (GGV) based on these more toxic substances. The reason for this proposal is that no distinct mode of action was identified for these more toxic aliphatic hydrocarbons, which would justify separate handling. This is different from n-hexane, where the effects on the peripheral nerve system are unique and, thus, permit the separation.

It was discussed, to also exempt trimethylpentanes from the respective group of C8 aliphatic hydrocarbon solvents, but even though the alleged tumour promoting potential is a distinct property, this classification currently not sufficiently confirmed. For the time being, we propose to reintegrate trimethylpentanes into the GGV. However, this decision is bound to further future discussions on this issue within the German MAK commission, in order to reconfirm or change the respective suspect category by DFG for trimethylpentanes. Similarly

suspect information on tumour promoting activities by further aliphatic hydrocarbon solvents is not sufficiently supported to separate these substances from the respective groups.

For decalin, the established OELs in Germany and the DNEL are significantly deviating from all other known aliphatic hydrocarbon solvents (apart from n-hexane). To set a group guidance value as low as would be necessary, if decalin were taken as a representative substance, is not justified as evidenced by mixture data. Therefore, this specific substance should be handled separately. A final conclusion on a SSV for decalin has not been established, because toxicologists from the manufacturing industry question the existing DNEL. It is proposed to a) exempt decalin from the GGV for the time being, b) to reconfirm or change the current SSV on this substance after consideration of new data and toxicological interpretations, c) to conclude on a maximum amount of decalin to be (ir)relevant in hydrocarbon solvent mixture to significantly influence the overall OEL, d) to derive an additional condition on the applicability of the overall OEL, if decalin is present in low quantities (percentage), or else, e) to explicitly include decalin into calculations with its SSV, if a higher percentage is present in the UVCB or mixture (note, that there are analytical difficulties to separately identify decalin within such a hydrocarbon mixture).

We did not decide on the relevance of the hepatotoxicity and haematological changes observed with a number of single substances and hydrocarbon solvent mixtures. It was felt that the current other toxicological data from aliphatic single substances and mixtures are sufficiently qualified to justify the proposed OELs or GGVs without further considering these controversial endpoints. However, if these effects were regarded as adverse effects (instead of adaptive, (liver) or species specific (haematological effects)) the current overall proposal would be strengthened.

A final decision on grouping and associated OELs for aliphatic hydrocarbon solvents should be done after also considering data on mixtures, which are discussed later in this analysis (see section 6).

5.13 C6- Aromatic Hydrocarbon Solvents

Benzene has to be assessed via its substance specific guidance value (SSV). No specific substance search was performed. Hydrocarbon solvent mixtures with benzene content > 0.1 % are exempted from application of the calculated mixture specific OELs.

5.14 C7- / C8 - Aromatic Hydrocarbon Solvents

According to preceding discussions, C7 and C8 hydrocarbon solvents should be assessed via their substance specific guidance values (SSV), because only few identified substances have to be addressed (toluene, ethylbenzene, xylenes). For the purpose of this study, we assigned an **OEL of 200 mg/m³** to all of these substances, in order to integrate the respective amounts into RCP calculations on mixtures (see section 4). However, this does not preclude that other (updated und substance-specific) OELs have to be selected, when RCP is applied in practice.

5.15 C9- Aromatic Hydrocarbon Solvents

5.15.1 Assigned group guidance value (RCP, German approach, TRGS 900)

For the group of C9-C15 aromatics currently in Germany the group guidance value is 100 mg/m³ (AGS, 2012).

5.15.2 Substance Search

We searched for experimental or epidemiological data on the substances:

- Indan (dihydroindene) (CASRN: 496-11-7)
- Ethyltoluene (CASRN: 25550-14-5)
- 1-Methyl-2-ethylbenzene (2-ethyltoluene) (CASRN: 611-14-3)
- 1-Methyl-4-ethylbenzene (p-ethyltoluene, 4-ethyltoluene, 4-ET) (CASRN: 622-96-8)
- 1-Methyl-3-ethylbenzene (3-ethyltoluene) (CASRN: 620-14-4)
- iso-Propylbenzene (2-phenylpropane; cumene) (CASRN: 98-82-8)
- 1,2,3-Trimethylbenzene (hemimellitene) (CASRN: 526-73-8)
- 1,2,5-Trimethylbenzene (1,2,4-trimethylbenzene, pseudocumene) (CASRN: 95-63-6)
- 1,3,5-Trimethylbenzene (mesitylene, 3,5-dimethyltoluene) (CASRN: 108-67-8)
- n-Propylbenzene (CASRN: 103-65-1),

and for the group in general (C9 aromatics).

5.15.3 Existing OEL or equivalent derived reference values (workers)

Substance	Type reference value	mg/m³	source
iso-Propylbenzene (cumene)	AGW (Germany)	50 (10 ppm)	(AGS, 2006; BMAS, 2014)
	MAK (Germany)	50 (10 ppm)	(DFG, 2014)
	DNEL (Europe)	100	(ECHA, 2014)
	SCOEL	100 (20 ppm)	(SCOEL, 1993) currently ongoing
Trimethylbenzenes (TMB)	AGW (Germany)	100 (20 ppm)	(AGS, 2006; BMAS, 2014)
	MAK (Germany)	100 (20 ppm)	(DFG, 2014)
1,3,5-TMB; 1,2,4-TMB	DNEL (Europe)	100	(ECHA, 2014)
Trimethylbenzenes (1,3,5-TMB; 1,2,4-TMB; 1,2,3-TMB)	SCOEL	100	(SCOEL, 1994)

5.15.4 Recent Data

- Neurobehavioural effects after acute exposure (3 times for 8 h) to 1,2,4-Trimethylbenzene (TMB, 99 % pure) or to C9 aromatic solvent (commercial product with CASRN 64742-95-6[3]) in rats were investigated by McKee and colleagues (2010). The NOAEC identified for 1,2,4-TMB was 1250 mg/m³. The results for the C9 aromatic solvent were very similar to that observed for 1,2,4-TMB, but more pronounced in visual discriminating testing (NOAEC= 200 mg/m³).
- 1,3,5-TMB: In 28 d inhalation test a LOAEC = 125 mg/m³ in male rats was identified for difference in active and passive avoidance test as well as sensitivity to pain in all test groups compared to control. But no concentration- effect relationship (Wiaderna et al., 2002).
- In a 90 day oral gavage toxicity study with 1,3,5-TMB a NOAEL of 600 mg/kg bw x d (i.e. highest dose tested) was identified as the observed effects on liver weights of rats were classed as adaptive response and other effects were not considered toxicologically relevant by the authors (Adenuga et al., 2014).
- In a two week oral gavage study with rats 21 aromatic solvents were investigated concerning their ototoxic activity (8.47 mmol/kg bw x d). n-propylbenzene was

[3] The OECD assessment for C9 aromatic hydrocarbon solvent category included mixed ethyltoluenes, 1,2,4-TMB, 1,3,5-TMB and Solvent naphtha, (petroleum), light aromatic OECD, Organisation for Economic Co-Operation and Development (2012c)
SIDS Initial Assessment Profile for C9 Aromatic Hydrocarbon Solvents Category. CoCAM 2, 17-19 April 2012 Paris, France . Commercially available C9 aromatic naphtha (i.e. CASRN 64742-95-6) contains typically: 20-45 % 1,2,4-TMB, 8-15 % 1,3,5-TMB, 25-35 % mixed ethyltoluenes, and 5-10 % C8 and C10 aromatic hydrocarbons. 1,2,3-TMB data are further used to support the category, which is also contained typically at approximately 6 % (weight) in C9 aromatic naphtha.

identified as potentially ototoxic, whereas iso-propylbenzene and 1-Methyl-4-ethylbenzene did not show this property (Gagnaire and Langlais, 2005).

In addition, the recent assessment by the German Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area (MAK Commission) on iso-propylbenzene (cumene), as mentioned above, already includes further recent data. For this substance the National Toxicology Program conducted a 2-year carcinogenicity study on mice and rats (inhalation, chronic, 6 h/d). Study results showed clear evidence for carcinogenic activity (NTP, 2009). In a summary report the same authors stated that there is mechanistic evidence that iso-propylbenzene has genotoxic potential (besides numerous negative results, positive results in COMET assay) and mutations in lung tumours observed in mice are similar to findings in humans, thus further strengthen the association that the substances is '*reasonably anticipated to be a human carcinogen*' (Hong et al., 2008; NTP, 2013). The German MAK Commission included classification into MAK carcinogenicity category 3B and lowered the existing MAK value from 250 mg/m³ to 50 mg/m³ (10 ppm) based on the BMDL (one standard deviation of control) of 35 ppm for increased liver weights (14 d study rats) and the BMDL05 of 42 ppm for adenoma in the nose of male rats (2 year study) (Hartwig, 2013). For this substance we additionally refer to positive results for *in vivo* micronucleus tests, as reported by EPA (EPA, 2012).

5.15.5 Assessment, discussion and conclusions

Iso-Propylbenzene (cumene)

For iso-propylbenzene, SCOEL concluded that the 90 day study conducted at the Bushy Run Research Center in 1989 was the best available basis for deriving an OEL. A NOAEC of 500 mg/m³ was established for CNS effects which resulted in the OEL of 100 mg/m³ after consideration of an uncertainty factor of 5 (SCOEL, 1993). Other assessments e.g. by OECD and the European Union concluded practically the same (ECB, 2001; OECD, 1996). However, the scientific committee is currently revisiting this assessment. According to AGW methodology an OEL of 50 mg/m³ would result based on the CNS effects observed (AF10 = $5_{variability}$*$2_{sc\text{-}c}$). Because a default assessment based on the AGW methodology would not significantly differ from the SCOEL assessment, it is not shown in Figure 5-8.

Within the EPA IRIS a reference concentration (RfC) 0.4 mg/m³ is presented. As basis a NOAEL (human equivalent concentration - HEC) of 435 mg/m³ was used and a standard assessment factor of 1000 was applied. Effects underpinning the NOAEL were increased kidney weights in female rats and adrenal weights in male and female rats from the 13 week toxicity study by Cushman et al. (1995; EPA, 2014, date of access: 05-DEC-2014). Consequently, an OEL of 22 mg/m³ would be derived here (AF20 = $5_{variability}$*$2_{6h\text{-}8h}$ *$2_{sc\text{-}c}$). Because this OEL is in good agreement with a number of other OELs already presented in Figure 5-8, it is not explicitly presented in this graph.

Key studies in the REACH registration dossier for iso-propylbenzene presented a NOAEC = 625 mg/m³ for rats and mice from 90 day inhalation toxicity studies (6 h whole body exposure per day; effect in rats: haematology, clinical chemistry, organ weights; mice: absolute organ weights, body weight gain). Results of the 2-year carcinogenicity studies on rats and mice were also presented. With a LOAEC of 250 ppm for adenoma in respiratory epithelium and adenoma and carcinoma in renal tubule of rats and a LOAEC of 125 ppm for alveolar/bronchiolar adenoma or carcinoma of mice (ECHA, 2014). Extrapolated OEL values

would be in the range of approximately 31 mg/m³ from the 90 day studies (AF20 = $5_{variability}*2_{6h-8h}*2_{sc-c}$), and 42 or 21 mg/m³ from the 2-year carcinogenicity studies for rats and mice, respectively, if a default AGW assessment was used instead of a ERB assessment for carcinogenic risk (AGS, 2014). Because this OEL is in good agreement with a number of other OELs already presented in Figure 5-8, it is not explicitly presented in this graph.

Various assessments of iso-propylbenzene focused on local irritation of the respiratory tract (nasal epithelium) leading to adenoma as the critical effect identified in the 2-year carcinogenicity study performed by the NTP. Differences in PODs thus lead to corresponding OELs in the range of 21 to 37 mg/m³ (German MAK commission: BMCL05 = 42 ppm (210 mg/m³) → AF10 = $5_{variability}*2_{6h-8h}$ → OEL = 21 mg/m³).[4] This assessment has a very similar starting point (POD) as the one by the German indoor commission (Ad-hoc-AG, 2012), who derived from the NTP data a BMCL10 of 370 mg/m³ for cumene.

Trimethylbenzenes

For trimethylbenzenes, the assessment conducted by SCOEL used the preferred value approach and established the OEL of 100 mg/m³. Background was the long-term inhalation toxicity data on rats (NOAEC 825 mg/m³ (165 ppm) according to mixture studies Clark et al. 1989 and Shell study 1982; uncertainty factor of 5 applied) (SCOEL, 1994). Because a default assessment based on the AGW methodology would not significantly differ from the SCOEL assessment, it is not shown in Figure 5-8.

