REVIEW REPORT FOR OCCUPATIONAL EXPOSURE LIMITS FOR HYDROCARBON SOLVENTS: THE RECIPROCAL CALCULATION PROCEDURE

OVERVIEW

Hydrocarbon solvents are complex substances with variable compositions of aliphatic and/or aromatic constituents. Because of the complex and variable nature of these substances, it was at one time difficult for manufacturers to provide consistent advice on occupational exposure limits (OELs). Accordingly, a means to calculate OELs from compositional information using a reciprocal formula was proposed in 1997. This reciprocal calculation procedure (RCP) was adopted by the European hydrocarbon solvent industry in 2000 and has been the method by which hydrocarbon solvents OELs have been calculated by the hydrocarbon solvents industry for the past 20 years. This report provides an update, considering newly available toxicology information, changes in occupational exposure recommendations for hydrocarbon solvent constituents, and the experience that has been gained since the method was adopted.

1. Introduction

Hydrocarbon solvents are liquid hydrocarbons derived from crude oil or their synthetic analogues and composed of molecules containing only hydrogen and carbon, with carbon numbers ranging from C5-C20. Although most hydrocarbon solvents have complex and variable compositions, the majority are relatively narrowly defined with carbon number ranges typically spanning about 3 carbon numbers and seldom covering more than 5 which means that constituents of the solvents have similar physical and chemical properties. Hydrocarbon solvents are composed of 4 types of constituents: normal (N-) paraffins; iso (I-) paraffins; cyclo-paraffins (also known as naphthenes); and aromatics, and, because these solvents are manufactured by several different processes, specific solvents may contain any or constituent types. Because many hydrocarbon solvents are volatile, occupational exposure limits (OELs) are needed to avoid over-exposure, particularly in the workplace. However, because many of the hydrocarbon solvents are complex with variable compositions, there were inconsistencies in historical OEL recommendations for these substances, and there can still be regional differences related to national regulations and/or local practices.

2. Reciprocal Calculation Procedure (RCP)

To provide a means by which manufacturers could calculate OELs from compositional information, the U.K. Health and Safety Executive (HSE, 1995) used an adaptation of the American Conference of Governmental Industrial Hygienists (ACGIH®) advice for calculating OELs for mixtures to develop a reciprocal calculation-based formula to calculate OELs for complex hydrocarbon solvents. Specifically:

$$Fr_a/OEL_a + FR_b/OEL_b + \ldots = 1/OEL_{mixture}$$

In which Fr_a is the vapor phase mole or liquid fraction of component$_a$, OEL_a is the occupational exposure limit for component$_a$ etc. [Note that normally the calculations can be based on the liquid fractions of the components, but in some situations the use of vapor phase fractions is more appropriate as discussed below.]

To calculate OELs for hydrocarbon solvents, the HSE grouped similar constituents and assigned "group guidance values (GGVs)" which could be used in the reciprocal formula as if they were OELs. Two specific hydrocarbon molecules, n-hexane and naphthalene that are classified due to their unusual toxicological properties and are specifically identified in the naming convention have been treated separately with "specific substance values (SSVs)" which provides one way to control exposures to these two substances when they are as constituents in hydrocarbon solvents. With some adjustments to the guidance values, the reciprocal calculation procedure (RCP), was endorsed by the European chemical industry (ECETOC, 1997), adopted by the European hydrocarbon solvent producers in 2000, formally published (McKee *et al*., 2005), incorporated into guidance published by the American Conference of Governmental Industrial Scientists (ACGIH), and was revised in 2017 (McKee *et al*., 2017).

3. Implementation

The efforts to establish the RCP had two goals: (i) to harmonize the approach to setting OELs for complex hydrocarbon solvents to allow manufacturers to provide consistent advice for compositionally similar commercial products and (ii) to avoid exceeding occupational exposure limits for hydrocarbon solvent constituents when the calculated OELs for the complex solvents were observed (ECETOC, 1997). However, it was recognized that these objectives would be difficult to achieve. One problem with international harmonization is that there are several national methods which reflect differing occupational control philosophies[1]. Accordingly, the recommendations of the ACGIH®, Threshold Limit Values, TLVs®, in the United States and those of the European Scientific Committee on Occupational Exposure Limits (SCOEL, Indicative Occupational Limit values, IOELvs) which are highly respected and widely used were adopted as the basis for GGV development to gain the widest possible acceptance. However, there are differences in some of the recommendations of these two groups, and, more importantly, adaptations to the general recommendations may be necessary to satisfy local regulations and/or conform to local practices. Advice relating to other national methods, regulatory requirements, or occupational exposure limits is beyond the scope of this document.

The potential for over-exposure to problematic hydrocarbon solvent constituents can also arise in some specific situations, particularly when constituents such as n-hexane are among the more volatile of the solvent components leading to over-representation of these constituents in the vapor phase. In such

[1] A discussion of national methods is beyond the scope of this document.

situations, the calculations should be based on the constituent fractions present in the vapor phase as described in more detail below.

4. Recommended Group Guidance Values (GGVs) and Specific Substance Values (SSVs)

The current recommendations are given in Table 1. Toxicological data and other information supporting these recommendations is summarized in Appendix B with more details available in recent publications, e.g., McKee *et al*. (2015; 2017), as well as in the original references.

4.1 C5-C8 aliphatic constituents (excepting n-hexane).

The recommended GGV for C5-C8 aliphatic constituents (1400 mg/m^3) was based on the ACGIH® TLV® of 1401 mg/m^3 for octane, the lowest TLV® of the aliphatic constituents in this group except for cyclohexane (350/700 mg/m^3)[2]. Thus, observing the calculated OEL of 1400 mg/m^3 for solvents composed of C5 – C8 aliphatic constituents ensures that exposures to all C5-C8 aliphatic constituents other than n-hexane and cyclohexane would not exceed their respective occupational exposure limits.

The potential for over-exposure to n-hexane is addressed separately with a specific substance value of 176/72 mg/m^3, as discussed in more detail below. Further information related to cyclohexane is provided in section 7.

4.2 C9-C15 aliphatic hydrocarbons (no exclusions)

The recommended GGV for C9-C15 aliphatic hydrocarbons is 1050 mg/m^3, based on the ACGIH® TLV of 1050 mg/m^3 for nonane. Following the logic of the preceding paragraph, as nonane is the only constituent in this group with its own TLV®, exposures to C9-C15 aliphatic constituents will not exceed their own occupational exposure levels if the calculated occupational exposure limits are not exceeded. Note that because of decreasing vapor pressures, constituents with carbon numbers > C10 are unlikely to make more than minimal contributions to the overall levels of hydrocarbon levels present in vapor. However, the reader should be aware that these recommendations relate only to hydrocarbons in the vapor phase. If aerosols are formed, it is recommended that the ACGIH® advice for "particulates not otherwise specified" be followed unless this is superseded by other specific regulatory advice (see McKee *et al*., 2005).

4.3 C9-C15 aromatic hydrocarbons (excluding naphthalene)

The recommended GGV for C9-C15 aromatic constituents is 50 mg/m^3 based on the current ACGIH® TLV for trimethylbenzene isomers (the SCOEL IOELv is 100 mg/m^3). The GGV is applied to all C9-C15 aromatic hydrocarbon, although there is an SSV of 50 mg/m^3 for naphthalene which reflects differences in hazard classification between naphthalene and other aromatic solvent constituents. Other C9-C11 aromatic

[2] When there are differences between the ACGIH and SCOEL recommendations, both values are listed as (ACGIH/SCOEL). In this case the ACGIH TLV® for cyclohexane is 350 mg/m^3 and the SCOEL IOELv is 700 mg/m^3.

constituents that need to be considered but do not necessarily require that the calculations be modified include cumene, indene, diethylbenzene isomers, triethylbenzene isomers, methylnaphthalene isomers, and biphenyl (see further discussion below and in Section 7).

4.4 Specific substance values

There are two hydrocarbon solvent constituents, n-hexane (176/72 mg/m^3), and naphthalene (50 mg/m^3) that are classified for their toxicological properties, and solvents containing these constituents have been differentiated by the naming convention (see McKee *et al*., 2015) and for purposes of REACH registration. Additionally, to avoid over-exposure, the occupational exposure levels for these two constituents were adopted as SSVs to be applied when calculating occupational exposure levels to solvents containing these constituents at classifiable levels, i.e., n-hexane $\geq$ 5% and naphthalene $\geq$ 1%. However, there are other constituents that may be present in hydrocarbon solvents including toluene, xylenes, ethylbenzene, cyclohexane, cumene, indene, diethylbenzene isomers, triethylbenzene isomers, methylnaphthalene isomers, and biphenyl that have their own occupational exposure limits which need to be carefully considered. In most cases, these other constituents are present at levels that are low enough that their own occupational exposure limits would not be exceeded when the RCP-based OELs are observed. However, in some cases measures should be taken to avoid the potential for over-exposure. Some general guidance that relates to situations in which constituents could be problematic and measures to be taken to avoid over-exposure is provided in Section 7, but ultimately it is the responsibility of the manufacturers to decide on the best course of action.