The German ad hoc working group for indoor air guideline values derived also a reference concentration for trimethylbenzenes based on Korsak et al. (2000a; respiratory toxicity, LOAEC = 490 mg/m³, subchronic, 6 h/d), which corresponds to an OEL of 8 mg/m³ (AF60 (=$5_{variability}*2_{sc-c}*2_{6h-8h}*3_{LOAEC-NOAEC}$)).

For exceedance factor of the derived MAK value for TMBs increased latency time for reaction to thermic irritation (hot plate test) and failure in performance of the Rotarod experiment identified by Korsak and Rydzynski (1996) in a 90 d inhalation toxicity study with rats was the critical finding. The NOAEC was 25 ppm for 1,2,4-TMB or 100 ppm for 1,2,3-TMB (i.e. approximately 125 or 500 mg/m³, respectively, with resulting potential OELs of 6.25 or 25 mg/m³; AF20 = $5_{variability}*2_{6h-8h}*2_{sc-c}$) (Greim, 2001). Because this OEL is in good agreement with a number of other OELs already presented in figure Figure 5-8, it is not explicitly presented in this graph.

For derivation of the MAK value the critical effect assessed (study was cited as API 1989) were delayed body weight gains in juvenile rats of a 3-generation toxicity study. Animals were exposed for 12 to 15 weeks with a C9 aromatic hydrocarbon mixture[5] (6h/d, each day of the week; 0; 103; 495; 1480 ppm). The LOAEC identified was 103 ppm (approximately 500 mg/m³) (Greim, 1998), consequently leading to an OEL of approximately 17 mg/m³ (AF30 = $5_{variability}*2_{6h-8h}*3_{LOAEC-NOAEC}$).

[4] Note: increased liver weights not considered for derivation as controversial discussion on adversity ongoing German commission on air quality (indoor): BMCL10 of 370 mg/m³ → AF10 = $5_{variability}*2_{6h-8h}$ → OEL = 37 mg/m³

[5] Mixture contained 40,5 % 1,2,4-TMB, 8,37 % 1,3,5-TMB, 6,18 % 1,2,3-TMB, 2,74 % Cumene, 3,2 % o-Xylene, 3,97 % n-Propylbenzene, 7,05 % 4-Ethyltoluene, 15,1 % 3-Ethyltoluene, 5,44 % 2-Ethyltoluene, 6,19 % >= C10 → total TMB content = 55 %, thus NOAEC TMBs = 57 ppm (~ 285 mg/m³)

Re-evaluation of this study by McKee et al. (1990) mentioned that the effects seen at the 495 ppm group and even on the high dose group 1480 ppm were only 'transient and had no postnatal consequences, if maternal exposure was terminated at any time prior to delivery.'

However in a draft document for derivation of Reference concentrations (RfC) for the trimethylbenzenes US EPA (EPA, 2013) used the same effect as MAK (decreased pain sensitivity identified in from Korsak and Rydzynski (1996)) as they stated that a multitude of studies supports the critical neurotoxicological effect induced by TMBs (e.g. Gralewicz and Wiaderna, 2001; Gralewicz et al., 1997; Wiaderna et al., 1998). Based on the PBPK model by Hissink et al. (2007) and a BMDL of one standard deviation human equivalent concentrations (HECs) of 15.68 mg/m³ for 1,2,4-TMB and 16.3 mg/m³ 1,2,3-TMB were calculated from the results of the subchronic exposure experiment. Starting from these low HECs OELs of around 0.8 mg/m³ would result (AF20 = $5_{variability}$*$2_{6h\text{-}8h}$*$2_{sc\text{-}c}$). Because this OEL is even lower than a number of other low OELs already presented in Figure 5-8, it is not explicitly presented in this graph.

REACH Registration dossiers for 1,2,4- and 1,3,5-TMB are available (ECHA, 2014). As key studies for repeated inhalation exposure both present the same studies, i.e. the mixture study (one year exposure) by Clark et al. (1989)[6] and most probably the results from the 90 day studies by Korsak (2000a; b) are presented.

The NOAEC of this one year toxicity study by Clark et al. according to OECD 452 was > 806 mg/m³ (6 h/d; i.e. the highest concentration tested as the authors stated no adverse effects (but initial reduction of body weight, transient haematological changes, liver and kidney weights increased in males); calculated for TMB-content from C9 concentration 1800 mg/m³ from nominal 125 ppm; 50:50 blend of SHELLSOL A and SOLVESSO 100 (containing 44.81% TMBs (32.7% 1,2,4-TMB)).

The studies by Korsak for either 1,2,4- or 1,3,5-TMB each identified a NOAEC = 1230 mg/m³ (90d study rats, 6 h exposure per day) as no relevant systemic toxicity was observed. Based on these studies a DNEL of 100 mg/m³ was established for workers in the registration dossier. An OEL derived from the C9/C10 aromatics mixture by Clark is ≥ 180 mg/m³ (AF10 = $5_{variability}$*$2_{6h\text{-}8h}$) and ≥ 61.5 mg/m³ from the subchronic toxicity studies (AF20 = $5_{variability}$*$2_{6h\text{-}8h}$*$2_{sc\text{-}c}$). Note that no investigation of neurotoxic effects was included in these studies. This OEL is not shown in Figure 5-8, below.

In Korsak et al. (1997) RD50 values of 578, 519, and 541 ppm were identified in mice for 1,2,4-TMB, 1,3,5-TMB, and 1,2,3-TMD, respectively. Based on these effects the authors stated that a 'threshold limit value of at least 10 ppm should be considered for the occupational exposure to trimethylbenzene isomers'. According to the traditional extrapolation to estimate an OEL based on sensory irritation in mice studies an extrapolation factor of 30 is applied. This leads to potential OELs in the range of 85-95 mg/m³. However, the assessment based on RD50 has been critisised (Bos et al., 2002) and provides only supportive evidence. These OELs are not shown in Figure 5-8, below.

Evaluation of recent data showed that based on the NOAEC of 1250 mg/m³ for 1,2,4-TMB identified for neurobehavioural effects (FOB, motor activity and visual discrimination testing) in rats after acute exposure (3 times for 8 h) by McKee and colleagues (2010). The results for the C9 aromatic solvent were similar to that observed for 1,2,4-TMB with slight differences.

[6] Mixture contained < 2.5 % C8 aromatics, ~80 % C9 aromatics and ~8.5 % C10 aromatics

For the C9 aromatic mixture the NOAEC identified for FOB and motor activity was in the same range (1000 mg/m³), but visual discrimination testing revealed effects at lower concentrations (NOAEC = 200 mg/m³). For C10/C11 mixture effects were slightly less pronounced (for details see 5.16). Corresponding OELs would be 250 mg/m³ for 1,2,4-TMB and 40 mg/m³ for the C9 aromatic mixture (AF5 = $5_{variability}$).

There is ongoing discussion on the adversity of liver effects seen in a study published by Adenuga et al. (2014). For this assessment, a NOAEL of ≥ 600 mg/kg bw x d (oral exposure pathway) was adapted to an inhalation no-adverse-effect-concentration of ≥ 1050 mg/m³ (assumptions: 4: allometric scaling rat; 70 kg body weight, 10 m³ respiratory volume during light activity of worker in 8 h shift), which would then result in a OEL of ≥ 100 mg/m³ (AF10 = $5_{variability}$*$2_{sc\text{-}c}$).

a) other isomers/ C9 aromatic hydrocarbon solvents

The ototoxic effect of **n-propylbenzene** identified in a two week oral gavage study with rats at a dose of 8.47 mmol/kg bw x d (i.e. 1020 mg/kg bw x d with a molecular weight of 120.2 mg/mmol) can be adapted to an inhalation concentration with the same assumptions as above. The effect concentration would be 1785 mg/m³, which results in a OEL of 60 mg/m³ (AF30 = $5_{variability}$*$6_{sa\text{-}c}$). Note that other members of this group did not reveal ototoxic activity, at least at this concentration tested (Gagnaire and Langlais, 2005). This extrapolated OEL is not shown in Figure 5-8, below.

From a rat 90 day day inhalation toxicity study a NOAEL of 1500 mg/m³ **1-Methyl-4-ethylbenzene** (EPA, 2009) was reported (based on changes in organ weights at the 4800 mg/m³ concentration). Using the foreseen assessment factors as described in the methodology section an OEL of 75 mg/m³ would results from these data (AF20 = $5_{variability}$*$2_{6h\text{-}8h}$ *$2_{sc\text{-}c}$). Note: In rabbits developmental effects were observed at 25 mg/kg bw x d, whereas maternal toxicity was observed only at 250 mg/kg bw x d (NOAEL = 200 mg/kg bw x d).

In the study by Swiercz et al. (2000) with 1-Methyl-4-ethylbenzene a RD50 value of 4216 mg/m³ in mice was established. According to default assessment an OEL of 140 mg/m³ would thus result (AF30), but OELs derived from RD50 values are only supporting evidence. This extrapolated OEL is not shown in Figure 5-8, below.

After exposure of rats (6h/d, 5d/w, 4 weeks) to 1-Methyl-4-ethylbenzene vapours a NOAEC of 477 mg/m³ was found (LOAEC = 2337 mg/m³ with increased bronchitis and pneumonia and perivascular lymphoid infiltrations). The resulting OEL is approximately 24 mg/m³ (AF20 = $5_{variability}$*$2_{6h\text{-}8h}$ *$2_{sc\text{-}c}$). This extrapolated OEL is not shown in Figure 5-8 below.

Conclusions

On the basis of the presented data above resulting OELs for members of the C9 aromatic hydrocarbon groups are in the range of 0.8 to 180 mg/m³. Neurotoxicological effects are most critical with OELs of 0.8 to 50 mg/m³ for TMBs and iso-propylbenzene. It is obvious that there is a discrepancy in interpretation of the effects observed in the Korsak studies as performed by different regulatory bodies and industry. The derived values for iso-propylbenzene on basis of CNS effects and 1-Methyl-4-ethylbenzene for general systemic

effects suggest a reduction of the currently existing GGV from 100 to 50 mg/m³. Volunteer studies as presented by industry (Jarnberg et al., 1996; 1997; Jones et al., 2006; Kostrzewski et al., 1997) found no evidence for acute CNS effects, respiratory irritation or clinical findings following exposure for 4-8 hours at levels of ≤ 150 mg/m^3. With a reduced variability factor of 3 values these studies would support an OEL of 50 mg/m³. Because of the many studies and assessments, not all of those potential OELs can be shown in Figure 5-8, below. However, the graphical presentation of some example extrapolations demonstrates the range of resulting OELs in comparison to the current GGV.

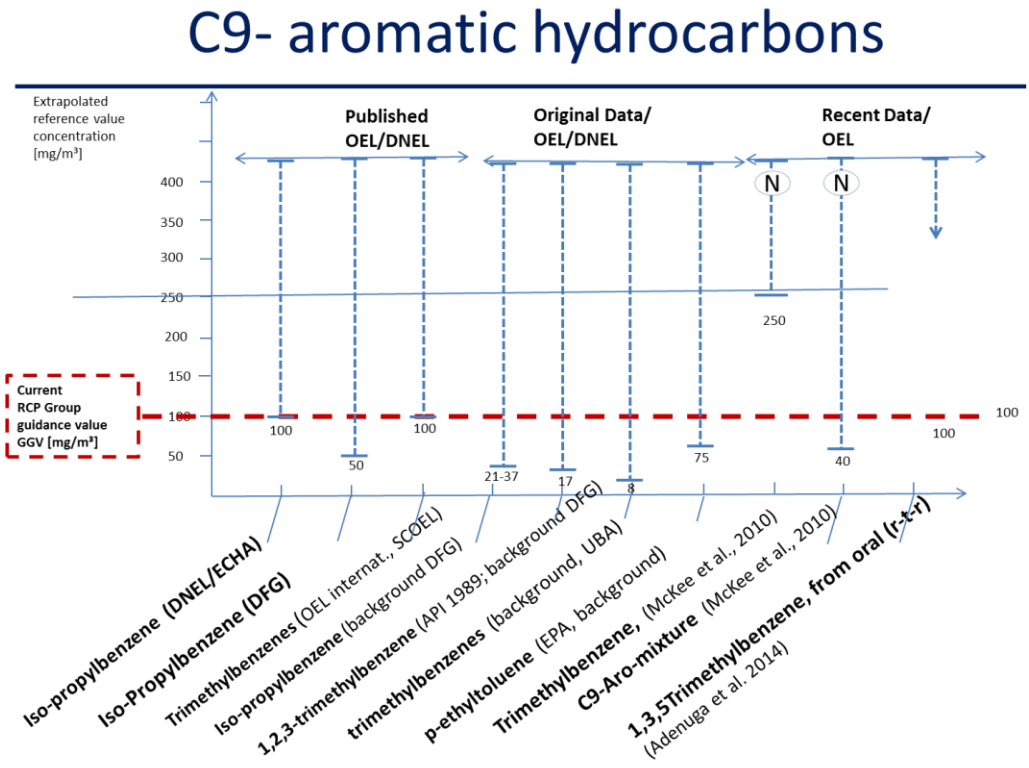

Figure 5-8: Schematic illustration of potential OELs for C9 aromatic hydrocarbon solvents (see Figure 4-2 for legend and comments in text)

5.16 C10- Aromatic Hydrocarbon Solvents

5.16.1 Assigned group guidance value (RCP, German approach, TRGS 900)

For the group of C9-C15 aromatics currently in Germany the group guidance value is 100 mg/m³ (AGS, 2012).