Table 1. Summary of Input Values for RCP calculations

Hydrocarbon Constituent Group	**Recommended GGV/SSV (mg/m^3)**	**ACGIH® TLV (mg/m^3)[1]**	**SCOEL IOELv (mg/m^3)**
C5-C8 aliphatic hydrocarbons	1400 mg/m^3		
		Pentane (all isomers) – 2950	3000
		Hexane (all isomers)[2] – 1760	1800
		Heptane (all isomers) – 1640	2085
		Octane (all isomers) – 1401	1450
		Cyclopentane – 1720	1720
		Cyclohexane – 350	700
		Methylcyclohexane – 1610	1600
C9-C15 aliphatic hydrocarbons	1050 mg/m^3	**Nonane – 1050**	No value
C7-C8 Aromatic hydrocarbons[3]	None	Toluene – 75	192
		Xylene (all isomers) – 87	221
		Ethylbenzene – 87	442

C9-C15 aromatic constituents[4]	50 mg/m^3	**Trimethylbenzene isomers – 50**	100
		Cumene –25	50
		Indene – 24	24
		Biphenyl – 1.3	1.2
		Methylnaphthalene isomers – 3[5]	2.5
		Diethyl-/Triethylbenzene – no value (28[3])	No value
Substances with SSVs			
n-hexane		176	72
Naphthalene		50	50

1. The TLV and IOELv values are correct as of 2022.
2. All hexane isomers excepting n-hexane for which there is a specific substance value.
3. Benzene levels are so low (< 100 ppm in most registered solvents, McKee *et al*., 2007) that the presence of benzene does not normally need to be included in the OEL calculations. However, if the concentration of benzene > 100 pm, then the potential for over-exposure needs to be considered. Note also that classification for carcinogenic properties is required if the benzene contents ≥ 1000 ppm.
4. All constituents not otherwise specified.
5. Note that in 2022 the ACGIH published a Notice for Intended Change (NIC) which, if adopted, would lower the ACGIH® TLV for methylnaphthalene to approximately 0.3 mg/m^3.

5. Calculating OELs for Hydrocarbon Solvents

Most hydrocarbon solvents are composed of similar components with relatively narrow boiling point ranges. For these solvents, the composition of hydrocarbons in the vapor phase approximates that in the liquid phase, and the mole fractions of the liquid phase components can be used to calculate the OELs as indicated below:

[3] In the absence of other regulatory advice, it is recommended that the AIHA Workplace Environmental Exposure Level (WEEL) value of 28 mg/m^3 be used for diethyl and triethyl benzene isomers.

5.1 Example Calculations

(i) **Regular white spirit**[4] – This calculation illustrates the potential impact of low levels of potentially toxic constituents on the calculated values. Regular white spirit is an aliphatic solvent containing approximately 80% C9-C12 aliphatic constituents and 20% aromatic hydrocarbons. In this example it is assumed that the solvent contains 80% C9-C15 aliphatic constituents, and 20% C9 aromatic constituents.

Table 2 Calculating the Occupational Exposure Limit for White Spirit

Constituent	Molar Fraction (liquid phase)	GGV (mg/m^3)	F/GGV	1/∑ (mg/m^3)
C9-C15 aliphatics	0.80	1050	0.00076	
C9-C15 aromatics	0.20	50	0.004	
Sum			0.00476	210

The RCP OEL = 210 mg/m^3 which becomes 200 mg/m^3 following the rounding rule convention.[5] Using 200 mg/m^3 as the occupational exposure limit, the exposure to all of the C9-C12 aliphatic constituents collectively would be approximately 160 mg/m^3 (0.8 x 200 = 160 mg/m^3) versus the GGV of 1050 mg/m^3; exposure to all of the C9 aromatic constituents collectively would be approximately 40 mg/m^3 (0.2 x 200 = 40 mg/m^3) versus a GGV of 50 mg/m^3. If we assume that the solvent contained 1% naphthalene and 1% diethylbenzene isomers, each comprises about 1% of the vapor phase, or approximately 2.0 mg/m^3 (versus an SSV of 50 mg/m^3 for naphthalene and a recommended occupational exposure limit of 28 mg/m^3 for diethylbenzene isomers).

(ii) **De-aromatized white spirit** – These solvents are like those in example (i) but have lower aromatic contents. De-aromatized white spirit grades are defined by the naming convention as containing < 2% aromatics. Using 2% aromatics as a boundary condition:

Table 3 Calculating the Occupational Exposure Limit for De-Aromatized (<2% aromatics) White Spirit

[4] "White Spirit" is a trade name widely used in Europe for a C9-C12 aliphatic solvent containing ≤25% aromatic constituents. In the United States solvents of this type are referred to as mineral spirits or Stoddard solvent.

[5] The calculated values should be rounded to preferred values following the ACGIH rounding rules in which values < 100 mg/m^3 are rounded to the closest 25; values > 100 mg/m^3, but < 600 mg/m^3 are rounded to the closest 50; and values > 600 mg/m^3 are rounded to the closest 200.

Constituent	Molar Fraction (liquid phase)	GGV (mg/m^3)	F/GGV	1/∑ (mg/m^3)
C9-C15 aliphatics	0.98	1050	0.00093	
C9-C15 aromatics	0.02	50	0.0004	
Sum			0.00133	752

the RCP OEL = 752 mg/m^3 which rounds to 800 mg/m^3. Note that had the aromatic contribution been ignored, the OEL would have been 1050 mg/m^3 (the GGV for the aliphatic constituents) which rounds to 1000 mg/m^3. In either case, exposure to the aliphatic fraction would be lower than the GGV of 1050 mg/m^3 and exposure to the aromatic fraction would be $\leq$ 20 mg/m^3 (versus a GGV of 50 mg/m^3).

(iii) **Varnish Maker's and Painters' (VM&P) Naphtha** – This example is based on historical data for a solvent which may no longer be commercially available. This is useful as an example because it is composed of constituents across a wide volatility range and is relevant to the concept of solvent blends which are discussed in the next section. As shown in Table 4, VM&P naphtha was composed of 47% C5-C8 aliphatic constituents, 41% C9-C11 aliphatic constituents, 2% toluene, 6% xylene, and 4% C9-C10 alkylbenzenes. Using the ACGIH TLV® values, the RCP OEL = 402 mg/m^3 (rounded to 400 mg/m^3).

Table 4 Calculating the Occupational Exposure Limit for Varnish Makers' and Painters' Naphtha

Constituent	Molar Fraction (liquid phase)	GGV (mg/m^3)	F/GGV	1/∑ (mg/m^3)
C5-C8 aliphatics	0.47	1400	0.00034	
C9-C15 aliphatics	0.41	1050	0.00039	
C9-C15 aromatics	0.04	50	0.00080	
Toluene	0.02	75	0.00027	
Xylene isomers	0.06	87	0.00069	
Sum			0.00249	402

As shown in the previous example, exposure to C5-C8 aliphatic hydrocarbons would be 188 mg/m^3 versus the guidance value of 1400 mg/m^3; exposure to C9-C15 aliphatic hydrocarbons would be 164 mg/m^3 versus the guidance value of 1050 mg/m^3; exposure to toluene would be 8 mg/m^3 versus the guidance value of 75 mg/m^3; exposure to xylenes would be 24 mg/m^3 versus the guidance value of 87 mg/m^3; and exposure to C9-C10 aromatic hydrocarbons would be 16 mg/m^3 versus the guidance value of 50 mg/m^3; In summary, vapor phase levels of all constituents would be below their individual occupational exposure recommendations assuming equivalence of liquid and vapor phase concentrations.

However, because of the relatively wide carbon number distribution of this solvent, the OEL should have been calculated using the molar fractions in the vapor phase; but that would be difficult without more detailed compositional information. Nevertheless, as a first approximation, using the vapor pressure for n-hexane as a surrogate, the C5-C8 fraction would comprise approximately 98% of the hydrocarbons in the vapor phase, and the calculated OEL would be approximately 1400 mg/m^3. Toluene would represent < 1% of the vapor phase hydrocarbons and its OEL of 75 mg/m^3 would not be exceeded. The remaining constituents would constitute a negligible fraction of the vapors. On the other hand, if n-hexane comprised more than 10% of the C5-C8 aliphatic hydrocarbon fraction (which approximates the classification and labelling limit), exposures to n-hexane would be greater than 140 mg/m^3, and the potential for n-hexane to exceed recommended levels would need to be carefully considered. This example illustrates the potential problems that can be associated with calculating OELs for hydrocarbon solvents encompassing a relatively wide carbon number range as well as the need to have detailed compositional information, particularly for any constituents with unusual toxicological properties.

5.2 Calculating OELs for solvent blends

The reciprocal calculation procedure can also be used for solvent blends when all components of the blend meet the same principle of additivity that applies to hydrocarbon solvents (see Appendix C for empirical evidence that hydrocarbon solvent constituents act additively); whether all blend constituents are additive is the responsibility of the blend manufacturers and beyond the scope of this paper. However, it should be noted that blends are more likely to cover wider carbon number ranges than hydrocarbon solvents, and it may be more appropriate to use the molar fractions in the vapor phase as the basis for the calculations as described in the following section. The potential for interactive effects should also be considered, particularly with n-hexane-containing solvents.

5.3 Liquid versus vapor phase calculations

For most of the hydrocarbon solvents, the vapor pressures of the constituents are sufficiently similar that the mole fractions in the liquid phase can be used in the calculations. However, for solvents or solvent blends with boiling ranges $\geq$ 45° C[6], it is better to use the vapor phase molar constituent fractions in the

[6] Advice from the ACGIH® and the Ontario Ministry of Labor is that the RCP should be "restricted to applications where the boiling points of the solvents in the mixture are relatively narrow", i.e., within a range of < 45°C and with vapor pressures within approximately one order of magnitude.

calculations to avoid the possibility of over-exposure to the more volatile components. As one example, consider a hypothetical hydrocarbon solvent blend containing 20% n-hexane, 40% n-octane and 40% n-nonane. If the liquid phase percentages and the ACGIH TLV® values are used in the reciprocal formula, the calculated vapor concentration is 556 mg/m^3 (which rounds to 550 mg/m^3).