5.16.2 Substance Search

We searched for experimental or epidemiological data on the substances:

- Tetralin (Tetrahydronaphthalene) (CASRN: 119-64-2)

- Methylindene (CASRN: 824-63-5)
- 1,2,3,4-Tetramethylbenzene (Prenitene, 1,2,3,4-TETMB) (CASRN: 488-23-3)
- 1,2,3,5-Tetramethylbenzene (Isodurene, 1,2,3,5 -TETMB) (CASRN: 527-53-7)
- 1,2,4,5-Tetramethylbenzene (Durene, 1,2,4,5 -TETMB) (CASRN: 95-93-2)
- Isobutylbenzene (CASRN: 538-93-2)
- 1-Methyl-2-propylbenzene (CASRN: 1074-17-5)
- 1,3-Diethylbenzene (1,3-DEB) (CASRN: 141-93-5)
- 1,4-Diethylbenzene (1,4-DEB) (CASRN: 105-05-5)
- 1-Methyl-4-propylbenzene (CASRN: 1074-55-1)
- 1-Methyl-3-propylbenzene (CASRN: 1074-43-7)

Several substances were already excluded from group guidance values and therefore no detailed substance search was performed and assessments were not further discussed:

- Naphthalene (CASRN: 91-20-3)
- 1,2-Diethylbenzene (CASRN: 135-01-3)

5.16.3 Existing OEL or equivalent derived reference values (workers)

Substance	Type reference value	mg/m³	source
Naphthalene	AGW analogue threshold (Germany)	0.5 mg/m³ (0.1 ppm) inhalable aerosol*	(AGS, 2006; BMAS, 2014)
	DNEL (Europe)	25 mg/m³**	(ECHA, 2014)
	OEL (various countries)	50 mg/m³	(IFA, 2014)
Tetrahydronaphthalene	MAK (Germany)	11 mg/m³ (2 ppm)*	(DFG, 2014)
	DNEL (Europe)	2.1 mg/m³	(ECHA, 2014)
1,4-Diethylbenzene	DNEL (Europe)	8.82 mg/m³	(ECHA, 2014)

* With no exceedance factor: short term value is the same as long-term value; ** national OELs (EU and USA) of generally 50 mg/m³ based on human experience with assessment factor 2

However, as stated above, naphthalene is currently exempted from GGV.

5.16.4 Recent Data

- Neurobehavioural effects after acute exposure (3 times for 8 h) to mixed isomer C10/C11 aromatic solvent (results for 1,2,4-TMB and C9 aromatic solvent see 5.15) in rats were investigated by McKee and colleagues (2010). The NOAEC identified for C10/C11 was 600 mg/m³. The results for the C10/C11 aromatic solvent were in general similar, but slightly less pronounced than that observed for C9 aromatic solvent.
- In a 28 d oral gavage study with rats thyroid dysfunction was observed given 1,3-diethylbenzene. Effects were found in all exposed groups, resulting a LOAEL of 10 mg/kg bw x d (Yamasaki et al., 2012).

- In a 2-Generation reproductive toxicity study with n-butylbenzene a threshold of 30 mg/kg bw x d in rats (Izumi et al., 2005; increased liver and kidney weights with histopathological changes at 100 and 300 mg/kg bw/d).

In addition, some recent studies on 1,2,3,5- and 1,2,4,5-TETMB by Jalowiecki and Janasik (2007; based on inhalation exposure of four male volunteers), on 1,3- or 1,4-DEB (Gagnaire and Boucard, 2014) and on the ototoxic potential of various aromatic hydrocarbon solvents (Gagnaire and Langlais, 2005) were found, but could not be used for OEL derivation.

5.16.5 Assessment, discussion and conclusions

Tetralin (tetrahydronaphthalene)

In the registration dossier for tetralin (tetrahydronaphthalene) a 90 d inhalation toxicity study (whole body exposure, 6 h/d) identified a NOAEC of 15 ppm (82.4 mg/m³) for nasal lesions in rats. Further results of NTP carcinogenicity studies in rats and mice are reported (2-years exposure, 6 h/d). The study in rats being positive, but no carcinogenic effects were observed in mice. No carcinogenicity was detected at 330 mg/m³ for rats and > 660 mg/m³ (i.e. highest dose tested) for mice. In rats and mice the LOAEC for non-neoplastic local effects in the nose was 165 mg/m³ (rats: significantly elevated incidences of olfactory epithelium degeneration, basal cell hyperplasia, metaplasia, and suppurative inflammation in all exposed groups compared to controls; mice: significantly elevated incidences of glandular hyperplasia, olfactory epithelium atrophy, and respiratory metaplasia in exposed groups compared to controls). A DNEL of 2.1 mg/m³ was reported (ECHA, 2014). Based on the methodology of this report OELs in the range of 4 to 5.5 mg/m³ would be derived (90 d study: AF20 = $5_{variability}$*$2_{6h\text{-}8h}$ *$2_{sc\text{-}c}$; 2-year studies: AF30 = $5_{variability}$*$2_{6h\text{-}8h}$ *$3_{LOAEC\text{-}NOAEC}$).

For the MAK value of tetralin the same studies were presented as given in the REACH registration dossier. Target organs identified were liver, kidney and after inhalation respiratory tract. With a NOAEC of 7.5 ppm for increased liver weights in female rats, in a 14 d as well as 90 d study thus we do not assume an increase of effect size with time with a NOAEC of 15 ppm for inflammation of olfactory epithelium (90 d study rats). Both NOAECs lead to MAK value of 2 ppm (according to preferred value approach, as BMDL modelling of 2 year carcinogenicity study is not possible) (Hartwig, 2013).

Tetramethylbenzene

For 1,2,4,5-TETMB for sensory irritation a RD50 value of 838 mg/m³ was identified, which would lead to an OEL of approximately 28 mg/m³ (Korsak et al., 1998; leading to proposed OEL of 25 mg/m³ in Poland) (leading to proposed OEL of 25 mg/m³ in Poland). We are aware, that OELs based on RD50 are associated with relevant uncertainties.

1,3-diethylbenzene

In the absence of repeated dose inhalation toxicity data for most of the substances oral toxicity studies were further evaluated. Having the oral toxicity study by Yamasaki et al. (2012) with a LOAEL of 10 mg/kg bw x d on 1,3-diethylbenzene for thyroidal dysfunction, an adaption to inhalation exposure has to be performed (route-to-route extrapolation; assumptions: 4: allometric scaling rat; 70 kg body weight, 10 m³ respiratory volume during light activity of worker in 8 h shift → LOAEC = 17.5 mg/m³), which would then result in an OEL of 0.6 mg/m³ (AF30 = $5_{variability}$*$2_{sc\text{-}c}$ *$3_{LOAEC\text{-}NOAEC}$).

1,4-diethylbenzene

In a Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test (OECD TG 422) in rats with oral gavage application a NOAEL of 30 mg/kg bw x d (effects in liver and kidney weights with histopathological findings in the high dose group) for 1,4-diethylbenzene was derived (ECHA, 2014; OECD, 1994). For 1,4-DEB besides the effects reported in OECD (1994) for the Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test with rats, in the REACH registration dossier further effects described were: in male rats increased BUN and GPT at 150 and 750 mg/kg x d; increases in total protein albumin, creatinine and total bilirubin, decrease in glucose at doses of 750 mg/kg x day and increase in kidney weight at 150 and 750 mg/kg x day; brown coloured livers and swelling of liver cells at 750 mg/kg bw x d. In male and female rats the effects observed were increase in liver weights at 750 mg/kg x day. Overall the NOAEL of 30 mg/kg bw x d was confirmed. With this NOAEL after adaption to inhalation (route-to-route extrapolation) as described above, an OEL of 5.25 mg/m³ would result (AF10 = $5_{variability}$*$2_{sc\text{-}c}$). Adaption to inhalation and correction of starting dose as referred to for DNEL derivation in the registration dossier (corrected NOAEC $_{Inhalation}$ = ($NOAEL_{oral}$/vSR_{rat}) * (vSR_{human}/$vWSR_{human}$) * ABS_{oral}/ABS_{inh} = (30/0.38) * (6.7/10) * (90/30) = 158.7 mg/m³. Based on the toxicokinetics assessment ABS_{oral} = 90 % and $ABS_{inhalation}$ = 30 %) would yield a slightly higher OEL of 15.8 mg/m³ (AF10 = $5_{variability}$*$2_{sc\text{-}c}$).

n-butylbenzene

A recent literature search did not confirm the findings that led to exclusion of this substance from RCR grouping in the existing version. However, the study by Izumi et al. (2005) provided a NOAEL of 30 mg/kg x d that corresponds to an OEL of ≤ 10 mg/m³ applying the default procedure.

C10/C11 mixtures and unspecified

In the acute exposure study by McKee and colleagues (2010; 3 times for 8 h), the NOAEC identified for C10/C11 was 600 mg/m³ based on FOB and visceral discrimination testing, thus leading to an OEL of 120 mg/m³ (AF5 = $5_{variability}$). The results for the C10/C11 aromatic solvent were in general similar, but slightly less pronounced than that observed for C9 aromatic solvent.

In the OECD SIDS document for C10-C13 Aromatic Hydrocarbon Solvents Category (OECD, 2012d) a 90 d repeated dose oral gavage study with a C10-C13 aromatic hydrocarbon solvent (CASRN 64742-94-5) is mentioned. 10 rats/sex/group including a 28 d satellite group, were exposed to 0, 300, 600 and 1200 mg/kg bw x d. The NOAEL identified was 300 mg/kg bw x d. After adaption to inhalation exposure (route-to-route extrapolation) and application of assessment factors (AF10 = $5_{variability}$*$2_{sc\text{-}c}$) an OEL of 52.5 mg/m³ is calculated.

Conclusions

Because of the classification as a carcinogen, naphthalene has been exempted from the GGV on ≥ C9 aromatic hydrocarbon solvents before.

In addition, 1,2-diethylbenzene has been exempted before because of the peripheric neuropathic effects resulting from metabolite 1,2-diacetylbenzene (low DNEL; 8,8 mg/m³) (Gagnaire et al., 1992; Gagnaire and Boucard, 2014; Gagnaire et al., 1990; Spencer et al., 2002).

As the other diethylbenzene isomers also are associated with similarly low DNELs (1,4-Dichlorbenzene) or similarly low OELs would be derived based on recent data (1,3-diethylbenzene), we propose to exempt all diethylbenzene isomers.

In addition, n-butylbenzene was exempted before. Based on the derived OEL of ≤ 10 mg/m³ the exemption of n-butylbenzene to the group of ≥C9 aromatic hydrocarbon solvents has to be maintained, if a) no (more appropriate) inhalation data are found that invalidate the derived OEL, and/or b) not only insignificant amounts of n-butylbenzene are present in ≥C9 aromatic hydrocarbon solvent mixtures.

However, we have not decided on a SSV for these substances and on the cut off criterion (irrelevant contributions) for all substances exempted from GGV mentioned above (naphthalene, dichlorobenzenes, n-butylbenzene) within this project.

The very limited data for C10 aromatic hydrocarbon solvents still covered in this group do not contradict the GGV derived from C9 compounds (50 mg/m³). Even though there appears to be an increased margin of safety, if just the neurotoxicity study by McKee et al. (2010) is considered, there remain relevant uncertainties because of the exemption of several C10 aromatic hydrocarbon solvents from this group, without a sufficient understanding, why those substances (1,3- diethylbenzene, 1,4-diethylbenzene and n-butylbenzene) would act via a distinct mode of action. Some potential for sensory irritation may have to be considered (TETMB), which supports a GGV of 50 mg/m³.

5.17 C11- Aromatic Hydrocarbon Solvents

5.17.1 Assigned group guidance value (RCP, German approach, TRGS 900)

For the group of C9-C15 aromatics currently in Germany the group guidance value is 100 mg/m³ (AGS, 2012).