Table 5 Calculating the Occupational Exposure Limit for a Hypothetical Solvent Blend Assuming Similarity of Liquid and Vapor Compositions

Constituent	Molar Fraction (liquid phase)	GGV (mg/m^3)	F/GGV	1/∑ (mg/m^3)
n-Hexane	0.20	176	0.0011	
n-Octane	0.40	1400	0.00029	
n-Nonane	0.40	1050	0.00038	
Sum			0.0018	556

However, n-hexane is by far the most volatile constituent, and, although it only accounts for 20% of the liquid fraction, it represents almost 80% of the hydrocarbons in the vapor phase. More specifically, according to Raoult's Law, the partial pressure of a component is equal to the mole fraction of that component in the liquid phase times the vapor pressure at 25°C. In this example, the vapor pressure for n-hexane = 19.68 kPa and its partial pressure = 3.94 kPa (0.2 x 19.68); the vapor pressure for n-octane = 1.97 kPa and its partial pressure = 0.79 kPa (0.4 x 1.97); and the vapor pressure for n-nonane = 0.59 kPa and its partial pressure = 0.24 kPa (0.4 x 0.59). Using Dalton's Law of partial pressures,[7] the fraction of n-hexane in the vapor phase = 3.94/(3.94 + 0.79 + 0.24) = 0.79, or 430 mg/m^3 which exceeds the recommended occupational exposure limit for n-hexane.

Table 6 Calculating the Occupational Exposure Limit for a Hypothetical Solvent Blend Assuming Using Estimated Vapor Phase Compositions

Constituent	Molar Fraction (vapor phase)	GGV (mg/m^3)	F/GGV	1/∑ (mg/m^3)
n-Hexane	0.79	176	0.0045	
n-Octane	0.16	1400	0.00011	
n-Nonane	0.05	1050	0.000048	
Sum			0.0047	213

[7] The total pressure exerted by a gas is equal to the sum of the partial pressures of the components.

Thus, to avoid over-exposure to n-hexane, it is necessary to revise the calculations using the fractions of the components in the vapor phase. With this revised calculation, the calculated OEL is 213 mg/m^3 (which rounds to 200 mg/mg^3), and, of this, approximately 80% or 160 mg/m^3 would be n-hexane. The estimated exposure to n-hexane is below the ACGIH TLV®; however, to avoid exceeding the SCOEL IOELv of 72 mg/m^3, it would be necessary to use the SCOEL value in the calculation which yields an occupational exposure level of approximately 80 mg/m^3 (which rounds to 75 mg/m^3). In other words, to avoid exceeding the SCOEL recommendations, this hypothetical solvent blend would best be treated as if it were n-hexane for occupational control purposes.

This simple calculation is a useful means of checking whether a recommended OEL is appropriate, especially in situations involving hydrocarbon solvents or solvent blends that contain components of unusual toxicity and/or unusually low national occupational exposure recommendations.

6.0. SSVs and Potentially Problematic Constituents

The RCP approach is a practical and scientifically justified means of controlling exposures to constituents of hydrocarbon solvents. One of the reasons why this is an effective approach is that most hydrocarbon solvent constituents cause similar systemic effects, most of which are additive and that there are no known non-additive interactive effects. Further, because the complex hydrocarbon solvents contain numerous isomeric structures, most constituents are normally present at relatively low levels, so that even if there are constituents with unique toxicological properties, levels would normally be low enough that the OELs calculated using the RCP method would be appropriate. However, there are some constituents for which the potential for occupational exposures should be carefully considered. These potentially problematic constituents are of two types, specifically:

Solvents with constituents that are classified for their toxicological properties such as n-hexane and naphthalene for which SSVs have been established to address situations in which over-exposure to these constituents might occur, and

Other hydrocarbon solvent constituents with their own occupational exposure recommendations including toluene, xylene, ethylbenzene, cyclohexane, cumene, diethyl benzene isomers, triethyl benzene isomers, methylnaphthalene isomers, indene, and biphenyl.

These various constituents present a range of challenges. This section provides general guidance on dealing with these situations, but it is ultimately the responsibility of the manufacturers to make the final decisions as they have the compositional information on the products that they sell.

6.1. Substances with SSVs (n-hexane, naphthalene)

6.1.1 n-Hexane (176 mg/m^3/72 mg/m^3) – n-Hexane may be the most challenging of the aliphatic hydrocarbon solvent constituents; it can cause a serious toxicological effect in humans (peripheral neuropathy); it has occupational exposure values (176/72 mg/m^3) that are well below the guidance value for other C5-C8 aliphatic constituents (1400 mg/m^3); and it has a relatively high vapor pressure. There are 3 types of hexane-containing solvents that need to be considered as well as solvent blends, specifically:

6.1.1.1 C6 aliphatic solvents containing < 5% n-hexane – For these solvents the n-hexane content is low enough that it is not necessary to apply the n-hexane SSV. If it is assumed that the volatility of n-hexane is not substantially different from other C6 isomers in the solvent, the recommended occupational exposure limit would be 1400 mg/m^3 (the GGV for C5-C8 aliphatic solvents) and the estimated n-hexane exposure would be approximately 70 mg/m^3 (0.05 x 1400 = 70 mg/m^3). [Note that this value is close to the SCOEL IOELv of 72 mg/m^3 for n-hexane, so, the potential for hexane exposure should always be considered, even if the n-hexane content is relatively low.] A similar logic applies to aliphatic solvents with constituents of higher molecular weight, but the greater the carbon number differences, the more important it is to consider vapor phase constituent distributions rather than relying on the concentration in the liquid phase.

6.1.1.2 C6 aliphatic solvents containing > 5% n-hexane, <80 n-hexane. An example of a solvent of this type is commercial hexane in which n-hexane represents approximately 50% of the composition. In this example the calculated OEL is 316 mg/m^3 [1/OEL = 0.5/176 + 0.5/1400 = 1/0.00316 = 316 mg/m^3] which rounds to 300 mg/m^3, and the estimated n-hexane exposure is 150 mg/m^3 which accords with the ACGIH TLV®. To avoid exceeding the IOELv, the calculated OEL is [0.5/72 + 0.5/1400 = 1/OEL] 137 mg/m^3 (which should be rounded down to 100 mg/m^3).

6.1.1.3 n-Hexane (i.e., solvents containing > 80% n-hexane) – In this case, the OEL becomes the SSV or 176 (or 72) mg/m^3 (see Table 1).

6.1.1.4 Solvent blends with n-hexane or n-hexane-containing solvents – In this case refer to the example in Section 5.3.

6.1.2 Naphthalene (50 mg/m^3) – Naphthalene is less challenging than n-hexane because its SSV of 50 mg/m^3 is the same as the respective group guidance value of 50 mg/m^3 and because it is less volatile than the trimethylbenzene isomers on which the group guidance value is based. Naphthalene-containing solvents are classified as potentially carcinogenic at levels > 1% and the use of the SSV is used to differentiate the solvents based on classification limits. However, for a hypothetical aromatic hydrocarbon solvent, the calculated OEL for an aromatic solvent containing 1% naphthalene would be about 50 mg/m^3, [1/OEL = 0.99/50 + 0.01/50. OEL = 50 mg/m^3] and the exposure to naphthalene would be about 0.5 mg/m^3. If, for purposes of illustration, it is assumed that the naphthalene content is 10%, the calculated occupational exposure limit would be 50 mg/m^3 which also rounds to 50 mg/m^3, and the naphthalene concentration in the vapor phase would be approximately 5 mg/m^3. In short, naphthalene can usually be ignored because it would not normally be present at concentrations high enough to have any impact on the calculations. It should also be noted that naphthalene is approximately half as volatile as trimethylbenzene isomers and twice as volatile as methylnaphthalene isomers, so, it will be under-represented in vapors of C9 aromatic solvents but over-represented in the vapors of higher molecular weight aromatic solvents.

6.2 Other Constituents with Occupational Exposure Limits

6.2.1 Low molecular weight aromatic molecules including toluene, xylene isomers and ethylbenzene may be present in hydrocarbon solvents at relatively low levels in the aromatic fractions. - The occupational exposure limits for the C7-C8 aromatic hydrocarbons include: toluene = 75 (192) mg/m^3; ethylbenzene = 87 (442) mg/m^3; and xylene isomers = 87 (221) mg/m^3. Because the occupational exposure levels for these constituents are higher than the GGV of 50 mg/m^3 for the C9 aromatic solvents in which they would most commonly be found, they can normally be considered unimportant. However, some of the individual occupational exposure limits could become important for solvent blends, depending on the relative volatilities of other blend components (see Section 5.1.iii).

6.2.2 Cumene (25/50 mg/m^3)[8] – Cumene which may be present in aromatic solvents, usually at levels $\leq$ 3%, but since the exposure limits are not far below the 50 mg/m^3 guidance values for aromatic solvents, cumene should not be problematic when present at low levels. Consider an aromatic solvent containing cumene at 3%. Using the ACGIH TLV®, the RCP calculation is (0.97/50) + (0.03/25) = [0.0194 + 0.0012 = 0.0206] = 49 mg/m^3 which rounds to 50 mg/m^3.

[8] The ACGIH and SCOEL referenced their occupational exposure recommendations to the same study, a chronic inhalation study in which cumene produced respiratory tract tumors in rats and mice for which the underlying mechanism is believed to be related to a repeated irritation process. The ACGIH focused on liver effects as the point of departure in developing the TLV® whereas SCOEL based its recommendation on respiratory irritation.

6.2.3 Cyclohexane (350/700 mg/m^3)[9] – Cyclohexane which may be present in C5-C8 aliphatic solvents presents challenges like those of n-hexane in that it has occupational exposure levels (350/700 mg/m^3) that are below the group guidance value (1400 mg/m^3), and it is volatile. As a first approximation, it could be assumed that at concentrations > 25%, exposure to cyclohexane would exceed the ACGIH TLV®,[10] but if cyclohexane levels are relatively low, no action may be necessary. However, when cyclohexane concentrations approach 25%, it becomes necessary to consider the impact of volatility to assure that cyclohexane is not over-represented in the vapor phase. This may be particularly important for solvent blends. As with cumene, the manufacturer may be able to limit cyclohexane levels in the commercial solvents or to take some other action; if not it may be necessary to adjust the occupational exposure limit calculations. Because the IOELv for cyclohexane is 700 mg/m^3, it may not be necessary to make any adjustments to limit exposure to cyclohexane unless it is present at relatively high concentrations or is one on the more volatile constituents of a complex solvent or solvent blend.

6.2.4 Diethyl- and triethylbenzene isomers (28 mg/m^3) – The diethyl- and triethylbenzene isomers are neurotoxic in animals and may be present at low levels in aromatic solvents. As neither SCOEL nor the ACGIH® have recommended occupational exposure limits, the AIHA WEEL of 28 mg/m^3 is suggested as an occupational control value. In practical terms, this is analogous to the situation with naphthalene, i.e., the concentrations of these constituents in hydrocarbon solvents are unlikely to ever be high enough (i.e., > approximately 56%) for over-exposure conditions to exist, but this needs to be verified, and, if necessary, appropriate measures need to be taken.

6.2.5 Methylnaphthalene isomers (3/2.5 mg/m^3) – The methylnaphthalene isomers situation is potentially the most problematic since the occupational exposure guidance is far below the GGV of 50 mg/m^3 for this group of solvents. The manufacturers will need to carefully consider the levels of the various constituents in this group of solvents to determine how best to deal with this situation. Note that the ACGIH has proposed to lower the TLV® of methylnaphthalene to 0.3 mg/m^3 and that may be even more problematic (i.e., 6% versus 0.6% concentration in the solvent).

6.2.6 Indene (24 mg/m^3) – Indene could be present in low levels in aromatic solvents. It seems unlikely that indene would be present at levels high enough (approximately 48%) that exposure could exceed its occupational exposure limit, but that would have to be determined by the manufacturer. This is analogous to the diethylbenzene and triethylbenzene isomers example above.

[9] Note that the difference between ACGIH and SCOEL relates to the interpretation of a volunteer study in which humans reported headaches following cyclohexane exposure. The ACGIH considered this to have been an adverse effect; SCOEL considered it to have been an incidental finding.

[10] 350 mg/m^3/1400 mg/m^3 = 0.25

6.2.7 Biphenyl (1.3/1.2 mg/m^3) - Biphenyl is a potential constituent of aromatic solvents which requires careful consideration due to its low occupational exposure limit. To avoid over-exposure, it may be necessary to either limit biphenyl concentrations in the solvent to less than 2.4% or to take the concentration of biphenyl into consideration in calculating the occupational exposure levels. Note that biphenyl is less volatile than C9 aromatic hydrocarbons and would likely be under-represented in the volatile fraction.

7. Toxicological justification for recommended GGV values

In the past occupational exposure guidance for complex hydrocarbon solvents was primarily focused on avoiding acute central nervous system (CNS) depression and upper respiratory tract irritation. As information has accumulated, it has been coming increasingly clear that, aside from a few well characterized hydrocarbon solvent constituents, hydrocarbon solvents do not cause relevant adverse effects, are not selective developmental toxicants, do not reduce fertility and are not genotoxic. Thus, the strategy of controlling exposures to avoid acute effects seems not only pragmatic but well supported by the data from animal studies. Additionally, studies of complex hydrocarbon solvents containing constituents of several molecular types have shown that the toxicological effects can be predicted from the types and levels of the components present. In other words, the principal of additivity for hydrocarbon solvents has been demonstrated empirically (see Appendix C). The guidance values include:

7.1 C5-C8 aliphatic constituents [excepting n-hexane] (1400 mg/m3) – The GGV for this group of constituents is based on the ACGIH TLV® of 1400 mg/m^3 for octane. These constituents can cause acute CNS effects in humans at high exposure levels (Patty and Yant, 1929), but animal studies indicate that current occupational exposure recommendations are below experimentally determined no effect levels in animals and are also below predicted no effect levels in humans (Lammers *et al*., 2009; 2011; McKee *et al*., 2011; 2019) (see Appendix A). The only systemic effects observed in animal studies have been liver enlargement, a compensatory and reversible effect, and renal nephropathy in male rats, a species-specific effect associated with α2u globulin induction. Although not all constituents have been studied in detail, animal studies have provided no evidence for developmental toxicity or effects on reproduction, and there is no evidence that any of the solvents or constituents is genotoxic. Further, aside from n-hexane (for which a specific substance value has been established), these solvents do not produce chronic neurotoxicity. In studies of acute CNS effects in rats, none of the n- or iso-paraffins was active at the highest concentrations tested, making 14000 mg/m^3 the lowest no effect level for all these constituents (Lammers *et al*., 2011; McKee *et al*., 2011). The lowest no effect level for the corresponding cycloparaffins was 4200 mg/m^3. Based on pharmacokinetic models validated with human data (Hissink *et al*. 2007; 2009), it is predicted that the no effect levels for n-and iso-paraffins in humans would be similar to those in rats but that the human no effect levels for cycloparaffins would be approximately half those in rats, making 2100 mg/m^3 the lowest no effect level for acute CNS effects for all of the C5-C8 aliphatic hydrocarbon

solvent constituents.[11] As there is no human evidence to contradict this prediction, the GGV of 1400 mg/m^3 seems protective for all of the toxicologically relevant effects associated with this group of solvents.

7.2 C9-C15 Aliphatic Solvents (1050 mg/m3) - The GGV for C9-C15 aliphatic constituents is based on the ACGIH® TLV which is itself based on a repeated dose inhalation toxicity study of n-nonane (8400 mg/m^3, Carpenter *et al*., 1978) in which the only effects at the highest exposure level were acute CNS effects and reduced weight gain; no systemic effects were observed. Other repeated dose studies of C9-C15 aliphatic solvents and their constituents provide evidence that normal paraffins do not cause systemic toxicity, are not developmental toxicants, do not affect fertility and are not genotoxic (summarized in Appendix B). Iso-paraffinic and cyclo-paraffinic constituents can cause liver enlargement and male rat kidney effects, and in some studies exposure to iso-paraffins has resulted in small but statistically significant reductions in hematological parameters, but none of these effects is toxicologically relevant to humans. It has been reported that acute CNS effects can be produced by nonane (Carpenter *et al*., 1978) and decane (McKee *et al*., 2011; 2019), but not by aliphatic constituents with carbon numbers > C10 (Nilsen *et al*., 1988). Accordingly, the lowest no effect levels for CNS effects associated with C9-C15 aliphatic constituents are 3000 mg/m^3 for decane (McKee *et al*., 2019) for which the predicted human no effect level is also 3000 mg/m^3, and 5000 mg/m^3 for a C10 cycloparaffinic solvent (McKee *et al*., 2011) for which the predicted human no effect level is 2500 mg/m^3 (see Appendix A). Following the logic discussed in the previous paragraph, the lowest predicted no effect level in humans for CNS effects of all C9-C15 aliphatic constituents is 2500 mg/m^3. In human studies there were no indications of either acute CNS effects or upper respiratory tract irritation (or any other clinical findings) at levels up to 1228 mg/m^3, the highest level tested (Pedersen and Cohr, 1984a; b). Accordingly, the GGV of 1050 mg/m^3 is supported by both toxicological data and empirical evidence.

7.3 C9-C15 aromatic solvents [excepting naphthalene] (50 mg/m3) – The GGV for this group of hydrocarbon solvent constituents was based on occupational exposure levels for trimethylbenzenes from ACGIH® (50 mg/m^3). Historically occupational exposure recommendations for aromatic solvents were based on observations of upper respiratory tract irritation in occupational environments among workers exposed at higher exposure levels (e.g., Battig *et al*., 1956; 1958). The recommendation was extended to other aromatic constituents based on evidence that acute CNS effects and upper respiratory tract irritation were the endpoints best suited for occupational exposure guidance. In studies of acute CNS effects (e.g., McKee *et al*., 2010), no effect levels for C9-C11 aromatic constituents ranged from 200 mg/m^3

[11] To relate acute CNS effects in rats and humans, behavioral studies were conducted in both species using cyclohexane and white spirit (a C9-C12 aliphatic solvent containing 25.6% C9 aromatic hydrocarbons) as model compounds (Hissink et al., 2007; 2009). Samples of blood and brain tissue were taken from rats at various times during and after the exposure period for use in developing toxicokinetic models. The models were validated by comparison to samples of blood and expired air from the volunteers. The models predicted that, at equivalent exposure levels, brain concentrations of normal paraffins would approximate in rats whereas the concentrations of aromatics and cycloparaffins would be approximately twice those in the rats. Assuming acute CNS effects to be similar at equivalent brain concentrations, consistent with the empirical evidence, the predicted no effect levels for normal paraffins in humans would be like those in rats whereas those of aromatics and cycloparaffins would be half those in rats.

– 1250 mg/m^3. Modeling indicates that CNS levels of aromatics in the central nervous system are approximately twice those of rats at equivalent external exposure levels predicting a human no effect level of approximately 100-600 mg/m^3. Human observations suggest that upper respiratory tract irritation may be the most sensitive indicator of the effects of these constituents. Studies with volunteers indicate that exposures ranging from approximately 125 – 250 mg/m^3 are well tolerated (Carpenter *et al*., 1975; 1977; Jarnberg *et al*., 1996; 1997; 1998; Jones *et al*., 2006). In short, both toxicological studies and empirical observations indicate that an occupational exposure limit of 50 mg/m^3 is appropriate to avoid the acute effects of C9-C15 aromatic hydrocarbon solvents.