5.17.2 Substance Search

We searched for experimental or epidemiological data on the substances:

- 2-Methylnaphthalene (CASRN: 91-57-6)
- 1-Methylnaphthalene (CASRN: 90-12-0)
- Methyltetralin (CASRN: 3877-19-8)
- 1,2,3,4,5-Pentamethylbenzene (CASRN: 700-12-9)
- n-Pentylbenzene (amylbenzene) (CASRN: 538-68-1)
- Butyltoluene (CASRN: 22458-20-4; 98-51-1)

5.17.3 Existing OEL or equivalent derived reference values (workers)

Substance	Type reference value	mg/m³	source
All single substances above	AGW (Germany)	No OEL values for	(AGS, 2006; BMAS, 2014)
	MAK (Germany)		(DFG, 2014)

	DNEL (Europe)	specific substances derived	(ECHA, 2014)
2-methylnaphthalene (also for 1-methylnaphthalene)	OEL (Belgium)	3 mg/m³	(IFA, 2014) lowest
2-methylnaphthalene	OEL (Poland)	25 mg/m³	(IFA, 2014)

5.17.4 Recent Data

- For 2-methylnaphthalene a 28 d inhalation study on rats was performed (6 h/d, 5 d/week, 4 weeks) and a NOAEC = 2 mg/m³ identified (Świercz et al., 2011).
- Neurobehavioural effects after acute exposure (3 times for 8 h) to mixed isomer C10/C11 aromatic solvent (results for 1,2,4-TMB and C9 aromatic solvent see 5.15) in rats were investigated by McKee and colleagues (2010). The NOAEC identified for C10/C11 aromatic hydrocarbon solvents was 600 mg/m³. The results for the C10/C11 aromatic solvent were in general similar, but slightly less pronounced than that observed for C9 aromatic solvent.
- A four weeks' inhalation study (7d/w; 6h/d) analysing neurotoxic effects of 4-tert-butyltoluene found no overt neurotoxic effects in rats after exposure to 20 ppm (240 mg/m³). However, some neurochemical parameters in brain had been changed even five month after termination of the study (Lam et al., 2000).

No further relevant studies were found and no full registration dossiers including relevant data are available according to REACH (ECHA, 2014).

5.17.5 Assessment, discussion and conclusions

Existing data and assessments including the recent 28d inhalation study (Świercz et al., 2011) lead to exclusion of 2-methylnaphthalene from GGV. For 1-methylnaphthalene, no sufficient isomer-specific data are available. However, as oral application of 1-methylnaphtalene caused severe effects after repeated oral exposure at low doses (ATSDR, 2005), we propose to also exclude 1-methylnaphthalene from GGV. However, we have not decided on a SSV for methylnaphthalenes and on the cut off criterion (irrelevant contributions) for these substances to be exempted from GGV.

Recent neurotoxicity data for C10/C11 aromatics identified a NOAEC of 600 mg/m³ (McKee et al., 2010), which is extrapolated to an OEL of 120 mg/m³.

Respiratory depression of amylbenzene in mice (RD50) was observed at 1416.8 mg/m³ (Nielsen and Alarie, 1982). By pragmatic extrapolation by a factor of 30 to address sensory irritation this would result in an OEL of 47 mg/m³. However, such an extrapolation would only provide supportive evidence.

Amylbenzene is also associated with relevant ototoxicity (much more than most other aromatic hydrocarbon solvents). However, there has been no adequate test after inhalation exposure (Gagnaire and Langlais, 2005). Therefore the impact on the OEL estimate may currently not be estimated.

For 4-tert-butyltoluene a NOAEC of 240 mg/m³ (subacute exposure; for 5d/w instead of 7d/W: POD 336 mg/m³) supports an OEL well below 30 mg/m³ (AF10 = $5_{variability}$*$2_{6h\text{-}8h}$ *>$1_{subacute\text{-}chronic}$). However, as there were no clear adverse effects identified, there is a relevant uncertainty on the NOAEC.

The very limited data for C11 aromatic hydrocarbon solvents covered in this group do not contradict the GGV derived from C9 compounds (50 mg/m³). Even though there appears to be an increased margin of safety, if just the neurotoxicity study by McKee et al. (2010) is considered, relevant uncertainties remain because of the exemption of several C10 and C11 aromatic hydrocarbon solvents from this group, without a sufficient understanding, why those substances would act via a distinct mode of action. Some potential for sensory irritation may have to be considered (amylbenzene) (Nielsen and Alarie, 1982), which supports a GGV of 50 mg/m³.

5.18 C12-Aromatic Hydrocarbon Solvents

5.18.1 Assigned group guidance value (RCP, German approach, TRGS 900)

For the group of C9-C15 aromatics currently in Germany the group guidance value is 100 mg/m³ (AGS, 2012).

5.18.2 Substance Search

We searched for experimental or epidemiological data on the substances:

- Acenaphthene (CASRN: 83-32-9)
- Acenaphthylene (CASRN: 208-96-8)
- Biphenyl (CASRN: 92-52-4)
- 1,2-Dimethylnaphthalene (CASRN: 573-98-8)
- 2,6-Dimethylnaphthalene (CASRN: 581-42-0)
- 2,7-Dimethylnaphthalene (CASRN: 582-16-1)
- 2-Ethylnaphthalene (CASRN: 939-27-5)
- 2,3-Dimethylnaphthalene (CASRN: 581-40-8)
- 1-Ethylnaphthalene (CASRN: 1127-76-0)
- 2,4-Dimethylnaphthalene (CASRN: 575-41-7)
- 1,4-Dimethyltetralin (CASRN: 4175-54-6)
- Ethyltetralin (CASRN: 32367-54-7)
- 1,2,3-Triethylbenzene (CASRN: 42205-08-3)
- 1,2,4-Triethylbenzene (CASRN: 877-44-1)
- 1,2,3,4,5,6-Hexamethylbenzene (CASRN: 87-85-4)
- n-Hexylbenzene (CASRN: 1077-16-3)

and for C12 aromatic hydrocarbons as such.

5.18.3 Existing OEL or equivalent derived reference values (workers)

Existing OEL or equivalent derived reference values (workers)Substance	Type reference value	mg/m³	source
Biphenyl	AGW (Germany)	-	(AGS, 2006; BMAS, 2014)
	MAK (Germany)	-	(DFG, 2014)
	DNEL (Europe)	11.17	(ECHA, 2014)
	OEL (USA-OSHA, NIOSH and various other countries)	1	(IFA, 2014)

5.18.4 Recent Data

No further relevant studies were found.

5.18.5 Assessment, discussion and conclusions

Biphenyl

For biphenyl very low OELs are reported. The substance should be exempted from GGV.

Acenaphthene

Acenaphthene is a suspect carcinogen with a NOAEL (28d, oral) of 12 mg/kg x d for nonneoplastic effect, which results in a very low OEL applying the default extrapolation factors (in combination with route-to-route extrapolation). Therefore acenaphthene should be exempted from GGV.

Acenaphthylene

Acenaphthylene is a suspect carcinogen with an elevated cancer risk at exposures at and below 1 mg/m³. Therefore acenaphthylene should be exempted from GGV.

1,2,4-Triethylbenzene

1,2,4-triethylbenzene is currently excluded from GGV in the existing version of RCP in Germany due to peripheric neuropathic effects at low concentrations (Gagnaire et al., 1993; Spencer et al., 2002; Tshala-Katumbay et al., 2006). The substance should remain excluded from GGV (≥ C9 aromatic hydrocarbon solvents).

Hexylbenzene

In a mouse study respiratory depression after exposure to hexylbenzene was observed at 843.75 mg/m³ (Nielsen and Alarie, 1982). By pragmatic extrapolation by a factor of 30 to address sensory irritation this would result in an OEL of 28 mg/m³. However, such an extrapolation would only provide supportive evidence.

Conclusion:

We have not decided on a SSV and on the cut off criterion (irrelevant contributions) for the substances exempted from GGV mentioned above (biphenyl, acenaphthene, acenaphthylene, 1,2,4-triethylbenzene) within this project.

No further specific data were found. Despite relevant uncertainty, we propose to apply the OEL for C9 aromatic hydrocarbon solvents also for the remaining C12 fraction. Sensory irritation observed with hexylbenzene supports an OEL of ≤ 50 mg/m³ for C12 compounds.

5.19 C13-Aromatic Hydrocarbon Solvents

5.19.1 Assigned group guidance value (RCP, German approach, TRGS 900)

For the group of C9-C15 aromatics currently in Germany the group guidance value is 100 mg/m³ (AGS, 2012).

5.19.2 Substance Search

We searched for experimental or epidemiological data on the substances:

- Fluorene (CASRN: 86-73-7)
- 2-iso-Propylnaphthalene (CASRN: 2027-17-0)
- 4-Methylbiphenyl (CASRN: 644-08-6)
- 1-Propylnaphthalene (CASRN: 2765-18-6)
- 1,2,4-Trimethylnaphthalene (CASRN: 2717-42-2)
- 1,2,5-Trimethylnaphthalene (CASRN: 641-91-8)
- n-Heptylbenzene (CASRN: 1078-71-3)

5.19.3 Existing OEL or equivalent derived reference values (workers)

Substance	Type reference value	mg/m³	source
All single substances above	AGW (Germany)	No OEL values for specific substances	(AGS, 2006; BMAS, 2014)
	MAK (Germany)		(DFG, 2014)
	DNEL (Europe)		(ECHA, 2014)
	OEL		(IFA, 2014)

5.19.4 Recent Data

Fluorene was applied to rats in a subacute inhalation study (nose only) with either 0, 0,01 or 1 mg/m³ of the substance. No adverse neurobehavioural effects were observed, but the data support, that the higher concentration was close to the NOAEC (1 mg/m³).

No further relevant studies were found.

5.19.5 Assessment, discussion and conclusions

Fluorene is a suspect carcinogen and causes neurobehavioral effects in subacute exposure in experimental animals at concentrations above 1 mg/m³ (NOAEC) (Peiffer et al., 2013). The substance should therefore be excluded from GGV (≥ C9 aromatic hydrocarbon solvents).

We have not decided on a SSV and on the cut off criterion (irrelevant contributions) for fluorene to be exempted from GGV. No further specific data were found. Despite relevant uncertainty, we propose to apply the OEL for C9 aromatic hydrocarbon solvents also for the remaining C13 fraction.

5.20 C14- Aromatic Hydrocarbon Solvents

5.20.1 Assigned group guidance value (RCP, German approach, TRGS 900)

For the group of C9-C15 aromatics currently in Germany the group guidance value is 100 mg/m³ (AGS, 2012).

5.20.2 Substance Search

We searched for experimental or epidemiological data on the substances:

- Anthracene (CASRN: 120-12-7)
- Phenanthrene (CASRN: 85-01-8)
- 4-Ethylbiphenyl (CASRN: 5707-44-8)
- 2-Butylnaphthalene (CASRN: 1134-62-9)
- 1-Butylnaphthalene (CASRN: 1634-09-9)
- n-Octylbenzene (CASRN: 2189-60-8)

5.20.3 Existing OEL or equivalent derived reference values (workers)

Substance	Type reference value	mg/m³	source
All single substances above	AGW (Germany)	No OEL values for specific substances derived	(AGS, 2006; BMAS, 2014)
	MAK (Germany)		(DFG, 2014)
	DNEL (Europe)		(ECHA, 2014)
	OEL		(IFA, 2014)

5.20.4 Recent Data

No further relevant studies were found.

5.20.5 Assessment, discussion and conclusions

Specifically, we did not find sufficient data on inhalation toxicity of Anthracene. However, EU (2008)[7] does not regard such studies to be necessary, because oral toxicity has been shown to be low (NOAEC 1000 mg/kg x d). There is no indication to support an exclusion of Anthracene from GGV. No further specific data were found (only data with mixtures, see section 6). Despite relevant uncertainty, we propose to apply the OEL for C9 aromatic hydrocarbon solvents also for the remaining C14 fraction.

5.21 C15- Aromatic Hydrocarbon Solvents

5.21.1 Assigned group guidance value (RCP, German approach, TRGS 900)

For the group of C9-C15 aromatics currently in Germany the group guidance value is 100 mg/m³ (AGS, 2012).