In studies of longer-term effects, a C9 aromatic solvent was evaluated for repeated dose toxicity in rats following exposure by inhalation for 13 weeks and 12 months (Clark *et al*., 1989). Increased weights of liver and kidneys were observed, but there were no pathological changes in these organs. Further, one group of rats was exposed to the highest concentration tested (1830 mg/m^3) for 12 months and then held for 4 weeks without treatment. As the organ weights were similar to control values at the end of the recovery study, the authors concluded that the increased organ weights had been adaptive responses rather than toxicologically significant effects, making the overall no observed adverse effect concentration in the 12-month study 1830 mg/m^3. Similar results have been reported in other studies of C9 aromatic solvents and solvent constituents (see Appendix B). In a repeated dose study of a C10-C13 aromatic solvent in which test material was administered by gavage, small but statistically significant reductions in hematological values which were reversed in a recovery study. The no effect level was reported as 300 mg/kg/day (summarized in McKee *et al*., 2015). C9 aromatic solvents and their constituents are not selective developmental toxicants (e.g., McKee *et al*., 1990) and do not affect fertility (McKee *et al*., 1990). Additionally, C9 aromatic solvents do not cause chronic neurotoxicity (Douglas *et al*., 1993) and they are not genotoxic (Schreiner *et al*., 1989). In the absence of any evidence that these aromatic solvents cause toxicologically important systemic effects, a decision to base occupational exposure limits on upper respiratory irritation is reasonable.

There are some C9-C15 aromatic hydrocarbon constituent issues that merit additional comment.

Naphthalene and cumene have been reported to cause respiratory tract tumors in rodents, and are classified as animal carcinogens); however, these tumors are thought to be the consequence of a process of repeated irritation which is considered to be the key effect. Accordingly, the occupational exposure levels recommended for these substances by SCOEL and/or ACGIH® are based on non-carcinogenic effects.

Diethyl- and triethylbenzene isomers have been found in rodent studies to produce pathological changes in the central nervous system.

Indene was reported to cause liver and kidney effects in experimental studies in animals at high exposure levels; and

Biphenyl was reported to cause bladder tumor formation in male rats and liver tumors in female mice in long term dietary studies (by a mechanism that may not be relevant to humans).

For purposes of the discussion here, these effects have been considered in the occupational exposure recommendations for these constituents (note, in the absence of specific guidance from either ACGIH® or SCOEL, the AIHA WEEL of 28 mg/m^3 is recommended for use in situations in which exposure to diethylbenzene and triethylbenzene isomers could be problematic) and more detailed information is provided in Appendix B.

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APPENDICES

(A) Acute effects: Acute Central Nervous System (CNS) Effects and Upper Respiratory Tract Irritation.
(B) Toxicological justification for recommended group guidance values
(C) Evidence that constituents of hydrocarbon solvents produce additive effects

Appendix A. Acute Effects: Acute Central Nervous System (CNS) Effects and Upper Respiratory Tract Irritation

Acute CNS effects and upper respiratory tract irritation have been used to set occupational exposure limits for hydrocarbon solvents for many years. Providing support for that strategy is that acute CNS effects are a common property of volatile hydrocarbon solvents (Ridgway *et al*., 2003); they are among the most sensitive effects associated with hydrocarbon solvent exposure; and they can be observed in humans in the occupational environment as well as in volunteer studies under controlled conditions. Under normal circumstances these changes rapidly resolve after termination of exposure, but more severe changes can develop if the exposures are prolonged or repeated. Because the acute central nervous system effects can be reproduced in rats, an experimental program was conducted to systematically characterize the acute CNS effects of hydrocarbon solvents and selected constituents in rats (Lammers *et al*., 2009; 2011; McKee *et al*., 2010; 2011; 2019) and to also obtain data that could be used in the development of physiologically-based pharmacokinetic (PBPK) models (Hissink *et al*., 2007; 2009). Additionally, data were collected in human volunteer studies that could be used for pharmacokinetic model validation (Lammers *et al*., 2007; 2011). Among other things, it was shown that, at equivalent external concentrations, the predicted brain levels of normal paraffins in humans approximated those measured in rats whereas those of cycloparaffins and aromatics were approximately twice those measured in rats (Hissink *et al*. 2007; 2009). Thus, if it is assumed that humans and rats would experience acute CNS effects at similar brain levels of hydrocarbons, external concentrations to produce low and no effect levels of normal and isoparaffins would be similar in both species, whereas those of cycloparaffins and aromatics in humans would be approximately half the values experimentally determined in rats.

In a complementary set of series of studies, Zahlsen and co-workers (Zahlsen *et al*., 1992; 1993) showed in rats that levels of hydrocarbons in the central nervous system increase with increasing carbon number to C9 (cycloparaffins) or C10 (normal and isoparaffins and aromatics). However, at carbon numbers > C10, uptake of hydrocarbons into the central nervous system is inhibited. It was shown experimentally that acute CNS effects could not be produced by aliphatic hydrocarbons > C10 at maximally attainable vapor concentrations (Nilsen *et al*. 1988). These results are summarized in figures A1 and A2.

GGV: C5-C8 Aliphatic Constituents (excluding n-hexane)

With respect to the recommended GGV for C5-C8 aliphatic solvents (1400 mg/m^3), the no effect levels associated with acute effects of C5-C8 n- and iso-paraffins in rats were above 14,000 mg/m^3. A C6/C7 cycloparaffinic solvent produced minor, reversible changes in latency to response in visual discrimination testing at 14,000 mg/m^3 with a no effect level of 4200 mg/m^3. Using the relationship between brain levels in humans and rats discussed above, the predicted human no effect level for acute CNS effects of C6/C7 cycloparaffins would be approximately 2100 mg/m^3. Both Patty and Yant (1929) and Carpenter *et al*. (1975) reported behavior suggestive of acute CNS effects at exposure levels > 1000 ppm (approximately 4000 mg/m^3) in humans. Thus, there is both experimental evidence in animals and empirical evidence from human experience supporting the expectation that an occupational exposure level of 1400 mg/m^3 would protect humans from acute CNS effects of C5-C8 aliphatic hydrocarbon solvent constituents.

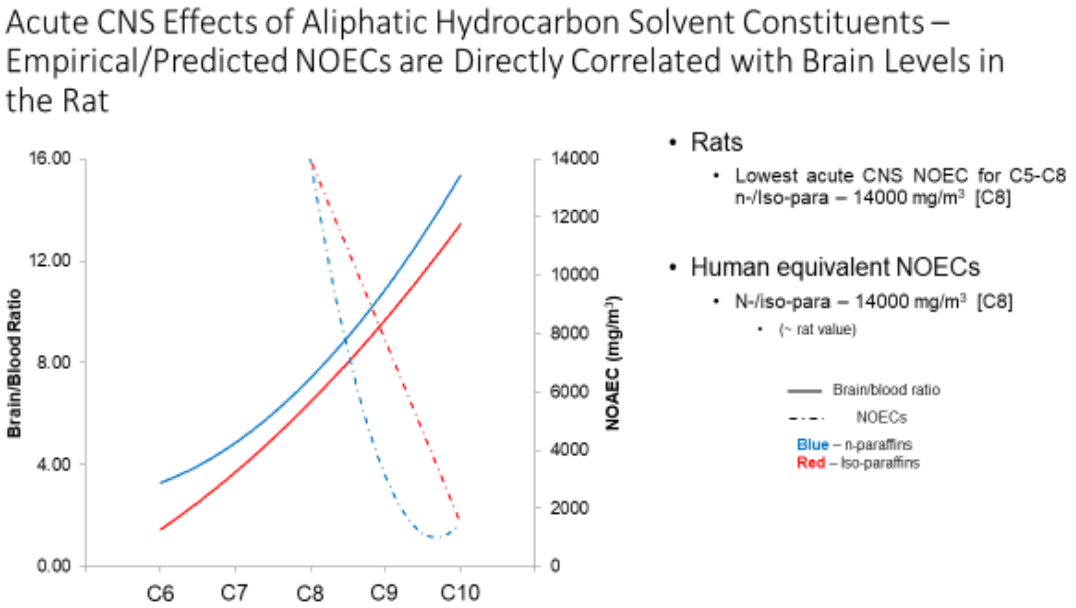
GGV: C9-C15 Aliphatic Constituents

With respect to the GGV for C9-C15 aliphatic hydrocarbons (1050 mg/m^3), the experimentally determined no effect level for acute CNS effects of C10 n-paraffins in rats is 3000 mg/m^3, corresponding to a predicted human no effect level of 3000 mg/m^3 (McKee *et al.*, 2019). The no effect level for C10 cycloparaffins in rats is 5000 mg/m^3 (McKee *et al*., 2011), corresponding to a predicted human no effect level of 2500 mg/m^3. Pedersen and Cohr (1984a; b) reported that there was no evidence for either acute CNS effects or upper respiratory tract irritation in volunteers exposed to a C9-C14 aliphatic solvent at levels up to 1228 mg/m^3. Thus, there is both experimental evidence in animals and empirical evidence from human experience showing that an occupational exposure level of 1050 mg/m^3 would protect humans from acute CNS effects of C9-C15 aliphatic hydrocarbon solvent constituents.