5.21.2 Substance Search

We searched for experimental or epidemiological data on the substances:

- 2-Methylphenanthrene (CASRN: 2531-84-2)
- 2-Methylanthracene (CASRN: 613-12-7)
- 9-Methylanthracene (CASRN: 779-02-2)
- n-Nonylbenzene (CASRN: 1081-77-2)

5.21.3 Existing OEL or equivalent derived reference values (workers)

Substance	Type reference value	mg/m³	source
All single substances above	AGW (Germany)	No OEL values for specific substances derived	(AGS, 2006; BMAS, 2014)
	MAK (Germany)		(DFG, 2014)
	DNEL (Europe)		(ECHA, 2014)
	OEL		(IFA, 2014)

5.21.4 Recent Data

No further relevant studies were found.

[7] EU RAR 2008 ..\Material\Aromaten\EU_RAR_2008_anthracene-report316.pdf

5.21.5 Assessment, discussion and conclusions

There exists an older study by Skyberg et al. (1990), where rats were exposed to vapours of C_{15}-C_{20} alkylbenzenes for 2 weeks (7h/d; 5d/w) at 70 and 700 mg/m³. Alkylbenzene A contained 45% Nonylbenzene (and 37% Decylbenzene), which were the main components (linear alkyl structure). A significant finding was a reduced weight gain (terminal weight 262.9 grams in control; 249.2 g at low ($p<0.05$) and 205.3 g at the high exposure group ($p<0.01$)). Liver and lung weight were elevated (dose-dependent; no comment on significance). Only insignificant changes in respiratory organs were observed (marginal bronchiolar epithelial lesions at high dose). If 700 mg/m³ is taken as a NOAEC, default extrapolation leads to an OEL of (clearly) < 50 mg/m³.

Nonylbenzene is included in US EPA assessment for Benzene, C6-12 Alkyl derivatives as supporting chemical, but no further relevant inhalation data is available for the substance. Despite relevant uncertainty, we therefore propose to apply the OEL for C9 aromatic hydrocarbon solvents also for the C15 fraction.

5.22 Concluding analysis from single substances (aromatic hydrocarbon solvents)

C7-C8 aromatic hydrocarbon solvents were exempted from GGV in preceding discussions, because OELs of single BTEX aromatics have been questioned recently, possibly calling for some differentiation within the group of C7-C8 aromatics. It appears far more flexible to use SSV to include these substances in the RCP calculations than to strive for an updated GGV applicable to the group of C7-C8 aromatics. Only few single substance OELs have to be compiled from actual regulatory lists (BMAS, 2014, search for the most recent version of TRGS 900). We did not discuss a maximum content of C7-C8 aromatic hydrocarbons (or of C6 for the case of benzene), below which a separate calculation of this fraction is not needed because of an insignificant contribution to the overall OEL derived with RCP.

Reduction of the GGV for C9-C15 aromatic hydrocarbon solvents was mainly driven by the recently lowered OEL for cumene in Germany from 100 mg/m³ to 50 mg/m³. However, there have been additional experimental results to support such a lowering for all C9-C15 aromatics, as a group:

- Experimental data and assessments by other institutions on trimethylbenzenes resulted in similar OELs as for cumene.
- Further studies on other C9-C15 aromatics also called for a lower OEL (EPA, 2009; Korsak et al., 1998; Nielsen and Alarie, 1982; OECD, 2012c; Skyberg et al., 1990)
- Sensory irritation data on hexyl- and amylbenzene supported lowering the GGV for > C9 aromatics.
- For some of the substances exempted from the GGV, there is no sufficient explanation on a distinct mode of action to justify this exemption; therefore, considering insufficient single substances testing data, there remains relevant uncertainty on how representative are the data which support a higher OEL. There could well be further substances with similar effect potency as the few exempted substances. The discussion on ototoxicity of amylbenzene (Gagnaire and Langlais, 2005) demonstrates major uncertainties and differences in mode of action within

aromatic hydrocarbon solvents, making it less clear how homogeneous this group of substances really behaves.

- There is only a minor increased margin of safety for most data supporting a higher OEL (like the studies on acute neurotoxicity by McKee et al. (2010)).
- Data on mixtures including those with a high aromatic fraction support the derived GGV, if sensitive endpoints (like neurotoxicity) were included and if assessment factors were similarly applied as suggested by the German AGW methodology.

Indications for even lower OELs appear not to be justified for this group of C9-C15 aromatic hydrocarbon solvents, because exposure concentrations will be low due to minor percentages in the total hydrocarbon solvent mixture and due to low vapour pressure.

A relevant number of substances had to be exempted from the C9-C15 aromatic hydrocarbon solvent GGV. Those include substances with a disctinct mode of action like 1,2-diethylbenzene and 1,2,4-triethylbenzene or the (suspected or clearly identified) carcinogens naphthalene, acenaphthene, acenaphthylene, biphenyl, tetrahydronaphthalene, and fluorine. But exemption of n-butylbenzene and other diethylbenzenes or 1- and 2-methylnaphthalene is less obvious. For the latter, the mode of action and, therefore, justification for exemption is not clear. Within this project, we did not fully elucidate the relevance of these exempted substances in frequently used hydrocarbon solvent mixtures. We did not identify maximum contents, below which it would not be necessary to exempt such substances because of insignificant contribution to the overall toxicity. We further did not establish SSVs for these single substances, if exempted from their GGV.

6 MIXTURE DATA

Below, we report results of relevant studies on toxic effects of hydrocarbon solvent mixtures or UVCB. Mostly, results on experimental animal studies are reported. However, where controlled studies with mixtures on humans were available, they also were documented. For each study, directly after data and effect reporting, we derived a potential OEL using the AGW methodology and applied to this specific study. Only in some single identified cases we deviated from default procedures, where such a deviation was obviously demanded by the specific data.

We structured existing studies on mixtures to “mostly aliphatics” (Section 4.1) and “mostly aromatics” (section 4.2). In section 4.1 we used a substructure to discriminate “mostly aliphatics with low aromatic content” (section 4.1.1) and “mostly aliphatics with high aromatic content” (section 4.1.2).

The same structuring was taken up in section 4.3, where we calculated the resulting overall OEL for the full mixture or UVCB with 4 alternative approaches:

- direct assessment with study specific default assessment as also shown in sections 4.1 or 4.2,
- assessment according to the existing RCP approach in Germany with grouping and GGV as in regulatory guidance, and
- assessment according to the alternative approach derived from the analysis in this report based on considerations in section 3; this alternative approach was found not to be a single unique proposal, but two potential solutions were further analysed (options A and B).

In section 4.3 we also demonstrate the range of differences between the direct assessment and the options A and B, respectively, in order to provide more transparency on the conservativism of either option. Finally, the approaches are compared and also discussed in combination with the single substance data from section 3 in section 5 of this study report.

6.1 Mostly aliphatics

6.1.1 Mostly aliphatics, ‘low’ aromatic content

- In a 13 week inhalation toxicity study in rats animals were exposed for 6 h/d on 5 days per week to 0, 2.4, 8.1 or 24.3 mg/L of a light alkylate naphtha distillate (LAND-2, CASRN: 64741-66-8; C4-C10 aliphatics; composition: C4-3.25 %; C5-33.30 %; C6-18.91 %; C7-9.81 %; C8-31.14 %; C9-3.21 %; C10-0.39 %). Motor activity, FOB and neuropathological investigations did not reveal any neurotoxic effects. And no other adverse effects were found up to the highest concentration tested (male rat kidney effects at high dose not relevant; increased liver weights in high dose with no histopathological correlate and reversible within 4 weeks). Based on this NOAEC of 24300 mg/m³ an OEL of (≥) 1215 mg/m³ would be established (AF20 = $5_{variability}$*$2_{6\text{-}8h}$*$2_{sc\text{-}c}$) (Schreiner et al., 1998).
- In a subchronic inhalation toxicity study (OECD TG 413) or in combined chronic and carcinogenicity study (OECD TG 453) rats were exposed for 6 h (plus T90 the theoretical value for the time to achieve 90% of the target concentration after the

beginning of vapour generation, i.e.12 min)/d on 5 days per week for 105 weeks to 0, 138, 550, 1100, and 2200 mg/m³ of Stoddard solvent IIC (CASRN: 64742-88-7; C10-13 n-paraffins, 2-25% aromatics; 'high flash' and low aromatic grade; composition: mixture of n-paraffins, isoparaffins, or cycloparaffins with 10 to 13 carbons, e.g. 1.70 % decane, 19.3 % undecane, and 5.73 % dodecane (no further details), 0.56 % decalin; aromatics 0.93 % and 0.58 %) (NTP, 2004). Within the registration dossier (ECHA, 2014): no adverse effects up to the highest concentration tested was identified in females. In males alpha 2u globulin related nephropathy starting already at 138 mg/m³ was observed but not accounted for as adverse as this is a species and sex specific effect not relevant for humans[8]. Note that no haematological or neurotoxicological examination was performed. Based on these observations a NOAEC of 2200 mg/m³ was established, leading to an OEL of (≥) 220 mg/m³ (AF10 = $5_{variability}*2_{6\text{-}8h}$).

- In a 90 d inhalation toxicity study (OECD TG 413) with rats animals were exposed for 6 h/d and 5 days per week to 0, 2600, 5200, and 10400 mg/m³ (nominal) of commercial product ShellSol (dearomatised white spirit; ~98.9% paraffins, 1.1% naphthenes, < 0.5 % aromatics; CASRN: 64741-65-7; C10-C12 isoparaffinic solvent; hydrocarbons, C10-C12 isoalkanes, <2% aromatics; composition: C8- 0.12 %; C9- 0.92 %; C10- 15.94 %; C11- 38.7 %; C12- 44.4 %). The NOAEC identified was the highest concentration tested, i.e. 10400 mg/m³ as no adverse effects were observed. Kidney effects in male rats are not relevant to humans and there is an ongoing discussion on whether liver weight increases are to be regarded as an adaptive response (Carrillo et al., 2013). If liver effects are disregarded the NOAEC is 10400 mg/m³. With the current methodology an OEL of (≥) 520 mg/m³ would result (AF20 = $5_{variability}*2_{6\text{-}8h}*2_{sc\text{-}c}$).
- The original study by Phillips and Egan (1984) was cited and used for comparison by Carrillo et al. (2013) and Nielsen et al. (2006). In this study, which was designed to examine kidney effects mostly, rats were exposed for 6 h/d on 5d/week for 12 weeks to 0, 300 or 900 ppm (nominal) of a C9-C11 isoparaffinic solvent. The test material was provided by Exxon and contained 100% isoparaffins, primarily C10-C11 (composition assumption: C9- 10 %, C10- 45 %, C11- 45 %). As no adverse effects (except for kidney effects in male rats, which are irrelevant for humans, and haematological changes in the range of historical control/normal variation) the NOAEC of this study was 900 ppm (i.e. 5273 mg/m³ = approx. 5300 mg/m³). Based on this NOAEC an OEL of (≥) 260 mg/m³ would be derived (AF20 = $5_{variability}*2_{6\text{-}8h}*2_{sc\text{-}c}$).
- In the same study by Phillips and Egan (1984) results for another hydrocarbon solvent mixture were presented (cited also in Nielsen et al., 2006). Exposure was performed as described above, the test material - dearomatized white spirit - was provided by Exxon and contained < 0.5%aromatics, 58% paraffins, 42% naphthenes - primarily C11 and C12 (composition assumption: based on the information provided the same composition as for commercial product Exxsol D40 was assumed, except for aromatic content which was assumed to be higher in earlier products, i.e. aliphatics C6- 0.04 %; C7- 0.1 %; C8- 1.2 %; C9- 12 %; C10- 42 %; C11- 37 %; C12- 8 %; C13- 0.1 %, aromatics C9- 0.49 %). Increased relative and/or absolute liver weights were reported

[8] NTP concluded that there is 'some evidence for carcinogenic activity in male rats based on adrenal medulla neoplasms, and equivocal evidence in female mice due to increased hepatocellular adenoma'.

at exposure to 1970 or 5610 mg/m³. No increases of ALAT or alkalic phosphatases in serum were seen in this study and male rats revealed increased kidney weights and pathological correlates (alpha 2 u globulin nephropathy, irrelevant for humans). If changes in liver weights are thought to be adaptive and reversible, thus not adverse, the NOAEC of this study is 5610 mg/m³, leading to an OEL of (≥) 280.5 mg/m³ (AF20 = $5_{variability}$*$2_{6\text{-}8h}$*$2_{sc\text{-}c}$).