GGV: C9-C15 Aromatic Constituents

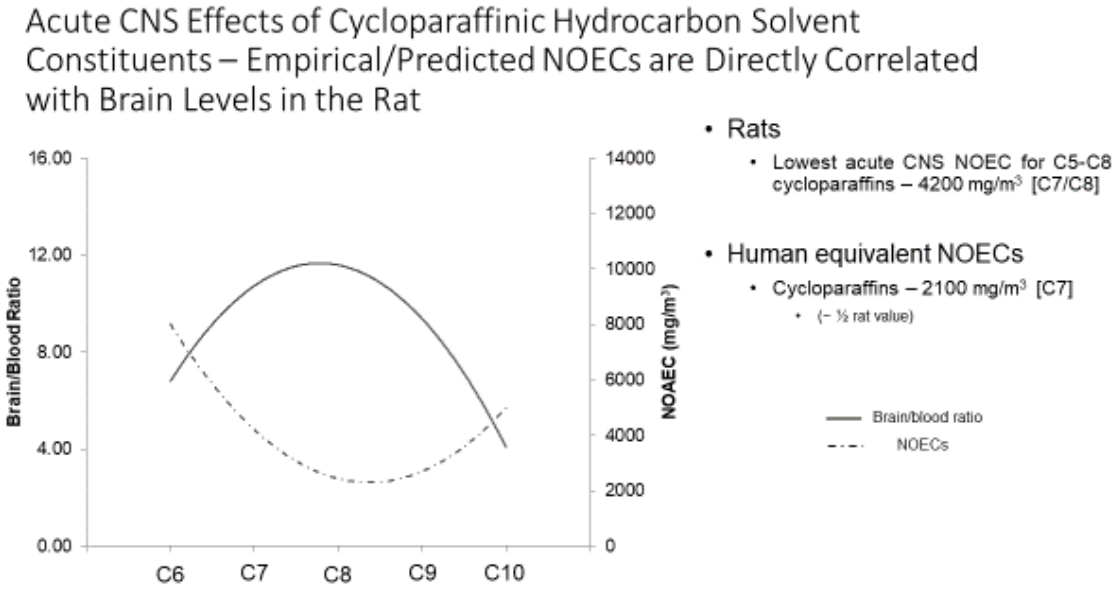
With respect to the GGV for C9-C15 aromatic constituents (50 mg/m^3), an experimental study in rats to systematically characterize the acute CNS effects of aromatic hydrocarbon solvents and their constituents, provided evidence that such effects were not produced at levels below 1000 mg/m^3 (McKee *et al*., 2010). Pharmacokinetic modeling (Hissink *et al*., 2007) predicted that brain concentrations of humans would be approximately twice those of rats at equivalent exposure levels, supporting a theoretical no effect level in humans for acute CNS effects of 500 mg/m^3. Neither upper respiratory tract irritation nor acute CNS effects were observed in volunteers exposed for 4-8 hours at exposure levels up to 150 mg/m^3 (Jarnberg *et al*., 1996; 1997; Jones *et al*., 2006; Krostrzewski *et al*. 1997). In summary, 50 mg/m^3 is supported by both experimental evidence and human experience as a protective level for acute CNS effects and respiratory irritation associated with exposure to C9-C15 aromatic hydrocarbon solvents and their constituents.

Figure A1. Acute CNS effects of aliphatic hydrocarbon solvent constituents.



1. Lammers et al, 2009; 2. Lammers et al., 2011; 3. McKee et al., 2011; 4. Zahlsen et al., 1992; 5. Zahlsen et al., 1993; 6. Carpenter et al., 1978;

Figure A2. Acute CNS effects of cycloparaffinic hydrocarbon solvent constituents.



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Appendix B. Toxicological justification for recommended group guidance values (repeated dose effects). An overview of the toxicological information with summary tables.

(1) C5-C8 Aliphatic Hydrocarbon Solvent Constituents (excluding n-hexane), Group Guidance Value = 1400 mg/m^3

(i) C5-C8 Normal Paraffins (excluding n-hexane)

N-Pentane (C5) – There have been two 90-day inhalation toxicity studies of n-pentane. In the first of these (McKee *et al*., 1998) male and female rats were exposed by inhalation to pentane vapors, 6 hours/day, 5 days/week for 90 days, at which point surviving animals were sacrificed and examined for changes in serum chemistry and hematological parameters, and gross and microscopic examinations were conducted on selected tissues. Exposure levels were 5000, 10,000 and 20,000 mg/m^3 (corresponding to systemic doses of approximately 170, 340 or 680 mg/kg[12]). There were no effects that were considered treatment-related, making the highest level tested the overall no–effect level for the study. These results were later confirmed in an independent study of similar design (Kim *et al*., 2012).

With respect to other endpoints, n-pentane had no effects on developmental toxicity in a study in which rats were given 2000 mg/kg/day by gavage on gestational days 5-15 (McKee *et al*., 1998), and was similarly without effect in a study in which pentane was administered by inhalation at levels up to 10,000 ppm (Hurtt and Kennedy, 1999). Kirwin *et al*. (1980) reported that n-pentane was inactive in *Salmonella*. It produced equivocal results in an *in vitro* chromosome aberration test but was negative in an *in vivo* micronucleus test using mouse bone marrow (McKee *et al*., 1998). Finally, n-pentane did not cause peripheral neuropathy when tested in rats (Takeuchi *et al*., 1980; Frontali *et al*., 1981).

N-Hexane (C6) – Because n-hexane is classified for its neurotoxic properties, it has a specific substance value which is described in more detail below. The information most directly relevant to the GGV for C5-C8 aliphatic solvent constituents is from a study of commercial hexane, a complex hexane solvent containing 52% n-hexane, 30% iso-hexane isomers, 15% methylcyclopentane, and 3% cyclohexane. In a repeated dose study rats were exposed to commercial hexane at exposure levels of 2700, 9000, or 27,000 mg/m^3 6 hours/day, 5 days/week for 90 days (Duffy *et al*., 1991). The necropsy revealed increased liver weights in the high exposure group. The pathological investigation provided evidence of α2u globulin-mediated male rat kidney effects along with some liver changes in high dose male rats. The no effect level was 9000 mg/m^3 (equivalent to a systemic dose of approximately 550 mg/kg).

[12] Systemic doses following inhalation exposure were estimated using relationships published by Dahl *et al*. (1989).

In other tests it was found that commercial hexane was not a developmental toxicant (Keenan *et al*., 1991; Daughtrey *et al*., 1994a), had no effects on fertility (Daughtrey *et al*., 1994a) and was not genotoxic under either *in vitro* or *in vivo* conditions (Kirwin *et al*., 1991; Daughtrey *et al*., 1994b).

N-Heptane (C7) - In a 26-week study, rats were exposed to n-heptane by inhalation at levels of 398 or 2970 ppm, 6 hours/day, 5 days/week (API, 1980). The estimated systemic doses associated with the exposure levels were 66 mg/kg and 475 mg/kg. No effects were reported, making the overall no effect level 475 mg/kg, the highest level tested.

In other studies n-heptane was reported as inactive in a battery of short-term tests for genetic toxicity (Brooks *et al*., 1988). Additionally, n-heptane does not cause chronic neurotoxicity (Takeuchi *et al*., 1980; Frontali *et al*., 1981).

N-octane (C8) - In a 13-week study rats were exposed to n-octane by inhalation at levels of approximately 195, 550, or 1571 ppm (930, 2620, 7480 mg/m^3), 6 hours/day, 5 days/week (Sung *et al*., 2010). The estimated systemic doses associated with these exposure levels were 53, 148, or 424 mg/kg. No effects were reported making the overall no effect level 424 mg/kg.

In summary, repeated dose studies have been conducted for all C5-C8 normal paraffins, and, except for the neurological effects associated with n-hexane, no systemic effects have been reported at the highest exposure levels assessed. Additionally, several of these constituents have been tested for developmental and/or reproductive toxicity with no effects being observed. Parenthetically, as discussed in more detail in the next section, there are data to show that C10 and C11 normal paraffins do not produce human-relevant systemic effects and are not developmental or reproductive toxicants. Thus, n-heptane, n-octane and n-nonane are covered on a read-across basis. Further, to the extent that data are available, none of the C5-C8 aliphatic constituents is genotoxic.

(ii) C5-C8 Isoparaffinic Constituents

Isopentane (2 methylbutane) – Yu *et al*. (2011) reported a one generation reproductive toxicity study in which rats were given isopentane by oral gavage in daily doses of 100, 300, or 1000 mg/kg/day. No effects were reported in any of the reproductive or developmental parameters measured. The overall no effect level was 1000 mg/kg. Additionally, isopentane was reported to be non-genotoxic (Kirwin *et al*., 1980).

C4-C9 isoparaffinic substance – The test material, a light paraffinic stream consisting of C4-C9 iso-paraffinic constituents, was tested for repeated dose effects in an inhalation toxicity study (Schreiner *et al*., 1998). Rats were exposed 6 hours/day, 5 days/week to vapor at levels of 668, 2220, or 2250 ppm. Estimated systemic doses were 71, 238, or 656 mg/kg.[13] The authors reported elevated kidney weights

[13] As α2u-globulin nephropathy is associated with iso-paraffins with carbon numbers ≥ C6 (Halder *et al*., 1985), the C4 and C5 constituents do not cause α2u globulin-mediated nephropathy and were excluded from the systemic dose calculations.

with evidence of α2u globulin-mediated nephropathy in male rats from all dose groups and elevated liver weights in both male and female rats from the high dose group. Accordingly, based on these data, the no effect level for male rat kidney effects is < 100 mg/kg and the low effect level for liver effects is > 238 mg/kg.

The same test material was inactive in studies of developmental and reproductive toxicity at levels up to 25000 mg/m^3 (Bui *et al*. 1998) and did not cause chronic neurotoxicity (Schreiner *et al*., 1998).

C6 Isoparaffins – Iso-hexanes did not cause peripheral neuropathy or provide other evidence of non-acute neurotoxic effects (Egan *et al*., 1980).

C8 iso-paraffinic solvent – the test material was a hydrocarbon solvent consisting almost entirely of C8 iso-paraffins (summarized in Carrillo *et al*., 2013). Male and female rats were exposed 6 hours/day, 5 days/week to vapor at levels of 400 or 1200 ppm, corresponding to systemic doses of approximately 100 or 300 mg/kg. Kidney weights were significantly elevated in males from the high exposure group, and there was histological evidence of kidney effects in males from both exposure groups, but there were no effects on liver weights in either of the exposed groups. The no effect level for male rat kidney effects (which are not relevant to humans) was < approximately 100 mg/kg and the low effect for liver weight effects was > 300 mg/kg.