- Ernstgard et al. (2009a) published their results obtained after exposure of volunteers to dearomatized white spirit (commercial product Exxsol D40; CASRN: 64742-48-9; composition: aliphatics C6- 0.04 %; C7- 0.1 %; C8- 1.2 %; C9- 12 %; C10- 42 %; C11- 37 %; C12- 8 %; C13- 0.1 %, aromatics C9- 0.002 %). The six male and six female healthy volunteers were exposed to 0, 100, or 300 mg/m³ for 4 h at rest on 5 occasions with at least 1 week break between exposures. As no significant effects observed, the resulting NOAEC = 300 mg/m³. This study result supports the 15 min STEL by SCOEL of 50 ppm (~ 300 mg/m³) (SCOEL, 2007). One of these preceding studies by Ernstgard et al. (2009b) is explicitly described as a range finding study with first significant CNS effects from 200 mg/m³ upwards. However, exposure duration was only 10 minutes at each concentrations step and lasted only for little more than one hour in total (Ernstgard et al., 2009b), thus this study was not used for derivation of an OEL. Based on the NOAEC of 300 mg/m³ of the main study an OEL of 50 mg/m³ is calculated with an overall default AF of 6 (AF6= $3_{variability}$; reduced as result from human exposure; factor $2_{4\text{-}8h}$) or, an OEL of 100 mg/m³ with a reduced overall AF of 3.
- The publication by Juran et al. (2014) reports additional evaluations based on the experiments already described in the Ernstgard study (Ernstgard et al., 2009a). In both treatment groups (100 and 300 mg/m³) minor, but inconsistent effects were observed in the neurobehavioral tasks and colour vision and balance tests performed with dearomatised white spirit and standard white spirit. Results were suggesting that aromatic content does not influence acute neurotoxic effects. The higher concentration is assumed not to be below the NOAEC, because of the preceding range finding studies by Ernstgard et al. (2009b).
- The study by Hass et al. (2001), which was the basis for derivation of acute indoor air guideline values in Germany (Sagunski and Mangelsdorf, 2005), used the same commercial product as test material (i.e. Exxsol D40 (< 0.4 % aromatics); CASRN: 64742-48-9; composition: assumed to be the same as in the Ernstgard studies). Rats were exposed via inhalation for 6 h/d on gestation days 7-20 either to 0 (control) or 4679 mg/m³. The offspring was followed for 5 months. In the pups from exposed dams learning and memory functions were significantly impaired, body weights of dams were decreased by 26%, but body weights of their offspring was increased by 7%. Thus 4679 mg/m³ is the LOAEC of this study, leading to an OEL of 26 mg/m³ (AF180 = $3_{LOAEC\text{-}NOAEC}$*$5_{variability}$*$2_{6\text{-}8h}$*$6_{sa\text{-}c}$).
- Neurobehavioral effects of acute exposure to isoparaffinic and cycloparaffinic hydrocarbons were investigated by McKee et al. (2011). Rats were exposed for 8h/day for 3 consecutive days to 0, 500, 1500, 5000 mg/m³ of a C9-C11 isoparaffinic solvent (CASRN: 90622-57-4; composition assumption: 33 % C9, C10, C11 aliphatics each). After minor acute CNS effects were observed in the high dose group a NOAEC of 1500 mg/m³ was established, which would result in an OEL of 300 mg/m³ (AF5 = $5_{variability}$).

- In the same study (McKee et al., 2011) a mixed C6/C7 cycloparaffinic solvent (CASRN: 64742-89-8; composition assumption: no details on purity but high purity assumed > 95 %, thus 47.5 % C6, C7 aliphatics each) was tested under the same test conditions. Reversible changes in latency to response in visual discrimination were identified (minor, reversible changes in latency to response in visual discrimination testing at 14 000 mg/m³) and a NOAEC of 4200 mg/m³ was established. An OEL of 840 mg/m³ would be derived based on these data (AF5 = $5_{variability}$).
- In the assessment for white spirit by SCOEL (2007; SCOEL value 20 ppm (i.e. 116 mg/m³) - based on WoE human experience) the study by Lund et al. 1996 was reported. In this study with test material Exxsol D40 (<0.4% aromatics; CASRN 64742-48-9) rats were exposed to 0, 400 or 800 ppm (i.e. 0, 2339 or 4679 mg/m³) for 6 h/d, 5d/week for 6 months followed by exposure free period (70-80 days) before neurophysiological examinations were performed. Decreased motor activity in 800 ppm group was observed, but there were also other effects in both exposure groups and the conclusion drawn was 'that dearomatised white spirit can induce longlasting and possibly irreversible effects at 400 and 800 ppm'. Thus a LOAEC of 2339 mg/m³ for electrophysiological changes is established. Also, Nielsen et al. (2006) describe 400 ppm (2339 mg/m³) as adverse effect concentration. The resulting OEL would be 117 mg/m³ (AF20 = $5_{variability}$*$2_{6\text{-}8h}$*$2_{LOAEC\text{-}NOAEC}$; NOAEC-LOAEC factor reduced based long-term inhalation animal study results provided by SCOEL – 'The NOAEL in rats, rabbits, monkeys and dogs was 1353 mg/m³ (233 ppm)').

Oral toxicity studies – only supportive evidence:

Carrillo et al. (2013) reported the results of a subchronic oral toxicity study (OECD TG 408). Rats were exposed via gavage on 7d/week for 13 weeks to 0, 100, 500, and 1000 mg/kg bw x d to dearomatized white spirits (C11-C15 isoparaffinic solvent; 67%isoparaffins, 33% naphthenes; Composition assumption: 20 % for C11-C12-C13-C14-C15 each). Effects observed in high dose group: haematological changes: haemoglobin, RBC, PVC (packed cell volume) decreased compared to control; statistically increased liver weights - which decreased over time in recovery groups; increased kidney weights - which were still increased at the end of recovery). According to the authors none of these effects is adverse thus a NOAEL of 1000 mg/kg bw x d was established. Adaption to inhalation would result in a NOAEC of 1750 mg/m³ (assumptions: 4: allometric scaling rat; 70 kg body weight, 10 m³ respiratory volume during light activity of worker in 8 h shift), thus leading to an OEL of (≥) 175 mg/m³ (AF10 = $5_{variability}$*$2_{sc\text{-}c}$). If liver effects were accounted for as adverse an OEL of 87.5 mg/m³ would be derived.

6.1.2 Mostly aliphatics, 'high' aromatic content

- In an inhalation toxicity study either rats or dogs were exposed for 6h/d, on 5d/week for 13 weeks to 0, 480, 1100 or 1900 mg/m³ of Stoddard solvent (i.e. 48% aliphatics, 38% cyclic aliphatics,14% aromatics – aliphatics and cyclics: C7- 2.4 %, C8- 5.2 %, C9- 17.2 %, C10- 37.7 %, C11- 21.4 %, C12- 5.4 %; aromatics: C7- 0.4 %, C8- 1.4 %, C9- 7.6 %, C10- 3.7 %, C11- 0.9 %, C12- 0.1 %). No adverse effects (besides kidney effects in male rats which are irrelevant to humans) were observed thus leading to a NOAEC of (≥) 1900 mg/m³ (Carpenter et al., 1975). An OEL of (≥) 158 mg/m³ (AF12 = $3_{variability}$*$2_{6\text{-}8h}$*$2_{sc\text{-}c}$; the variability factor has been reduced as two species showed the same effects).

- In the same study (Carpenter et al., 1975) human volunteers were exposed to vapours of the same test material. On different all of the volunteers were exposed for 15 minutes to vapour concentrations of the test material in the order of 140, 2700 and 850 mg/m³ (one exposure per day). At 2700 mg/m³ six out of six subjects reported irritation of the eyes; at 850 mg/m³ only one out of 6 subjects reported eye irritation. Other effects observed included e.g. olfactory fatigue (all exposure group), throat irritation, tears (all other effect only in high exposure group). All effects were reversible 15 minutes after leaving the exposure chamber. The NOAEC based on irritation of eyes is ≤ 850 mg/m³. Even if extrapolation from 15 Minutes to a full shift is not considered the OEL based on this study would be ≤ 170 mg/m³ (AF5 = $5_{variability}$).
- A yet unpublished study result was reported by Carrillo et al. (2014a). In this 90 d inhalation toxicity study (OECD TG 413) rats were exposed for 6 h/d on 5d/week for 13 weeks to 0, 2000, 4000, 8000 mg/m³ of white spirits (CASRN: 64742-82-1; C9-C14 aliphatic HCs with ~ 20 % aromatics (i.e. HSPA convention: Category 3); low aromatic white spirit (LAWS): 56 % C9-C11 n- and iso-paraffins, 25 % C9-C11 naphthenes, 19 % C9--C10 aromatics; composition assumption (for calculation): total n-, iso-, and cyclic paraffins = 81 % → even split to 27 % of C9, C10 and C11 aliphatics each; 19% aromatics → split to 9.5 % C9 and C10 aromatics each). Effects observed in high dose group included: acute CNS effects, decreased terminal body weight, increased liver, spleen and kidney weights (but only pathological correlate in kidneys of male rats - alpha 2u glubolin associated nephropathy – not relevant for humans), significant changes in clinical and haematological parameters, but within normal physiological limits. The overall NOAEC therefore is 4000mg/m³, leading to an OEL of 200 mg/m³ (AF20 = $5_{variability}$*$2_{6\text{-}8h}$*$2_{sc\text{-}c}$).
- Ernstgard et al. (2009a; 2009b) was already mentioned above with their results obtained for dearomatized white spirit (Exxsol D40; CASRN: 64742-48-9). In these publications additional testing was performed for standard white spirit as well (commercial product Varsol 40 R, CASRN: 64742-82-1; composition: aliphatics C6- 0.04 %; C7- 0.3 %; C8- 0.8 %; C9- 2.2 %; C10- 29.6 %; C11- 35.8 %; C12- 11 %; C13- 0.1 %, aromatics C8- 0.6 %; C9- 6.8 %; C10- 9.4 %; C11- 3.2 %). In high exposure group (300 mg/m³) there was a significant increase in subjective ratings for eye irritation compared to clean air, but no effects seen in objective measurements. The overall conclusion is that standard white spirit slightly more irritating than dearomatised white spirit, but the resulting NOAEC from this study used for assessment would be 300 mg/m³ as well, leading to an OEL of ≤ 100 mg/m³ (AF3= $3_{variability}$; additionally time extrapolation from 4h to 8h could be considered).
- As mentioned above the publication by Juran et al. (2014) reports additional evaluations based on the experiments already described in the Ernstgard study (Ernstgard et al., 2009a). Weak and insignificantly elevated chemosensory response did not differ too much with either dearomatised or standard white spirit, thus suggesting that aromatic content does not enhance acute neurotoxic effects.
- In a test to evaluate neurobehavioural effects rats or human volunteers were exposed to white spirit (CASRN: 64742-82-1; type 1 mineral spirit, BP 160°C, 21.3% aromatics (increased to 25.6%), C9-C12 straight chain and branched paraffines and naphthenes; composition assumption: 25.6% aromatics (with 7.8% 1,2,4-TMB) split to C9 and C10 aromatics; 74 % aliphatics/alicyclics remaining (known that 10% n-

decane), even split to 18 % of C9, C10, C11 and C12 aliphatics) (Hissink et al., 2007; Lammers et al., 2007)
    - Rats were exposed for 8 h/d on three consecutive days to 0, 600, 2400, 2800 mg/m³. The NOEC for acute CNS effects was 600 mg/m³, resulting in an OEL of 120 mg/m³ (AF5= $5_{variability}$).
    - 12 healthy male subjects were exposed to either 57 or 570 mg/m³(≈ 100 ppm) for 4 h in two test sessions with at 7 days break between exposures. Some subtle performance deficits were found in humans. According to the authors the test results indicate that a 'qualitative similarity in response between rats and humans' is proved and rodent tests can be used to derive adequate OELs. From this study (assumed NOAEC of 570 mg/m³) an OEL of 95 mg/m³ would be derived (AF6= $3_{variability}$*$2_{4\text{-}8h}$; variability reduced as result from human exposure).
- Rats were exposed for 8 h/d for 26 weeks to 0, 1200, 2400 and 4800 mg/m³ of white spirit (composition: 44% aliphatics, 36% cyclic aliphatics, 18% aromatics; assumed distribution for calculation: as white spirit predominantly C9-C12 total sum aliphatics and cyclic = 80%, split evenly, i.e. 20 % each; 18 % aromatics split to C9 and C10) (Kulig et al. 1989 and 1990 as cited from SCOEL, 2007). Psychomotor slowing was observed, but there was no carryover of effect into the post-exposure period. Measurements of tail nerve conduction velocity showed significant lower conduction velocities in the high exposure group, thus resulting in a NOAEC of 2400 mg/m³. This NOEC would yield an OEL of 240 mg/m³ after application of extrapolation factors (AF10 = $5_{variability}$*$2_{sc\text{-}c}$).

6.2 Mostly aromatics

- McKee an colleagues applied their acute exposure pattern (8 h per day on three consecutive days) to rats investigating neurobehavioural effects of other test materials than described above, i.e.:
    - Mixed C9 aromatic solvent (CASRN 64742-95-6, purity: > 99 %): NOAEC = 200 mg/m³ (based on visual discrimination testing, authors reported NOAEC = 1000 mg/m³), thus leading to an OEL of 40 mg/m³ (AF5 = $5_{variability}$). The results for the C9 aromatic solvent were very similar to that observed for 1,2,4-TMB alone (McKee et al., 2010).
    - Mixed C10/C11 aromatic solvent (CASRN 64742-94-5, purity: > 99.8 %): NOAEC = 600 mg/m³, thus leading to an OEL of 120 mg/m³ (AF5 = $5_{variability}$) (McKee et al., 2010).
- The study performed by Clark et al. (1989) used a test material containing mostly aromatic hydrocarbons, i.e. C8-2.27 % (o-xylene), C9-79.82 % and C10-8.31 % (50:50 blend of SHELLSOL A and SOLVESSO 100). As mostly trimethylbenzenes are contained in the C9 aromatic fraction (44.81 % TMBs) this study was used by different assessors to generate occupational exposure levels for trimethylbenzenes:
    - (SCOEL, 1994) OEL of 100 mg/m³ basis NOAEC 825 mg/m³ (165 ppm);
    - Registration dossiers for 1,2,4- and 1,3,5-TMB (ECHA, 2014): DNEL = 100 mg/m³ (NOAEC = 1800 mg/m³, but recalculation to TMB content ≈ 806 mg/m³).

In this one year inhalation study rats were exposed for 6 h/day and 5 days per week to 0, 450, 900 and 1800 m g/m³ of the C9/C10 mixture. The authors stated that there were no adverse effects up to the highest concentration tested (effects observed but not accounted for as adverse: initial reduction of body weight, transient haematological changes, liver and kidney weights increased in males). With this NOAEC of ≥ 1800 mg/m³ an OEL of (≥) 180 mg/m³ is derived (AF10 = $5_{variability}$*2_{6h-8h}). Note that no investigation of neurotoxic effects was included in these studies.

Oral toxicity studies – only supportive evidence:

In a 90 d repeated dose oral gavage study 10 rats/sex/group including 28 d satellite group were exposed to 0, 300, 600 and 1200 mg/kg bw x d C10-C13 aromatic hydrocarbon solvent (CASRN 64742-94-5, no further details provided; but as CASRN is the same as in the McKee study (McKee et al., 2010) a similar purity was assumed: > 99.8 %). The NOAEL established was 300 mg/kg bw x d based on final conclusions ('The relative organ weights, clinical chemistry and haematology data indicated recovery during the 28 day recovery period. The liver, thyroid, and stomach, changes seen at the 90-day termination, appeared to be reversible findings as they were not observed or returned to background levels in the satellite recovery group after the 28-day recovery period. The changes seen in the spleen at the main study termination were at lower incidence and/or severity in the satellite recovery group, which indicates a trend towards reversibility.') (OECD, 2012d). After adaption to inhalation (NOAEC = 525 mg/m³), an OEL of 52.5 mg/m³ would be calculated (AF10 = $5_{variability}$*2_{sc-c}).

6.3 Comparison mixture results with current RCP approach and future options (A, B)

The following Table 6-1 provides the consequences of 4 approaches to calculate an OEL for a hydrocarbon solvent mixture, either (1) by the specific data on the specific mixture by "direct extrapolation", or (2) by the original RCP method as currently implemented in Germany, or by (3) a simple Option A for an RCP update as explained in section 3 with GGV C6-C15 aliphatics: 300 mg/m³ and for C9-C15 aromatics: 50 mg/m³, or by (4) a simple Option B for an RCP update as explained in section 3 with GGV C6-C8 aliphatics: 700 mg/m³; C9-C15 aliphatics: 300 mg/m³ and for C9-C15 aromatics: 50 mg/m³. For C5 aliphatics we used 3000 mg/m³ in these calculations (which may be the SSV for pentanes), for C7-C8 aromatics we used 200 mg/m³ for this calculation, although no updated SSV has been decided on.

Table 6-1: OEL derivation from mixture data (direct) in comparison to OEL derivation with two optional groupings (options A, B) and according to current RCP approach (Germany)

Mixture	**Source**	**Direct NOAEC [mg/m³]**	**Direct Extra-polated OEL [mg/m³]**	**RCP (original approach, Germany, ≤2014), resulting OEL C5-C8 ali: 1500 C9-C15 ali: 600 C9-C15 aro: 100 [mg/m³] (factor)***	**RCP (this report), Option A) C5 ali: 3000 C6-C15 ali: 300 C9-C15 aro: 50 [mg/m³] (factor)***	**RCP (this report), Option B) C5 ali: 3000 C6-C8 ali: 700 C9-C15 ali: 300 C9-C15 aro: 50 [mg/m³] (factor)***
Mostly aliphatics, 'low' aromatic content						
LAND-2 (C4-C10 aliphatics) CASRN: 64741-66-8; C4-3.25 %; C5-33.30 %; C6-18.91 %; C7-9.81 %; C8-31.14 %; C9-3.21 %; C10-0.39 %	(Schreiner et al., 1998)	(≥) 24300	(≥) 1215 (405)**	1468 (0.83)	449 (2.7) (0.90)**	920 (1.3)
Stoddard solvent IIC (C10-13 n-paraffins) CASRN: 64742-88-7 0.56 % decalin, 0.93 % and 0.58 % aromatics	(NTP, 2004)	(≥) 2200	(≥) 220	604 (0.36)	316 (0.7)	320 (0.6)
ShellSol (dearomatised white spirit) CASRN: 64741-65-7 composition: ~98.9% paraffins, 1.1% naphthenes, < 0.5 % aromatics; hydrocarbons, C10-C12 isoalkanes, <2% aromatics; for calculation: C8-0.12 %; C9-0.92 %; C10-15.94 %; C11-38.7 %; C12-44.4 %	Shellsol Study, 1980 (Carrillo et al., 2013)	(≥) 10400	(≥) 520 (40)**	600 (0.87)	300 (1.7) (0.13)**	300(1.7) (0.13)**
C9-C11 isoparaffinic CASRN: - Exxon provided, contains 100% isoparaffins, primarily C10-C11 (composition assumption for calculation: C9- 10 %, C10- 45 %, C11- 45 %).	(Phillips and Egan, 1984) (Carrillo et al., 2013)	(≥) 5300	(≥) 260	600 (0.43)	300 (0.88)	295 (0.87)
dearomatized white spirit	(Phillips and Egan,	(≥) 5610	(≥) 280	585 (0.48)	290 (0.97)	290 (0.97)

CASRN: - Exxon provided, contains < 0.5% aromatics, 58% paraffins, 42% naphthenes - primarily C11 and C12 (composition assumption for calculation: Exxsol D40 was assumed, except for higher aromatic content, i.e. aliphatics C6- 0.04 % ; C7- 0.1 %; C8- 1.2 %; C9- 12 %; C10- 42 %; C11- 37 %; C12- 8 %; C13- 0.1 %, aromatics C9- 0.49 %)	1984) (Nielsen et al., 2006)		(98.5)**			
dearomatized white spirit CASRN: 64742-48-9; commercial product Exxsol D40 composition: aliphatics C6- 0.04 %; C7- 0.1 %; C8- 1.2 %; C9- 12 %; C10- 42 %; C11- 37 %; C12- 8 %; C13- 0.1 %, aromatics C9- 0.002 %).	(Ernstgard et al., 2009a; Ernstgard et al., 2009b) Additional evaluation (Juran et al., 2014)	300	(≤) 100	602 (0.17)	298 (0.34)	300 (0.33)
C9-C11 isoparaffinic solvent CASRN: 90622-57-4; composition assumption: 33 % C9, C10, C11 aliphatics	(McKee et al., 2011)	1500	300	606 (0.5)	303 (1.0)	303 (1.0)
C6-C7 cycloparaffinic solvent CASRN: 64742-89-8; composition assumption: 47.5 % C6, C7 aliphatics	(McKee et al., 2011)	4200	840	1578 (0.53)	315 (2.67)	736 (1,14)
dearomatized white spirit CASRN: 64742-48-9; commercial product Exxsol D40 composition: as above	(Hass et al., 2001)	4679	26	602 (0.043)	298 (0.087)	298 (0.087)
Exxsol D40 (<0.4% aromatics) CASRN 64742-48-9	Lund et al. 1996 cited from SCOEL, 2007	2339	117	602 (0.19)	298 (0.40)	300 (0.40)
dearomatized white spirits CASRN: - C11-C15 isoparaffinic solvent; 67%isoparaffins, 33% naphthenes; Composition assumption for calculation: 20 % for C11-C12-C13-C14-C15 each	90 d oral study, OECD TG 408 (Carrillo et al., 2013)	(≥) 1750	(≥) 175 (87.5)**	600 (0.29) (0.15)**	300 (0.58) (0.29)**	300 (0.58) (0.29)**

Mostly aliphatics, 'high' aromatic content						
Stoddard solvent CASRN: - composition: 48% aliphatics, 38% cyclic aliphatics,14% aromatics – aliphatics and cyclics: C7- 2.4 %, C8- 5.2 %, C9- 17.2 %, C10- 37.7 %, C11- 21.4 %, C12- 5.4 %; aromatics: C7- 0.4 %, C8- 1.4 %, C9- 7.6 %, C10- 3.7 %, C11- 0.9 %, C12- 0.1 %	(Carpenter et al., 1975) 0.1 % Benzene not considered for calculation! Default value of 200 mg/m³ used for calculation of ∑ C7/C8 aromatics = 1.8 %	(≥) 1900	(≥) 158	375 (0.42)	185 (0.85)	190 (0,83)
white spirits CASRN: 64742-82-1 composition: C9-C14 aliphatic HCs with ~ 20 % aromatics (i.e. HSPA convention: Category 3); low aromatic white spirit (LAWS): 56 % C9-C11 n- and iso-paraffins, 25 % C9-C11 naphthenes, 19 % C9--C10 aromatics; composition assumption for calculation: total n-, iso-, and cyclic paraffins = 81 % → 27 % of C9, C10 and C11 aliphatics each; 19% aromatics→ 9.5 % C9 and C10 aromatics each	(Carrillo et al., 2014a)	4000	200	307 (0.65)	153 (1.3)	153 (1.3)
Standard white spirit CASRN: 64742-82-1; commercial product Varsol 40 R composition: aliphatics C6- 0.04 %; C7- 0.3 %; C8- 0.8 %; C9- 2.2 %; C10- 29.6 %; C11- 35.8 %; C12- 11 %; C13- 0.1 %, aromatics C8- 0.6 %; C9- 6.8 %; C10- 9.4 %; C11- 3.2 %	(Ernstgard et al., 2009a; Ernstgard et al., 2009b) Default value of 200 mg/m³ used for calculation of C8 aromatics = 0.6 % Additional evaluation (Juran et al., 2014)	300 (effect slightly more pronounced than in dearomatised white spirit)	(≤) 100	304 (0.33)	152 (0.66)	152 (0.66)

Standard white spirit CASRN: 64742-82-1; type 1 mineral spirit, BP 160°C, 21.3% aromatics (increased to 25.6%), C9-C12 straight chain and branched paraffines and naphthenes; composition assumption for calculation: 25.6% aromatics C9 and C10 aromatics; 74 % aliphatics/alicyclics 18 % of C9, C10, C11, C12 each	(Hissink et al., 2007; Lammers et al., 2007)	600 (rats)	120	266 (0.45)	133 (0.90)	133 (0.90)
		570 (human volunteer)	95	266 (0.35)	133 (0.71)	133 (0.71)
white spirit (44% aliphatics, 36% cyclic aliphatics, 18% aromatics)CASRN: -; assumed distribution for calculation: total sum aliphatics and cyclic = 80%, split evenly to C9-C12, i.e. 20 % each; 18 % aromatics split to C9 and C10	(Kulig et al. 1989 and 1990 as cited from SCOEL, 2007).	2400	240	319 (0.75)	160 (1.5)	160 (1.5)
Mostly aromatics						
50:50 blend of SHELLSOL A and SOLVESSO 100 CASRN: - C8-2.27 % (i.e. o-xylene), C9-79.82 %, C10-8.31 %	(Clark et al., 1989) not included in calculation: diethyl-benzene, low DNEL!)	(>) 1800	(>) 180 (90)**	112 (1.6)	56 (3.2) (1.6)**	56 (3.2) (1.6)**
Mixed C9 aromatic solvent CASRN: 64542-95-6, purity: > 99 %:	(McKee et al., 2010)	200	40	100 (0.4)	50 (0.8)	50 (0.8)
Mixed C10/C11 aromatic solvent CASRN: 64742-94-5, purity: > 99.8 %	(McKee et al., 2010)	600	120	100 (1.2)	50 (2.4)	50 (2.4)
C10-C13 aromatic solvent CASRN 64742-94-5, no further details as CASRN is the same as in the McKee study (2010) similar purity assumed: > 99.8 %	90 d oral study (OECD, 2012d)	525	52.5 (17.5)**	100 (0.53) (0.175)**	50 (1.05) (0.35)**	50 (1.05) (0.35)**

*factor = OEL extrapolated from experimental data direct divided by OEL based on RCP-models (this report; Option A, etc.); **value in brackets based on hepatic alterations, for further details see discussion below

7 DISCUSSION AND CONCLUSION, ANALYSIS OF ALTERNATIVE OPTIONS (A,B)

If, in the table in section 4.3, a value of < 1 appears in brackets, this indicates a possible underestimation of hazards by RCP, if GGV, given at the head of the respective column, are used for that calculation. For example, the direct extrapolated OEL based on the study by Schreiner et al. (1998) was 1215 mg/m³. The former (and current) RCP assessment in Germany would lead to a somewhat higher OEL for the data from the Schreiner et al. study (OEL of 1468 mg/m³). This could mean a minor underestimate of the "real" OEL (factor 0.83 instead of 1). The alternative new approaches (option A, B) lead to potential overestimates of the OEL (OEL is "too conservative") by a factor of 2.7 or 1.3. This indicates that, in this case, option B or the existing RCP approach may fit best to the data from this single mixture study.