C8 Isoparaffinic Solvent - A C8 iso-paraffinic solvent did not cause selective developmental effects (Johnson *et al*., 2012). Additionally, the same C8 isoparaffinic solvent was not mutagenic in a mouse lymphoma test, did not induce mutation or sister chromatid exchange in human lymphocytes (TK 6 C3H cells), and did not induce unscheduled DNA synthesis in rat or mouse hepatocytes tested under both *in vitro* and *in vivo* conditions. Finally, this solvent was reported to have been inactive in a dominant lethal test in Sprague-Dawley rats following exposure by inhalation at 1200 ppm.

In summary, C5-C8 isoparaffins caused liver enlargement and the high molecular weight species caused α2u globulin-mediated nephropathy in male rats, but neither of these effects is relative to humans. Similarly, the data indicated that C5-C8 isoparaffins were not reproductive or developmental toxicants and did not cause neurological effects. Finally, the mutagenicity data did not provide any indication that C5-C8 isoparaffins were genotoxic.

(iii) C5-C8 Cycloparaffinic Constituents

C5 Cycloparaffins (cyclopentane) – The potential for systemic effects associated with cyclopentane was assessed in a 90-day inhalation toxicity study in rats with target exposure levels of 5000, 10000, or 30000 mg/m^3 (summarized in Galvin and Maraschi, 1999). There were no treatment related effects, and the overall no effect level was the analytically determined concentration of 30000 mg/m^3 (equivalent to an absorbed dose of approximately 260 mg/kg/day). In other studies, cyclopentane was also found to be

inactive in a battery of tests for genetic toxicity including *Salmonella*, mouse lymphoma, an *in vitro* chromosome aberration assay in human lymphocytes and an *in vivo* micronucleus test in mouse bone marrow (Galvin and Maraschi, 1999).

C6 (Cycloparaffin, Cyclohexane) – Malley *et al*. (2000) reported that in a study in which rats were exposed 6 hours/day, 5 days/week for 14 weeks to cyclohexane at levels of 500, 2000, or 7000 ppm (estimated systemic doses of 75, 300, or 1000 mg/kg), liver weights were elevated in the animals from the highest exposure group (NOEL = 300 mg/kg), but there were no effects in male rat kidneys (NOEL = > 1000 mg/kg). The liver weights of treated rats were not significantly different from control values at the end of a 4-week recovery period.

In other studies, cyclohexane was not a developmental toxicant in rats or rabbits (Kreckman *et al.,* 2000) and had no effects on fertility when tested in rats in a two-generation reproductive toxicity test (Kreckman *et al.,* 2000). A summary of published and unpublished information provided no indication that cyclohexane was mutagenic under *in vitro* or *in vivo* conditions (U.S. EPA, 2003). And, finally, cyclohexane exposure did not cause chronic neurotoxicity (Frontali *et al*., 1981; Malley *et al*., 2000).

C6 (methylcyclopentane) – Yang *et al*., (2014) reported a study in which rats were exposed to methylcyclopentane by inhalation at levels of 880, 3900 or 18000 mg/m^3, 6 hours/day, 5 days/week for 90 days. The only effects reported were some small increases in liver and kidney weights, without pathological changes, in the high dose group animals. The no effect level was the highest exposure level tested, 18000 mg/m^3.

C7 (Methylcyclohexane) – Kinkead *et al*. (1985) reported that in a study in which rats were exposed to methylcyclohexane, 6 hours/day, 5 days/week for 12 months at concentrations of 400 or 4000 ppm (estimated systemic doses were 71 and 710 mg/kg), male rat kidney effects were observed in the high exposure group (NOEL = 710 mg/kg based on the 400 ppm exposure level). Organ weight data were not provided in the study report.

In summary, based on the examples tested, the C5-C8 aliphatic constituents do not cause systemic effects other than liver enlargement and α2u globulin-mediated male rat kidney effects. As neither of these effects is human relevant, the no adverse effect levels were the highest tested in the respective studies. More specifically, reversible liver enlargement in the absence of pathological changes or elevations of liver enzyme markers is an adaptive response and not an adverse effect (Maranpot, *et al*., 2010). The kidney changes in male rats were the consequence of an α2u globulin-mediated process that is male rat specific and not relevant to humans (Swenberg and McKeeman, 1998; U.S. EPA, 1991). The data indicate that these constituents are not developmental toxicants, and there is no evidence to suggest that they might be reproductive toxicants. C5-C8 aliphatic constituents are not genotoxic and do not cause chronic neurotoxicity.

Table A1. Summarized results of studies of C5-C8 aliphatic hydrocarbon solvent constituents.

Substance	Repeated Dose (NOAEL)	Developmental Toxicity	Reproductive Toxicity	Genetic Toxicity	Chronic neurotoxicity
n-pentane	10,000 ppm [1]	No effects on development	No data reported	Not genotoxic	Not neurotoxic
Iso-pentane	2,250 ppm [2]	No effects on development [2]	No effects on fertility	Not genotoxic	Not neurotoxic
Cyclo-pentane	10,500 ppm [1]	No data reported	No data reported	Not genotoxic	No data reported
Commercial hexane	9000 mg/m^3	No effects on development	No effects on fertility	Not genotoxic	Not neurotoxic
Iso-hexane	2,250 ppm [2]	No effects on development [2]	No effects on fertility [2]	Not genotoxic	Not neurotoxic
Cyclo-hexane	7000 ppm [2]	No effects on development [2]	No effects on fertility [2]	Not genotoxic	Not neurotoxic
Methyl cyclopentane	18,000 mg/m^3 [2]	No data reported	No data reported	No data reported	No data reported
N-heptane	2970 ppm [1]	No data reported	No data reported	Not genotoxic	Not neurotoxic
Iso-heptane		No effects on development [2]	No effects on fertility [2]	No data reported	Not neurotoxic [2]
Methyl cyclohexane	4000 ppm [1]	No data reported	No data reported	No data reported	No data reported
n-octane	1571 ppm [1]	No data reported	No data reported	No data reported	No data reported
Iso-octane	1200 ppm [1]	Not a developmental toxicant	No effects on fertility [2]	Not genotoxic	Not neurotoxic [2]
C8 cycloparaffinic solvent		No data reported	No data reported	No data reported	No data reported

1. No effects observed at the highest level tested.
2. The test material was an isoparaffinic process stream with carbon numbers ranging from C4-C9

In summary, across the range of C5-C8 aliphatic solvent constituents (other than n-hexane), the only systemic effects reported were liver enlargement, a physiological response which is not considered to be an adverse finding (Maranpot *et al*., 2010) and α2u globulin-mediated changes in the kidneys of male rat, a species-specific effect not relevant to humans (Swenberg and McKeeman, 1998; U.S. EPA, 1991). To the extent data are available, none of the C5-C8 aliphatic constituents is a developmental toxicant or affects fertility; none is genotoxic; and none (other than n-hexane which is addressed separately) produces non-acute neurological effects. Although these constituents do produce acute CNS effects, as discussed in Appendix A, the recommended group guidance value is lower than the lowest anticipated no effect levels of the C5-C8 aliphatic constituents as discussed in Appendix A, and there is no human evidence that the occupational exposure levels that were the basis for GGV selection are problematic. Accordingly, the recommendation to use 1400 mg/m^3 as a GGV for C5-C8 aliphatic hydrocarbon solvent constituents, other than n-hexane, is well supported.

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(2) C9-C15 Aliphatic Hydrocarbon Solvent Constituents, Group Guidance Value = 1050 mg/m3

A particular consideration for the C9-C15 aliphatic constituents is that, because of decreasing volatility with increasing carbon number, aliphatic hydrocarbons with carbon numbers > C10 do not contribute substantially to the vapor phase hydrocarbon concentrations. Further, as discussed in more detail above, the potential for aliphatic hydrocarbons with carbon numbers ≥ C10 to cross the blood brain barrier is limited (McKee *et al*., 2019). Finally, aliphatic hydrocarbon constituents > C10 do not produce acute CNS effects as shown empirically in rodent studies (Nilsen *et al*., 1988). Accordingly, the aliphatic constituents with carbon numbers > C10 are probably unimportant in the context of possible exposures by inhalation but are included in this guidance value for calculation purposes. Exposures to aliphatic constituents with carbon numbers > C15 are more likely to involve aerosol formation and should be considered as "particulates not otherwise specified" for exposure control purposes.

(i) C9-C15 Normal paraffins

n-nonane (C9) - In a 13-week study rats were exposed to n-nonane by inhalation at levels of approximately 360, 590, or 1600 ppm, 6 hours/day, 5 days/week (Carpenter *et al*. 1978). The estimated systemic doses were 144, 236, or 640 mg/kg. No systemic effects were reported making the overall no effect level 640 mg/kg, the highest level tested.

n-nonane was inactive in an *in vitro* mutagenesis assay in *Salmonella* and in an *in vitro* assay for cell transformation (summarized in Amoruso *et al*., 2008).

n-decane (C10) - In a 13-week feeding study, rats were given n-decane by oral gavage in doses of 25, 150, or 1000 mg/kg/day, corresponding to systemic doses of approximately 19, 112, or 750 mg/kg. No effects were reported (study summarized in OECD 2012).

n-decane was tested for developmental and reproductive toxicity in an OECD 422 reproductive/developmental screening test using daily oral doses of 25, 150, or 1000 mg/kg. There were no statistically significant differences in any of the reproductive and developmental parameters; nor were there any significant clinical, hematological or pathological findings. The overall no adverse effect level was 1000 mg/kg/day (OECD, 2012).