Key conclusions from further analysis are:

- The current RCP approach in Germany very often leads to underestimations of the directly extrapolated OEL: 19 of 21 derivations indicated a factor of < 1, only 2 derivations provided a factor > 1. Therefore, only for the study by McKee et al. (2010) on C10/C11 aromatic solvents and the study by Clark et al. (1989) the existing RCP approach appeared to provide a (more than) sufficient margin of safety. The conservatism based on these two studies was marginal (factor ≤ 1.6). The lowest factor was 0.17 for the study by Ernstgard et al., which means that the current RCP approach may have implicated an underestimation of the OEL by a factor close to 6 (in case of the Ernstgard et al. study (2009a,b) on white spirit). The study by Hass et al. on dearomatised white spirits with a very low directly calculated OEL of 26 mg/m³ appears to be an outlier and is not further discussed.
- The two new options contain 8 comparisons where the factor "new option"/ direct extrapolation is potentially overly conservative (factor >1) and 13 comparisons, where a factor ≤ 1 resulted (which means a possible underestimation of hazard by the calculated OEL). For the study by Ernstgard et al. the new options may also lead to underestimation of the associated hazard. However, this possible underestimation is restricted to a factor of 3. On the other hand, there also may be an overestimation of potential hazard based on the study by Clark et al. (1989) by a factor of 3.2. In most cases, both new options showed only minor deviations from the direct estimate based on the single mixture study.
- Obviously, the two options A and B only differ, if a relevant amount of ≤ C8 aliphatics is contained in the mixture or UVCB. There are just 2 studies where this difference becomes significant: The Schreiner et al. study (1998) on C4-C10 aliphatics and the study by McKee et al. (2011) on a C6-C7 cycloparaffinic solvent. However, for both studies the two options provided conservative estimates, where option B might be closer to reality than option B (factors 2.7 vs. 1.3 for the Schreiner et al. study and 2.67 vs. 1.14 for the McKee et al. study). Option B therefore appears to provide a sufficient margin of safety in most cases with ≤ C8 aliphatics and is equally conservative for all other compositions of mixtures.
- There is an ongoing controversial discussion on the adversity of observed liver effects in some of the studies. We documented the resulting OEL from direct extrapolation usually without addressing this special controversial issue, assuming that the respective effects were adaptive and not adverse. However, for the purpose of

comparison we also calculated the deviating OEL, if we included hepatic effects as adverse effects. The respective values are given in brackets and marked with a double asterix (OEL)**. Obviously, there were three studies where this discussion could be important: two studies reported in Carrillo et al. (2013) on a dearomatised white spirit and one oral study referred to in a SIDS document (OECD, 2012d) on an aromatic C10-C13 solvent. Only, for the ShellSol-Study the assessment of hepatic effects as being adverse would lead to an underestimation of adverse effects by a large factor of up to 7.7.

- However, for this possible underestimation of a potential hazard we also have to be aware, that we mostly used default assessment factors to derive an OEL, what may not always be warranted after a more detailed single study and single substance analysis. Moreover, very often the NOAEC was assumed to be identical to the highest concentration tested and taken as POD for deriving the OEL. This introduces relevant uncertainties and is a conservative approach (potential overestimation of a hazard). We marked the respective OELs by a sign: “greater or equal” (≥) to indicate this uncertainty.
- Note, that the selection of mixture studies in this analysis was not representative and just reflects a selection of often cited publications with heterogeneous composition of hydrocarbon solvents.
- We do not provide a final conclusion, which of the two options (A,B) should be implemented. Option A is more conservative with respect to ≤ C8 aliphatics. From analyzing the mixture data, it does not seem to be necessary to decide for this more conservative option A. However, it should be acknowledged that option A may be easier in handling (calculations and analytical control). On the other hand, option B may be toxicologically adequate if these simplifications are not regarded as necessary and if there is a substantial interest to maintain elevated permitted concentrations of ≤ C8 aliphatics due to usual handling and exposure conditions according to the “state of the art”. Consequences of the respective options in comparison to the HSPA classification scheme and grouping (see section 4.3.2 and Figure 4-1) are visualised below for option A (Figure 7-1) and B (Figure 7-2).

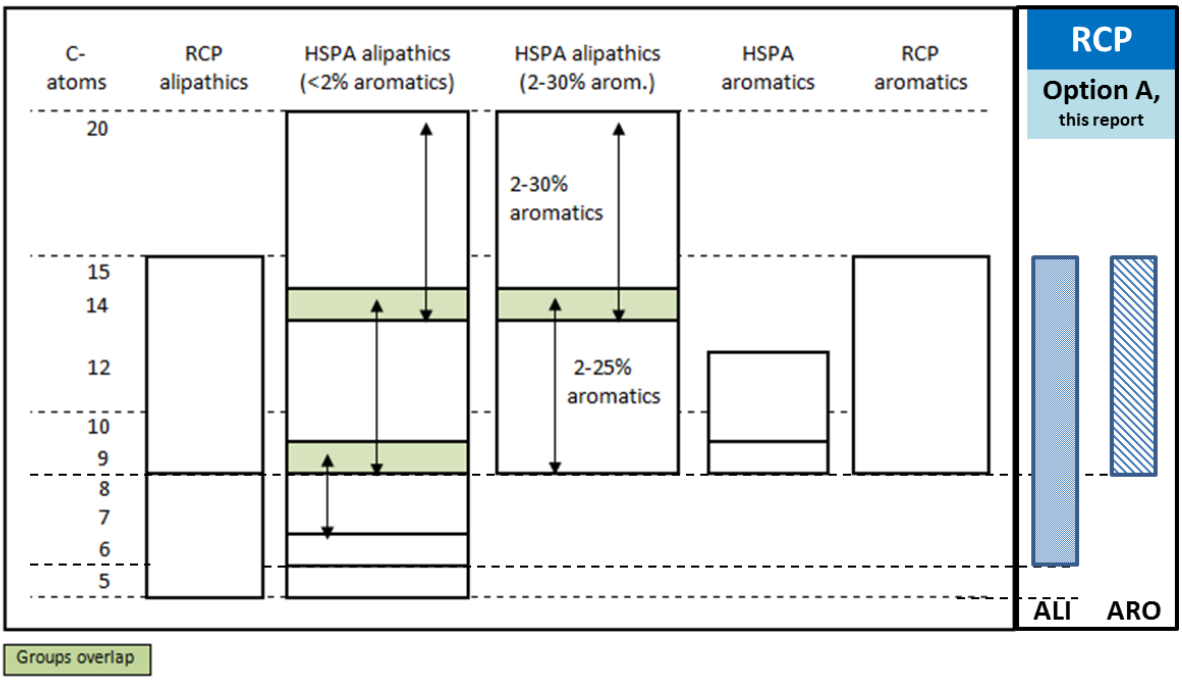

Figure 7-1: Schematic presentation of grouping HSPA approach vs. option A (this report)

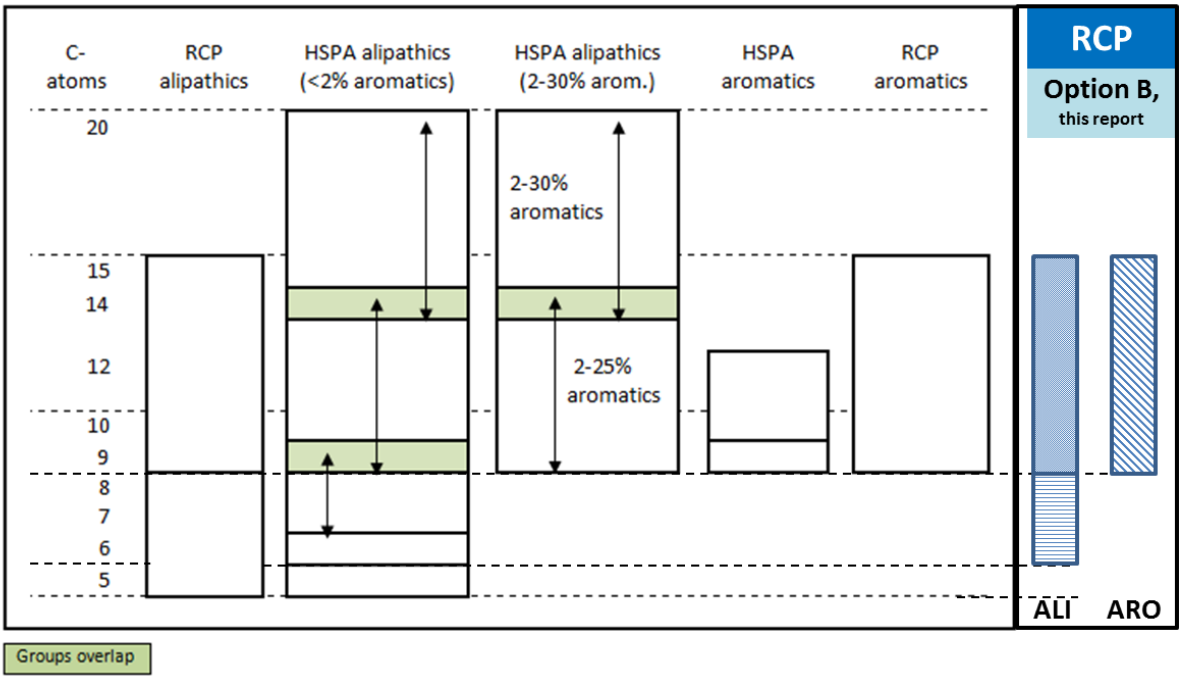

Figure 7-2: Schematic presentation of grouping HSPA approach vs. option B (this report)

ABBREVIATIONS

↑	increase(d) / elevation (elevated)
AF	assessment factor = extrapolation factor
AGW	Arbeitsplatzgrenzwert (OELs, official AGW are published in German regulatory document: TRGS 900)
BP	Boiling point
Bw	Body weight
DEB	Diethylbenzene
DFG	Deutsche Forschungsgemeinschaft
ERB	Expositions-Risikobeziehung (exposure risk relationship; according to AGS, 2014) for carcinogens
FOB	Functional observation battery
GGV	Group guidance value
HSPA	Hydrocarbon Solvents Producers Association
LAB	linear alkylbenzenes (mostly used as intermediates, surfactants)
LOAEC	Lowest observed adverse effect concentration
OEL	Occupational exposure limit
MAK	Maximale Arbeitsplatzkonzentration (usually developed by DFG)
NOAEC	No observed adverse effect concentration
PBTK	Physiologically-based toxicokinetic models, simulate absorption, distribution and excretion of xenobiotics
POD	point of departure (starting point for extrapolation)
RD50	50 % depression of respiratory rate in mice
REL	Recommended Exposure Limit
SD	standard deviation
SSV	single substance value/ substance specific guidance value
STEL	short term exposure limit
TLV	Threshold limit value
TMB	Trimethylbenzene
TETMB	Tetramethylbenzene
UVCB	Substances of unknown or variable composition, complex reaction products or biological materials

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