N-decane was inactive in an *in vitro* mutation assay in *Salmonella*, a forward mutation assay in V79 cells, a cytogenetics assay in V79 cells and an *in vitro* cell transformation assay (summarized in Amoruso *et al*., 2008).

n-undecane (C11) - In a 13-week feeding study rats were given n-undecane by oral gavage in doses of 25, 150, or 1000 mg/kg/day corresponding to systemic doses of approximately 18, 106, and 710 mg/kg. No effects were reported (Japanese Ministry of Health and Welfare, 1996).

N-undecane was tested for developmental and reproductive toxicity in an OECD 422 reproductive/developmental screening test using daily oral doses of 100, 300, or 1000 mg/kg. There were no statistically significant differences in any of the reproductive and developmental parameters; nor were there any significant clinical, hematological or pathological findings. The overall no adverse effect level was 1000 mg/kg/day (Japanese Ministry of Health and Welfare, 1996).

n-Dodecane (C12) - n-Dodecane was inactive in an *in vitro* mutation assay in *Salmonella* and in *in vitro* studies of cell transformation (summarized in Amoruso *et al*., 2008).

Table A2 – Summarized results of C9-C15 normal paraffinic constituents

Substance	NOAEL Repeated Dose	NOAEL Developmental Toxicity	NOAEL Reproductive Toxicity	Genotoxicity
n-Nonane	1600 ppm [1]	No data reported	No data reported	Not genotoxic
n-decane	1000 mg/kg (gavage) [1]	1000 mg/kg (gavage) [1]	1000 mg/kg (gavage) [1]	Not genotoxic
n-undecane	1000 mg/kg (gavage) [1]	1000 mg/kg (gavage) [1]	1000 mg/kg (gavage) [1]	No data reported
n-dodecane	No data reported	No data reported	No data reported	Not genotoxic

Summary – As discussed above, normal paraffins with carbon numbers between C9 and C11 did not produce systemic toxicity at the highest doses tested in animal studies. Additionally, n-C10 and n-C11 were not developmental toxicants and did not reduce fertility, and the C9, C10, C12 constituents were not genotoxic. The data on higher molecular weight constituents is more limited, but these constituents have such low vapor pressures that they are unlikely to make more than minimal contributions to the vapor phase, limiting exposure by inhalation.

(ii) C9-C15 Isoparaffins

Because the majority of the isoparaffinic solvents in this group are complex and include constituents across a wide carbon number range, it is more meaningful to discuss the effects of this group of solvents on an endpoint basis rather than by carbon number. Complex isoparaffinic solvents covering the C9-C15 carbon number range have been extensively tested. Additionally, there are two "single isomer" isoparaffins, C12 (isododecane) and C16 (2,2,4,4,6,8,8 heptamethyl nonane) for which comparative data are available.

Repeated Dose Toxicity - Repeated dose toxicity tests have been conducted on at least 3 isoparaffinic hydrocarbon solvents with carbon numbers ranging from C9-C15, specifically C9-C11, C10-C13, and C11-C15 (Carrillo *et al*., 2013). The studies of the C9-C11 and C10-C13 solvents used inhalation as the route of administration. The study of the C11-C15 solvent was by oral administration.

Using the study of the C10-C12 isoparaffinic solvent as an example, male and female rats were exposed to hydrocarbon solvent vapor at levels of 359, 737, or 1444 ppm; 6 hours/day, 5 days/week for 13 weeks. At study termination the rats were sacrificed and examined for toxicological effects. The principal findings included evidence of liver enlargement without pathological changes or elevated levels of liver enzymes and α2u globulin-mediated nephropathy in the kidneys of male rats. Also reported was a small but statistically significant reduction in hematological parameters. The elevated liver weights are a physiological response and not considered adverse (Maranpot *et al*., 2010); the male rat kidney effects are rat specific and not relevant to humans (Swenberg and McKeeman, 1998; U.S. EPA, 1991); and the hematological effects, although statistically significant, were within normal physiological variability and are considered to lack toxicological importance (Car *et al*., 2006). The study of the C9-C11 isoparaffinic solvent was similar in design, and the outcome was similar to the study of the C10-C12 isoparaffinic solvent but the exposure levels tested (300 ppm and 900 ppm) were somewhat lower. One difference between the studies is that the study of the C9-C11 isoparaffinic solvent included an additional group in which rats were exposed for 13 weeks at the high exposure level and then held without exposure for 4 additional weeks to assess recovery. This study provided evidence that both liver enlargement and reductions in hematological parameters reversed quickly when exposures were terminated.

The study of the C11-C15 isoparaffinic solvent was conducted by the oral route of administration, although all three studies provided similar data. In this test rats were given daily doses of 100, 500, or 1000 mg/kg/day for 13 weeks. At scheduled termination samples were taken from the rats for clinical and hematological changes, and the rats were then sacrificed and examined at the gross level, and tissue samples were taken for pathological examination. One group of rats was given the high dose for 13 weeks and then held for 4 weeks without treatment to assess recovery.

At sacrifice the only statistically significant findings were increased liver weights and reductions in hematocrit. Increased liver weights which are commonly observed in toxicology studies, are reflective of an adaptive response to increased metabolic demands, and not toxicologically important unless they are

associated with either pathological changes or elevated levels of enzymes that are markers for liver damage (Maranpot *et al.*, 2010). In the present study neither pathological changes nor elevated marker enzymes were observed, and the effects were reversed in the recovery study. Accordingly, the increased liver weights were not considered to have been adverse findings. The reduction in hematological parameters is, similarly, considered an incidental finding. Small reductions in hematological parameters are commonly found in repeated dose studies and are believed to be without toxicological significance if they are within the normal physiological range (Car *et al*., 2006) and reversible, as was the case in this study. In summary, the no observed adverse effect level in this study was the highest level tested, 1000 mg/kg/day.

C12 iso-paraffinic solvent (iso-dodecane) – In a draft summary from Health Canada (2020), iso-dodecane was reported to have been tested in a repeated oral toxicity test at levels of 330, 1000 and 3000 mg/kg/day. The principal observations in this study were liver enlargement with some evidence of inflammation and degenerative changes in the 1000 mg/kg/day group but no effects in the next lower dose group (330 mg/kg/day). Male rat kidney effects (α2u globulin-mediated effects) were also noted, but there were no other toxicologically relevant effects.[14] If the liver effects at 1000 mg/kg/day were considered to have been adverse, the no adverse effect level in this study was 330 mg/kg/day.

C16 isoparaffinic solvent – In a reproductive/developmental toxicity screening test, a C16 isoparaffin (C16 I (2,2,4,4,6,8,8 heptamethyl nonane) caused liver enlargement at levels of 300 mg/kg and higher, but, as the liver enlargement was not accompanied by pathological changes, the liver effects were not judged to have been adverse. The C16 isoparaffin did not induce α2u globulin-mediated male rat kidney changes; nor did treatment result in any reductions in hemoglobin levels or hematocrit. Finally, this substance did not cause mutation or chromosomal aberrations when tested under *in vitro* conditions. In summary, the no observed adverse effect level for all adverse repeated dose effects was the highest level tested (1000 mg/kg/day).

Developmental and reproductive Toxicity:

A C10-C11 isoparaffinic solvent did not produce developmental toxicity when tested by inhalation at levels of 300 or 900 ppm (Johnson *et al*., 2012).

C16 isoparaffin – A single isomer C16 isoparaffin did not produce developmental and/or reproductive effects following repeated oral administration at levels of 100, 300, or 1000 mg/kg (Health Canada, 2020).

[14] https://www.canada.ca/en/environment-climate-change/services/evaluating-existing-substances/draft-screening-assessment-heptamethylnonane.html

Genetic Toxicity

There have been genetic toxicity tests of several isoparaffinic solvents with carbon numbers ranging from C10-C13 and all studies produced negative results, *i.e*., the test substances were not genotoxic (Johnson *et al*., 2012).

Additionally, a C16 isoparaffinic solvent was not genotoxic. (Health Canada, 2020).

Summary – In repeated dose studies by inhalation or oral administration, isoparaffinic solvents can cause liver enlargement, kidney effects in male rats, and small but statistically significant reductions in hemoglobin-related parameters. However, none of these effects is toxicologically important or relevant to humans. Moreover, these solvents are not developmental toxicants and are not genotoxic. The C16 single isomer isoparaffin did not produce reproductive effects, and, although none of the other solvents has been tested for reproductive toxicity, it has been shown that reproductive organs were not affected in repeated dose studies. Finally, C9-C15 isoparaffinic hydrocarbon solvent constituents are not genotoxic.

Table A3. Summarized results of studies of isoparaffinic solvents

Isoparaffinic solvent	Repeated dose toxicity (NOAEL)	Developmental Toxicity	Reproductive Toxicity	Genetic Toxicity
C9-C11(97% isoparaffins) [1]	10,000 mg/m^3 [2]	No data reported	No data reported	Not genotoxic
C10-C11 isoparaffinic solvent	No data reported	Not a developmental toxicant	No data reported	Not genotoxic
C10-C12 (99% isoparaffins)	5300 mg/m^3 [2]	No data reported	No data reported	Not genotoxic
C11-C15 (67% isoparaffins)	1000 mg/kg [2]	No data reported	No data reported	Not genotoxic
C12 (100% isoparaffins, single isomer)	330 mg/kg	No data reported	No data reported	Not genotoxic
C16 (100% isoparaffins, single isomer)	1000 mg/kg	Not a developmental toxicant	Not a reproductive toxicant	Not genotoxic

1. When the isoparaffinic content is < 100%, the other constituents are cyclo-paraffins with similar carbon numbers.
2. The test material did not produce effects at the highest level tested.

(iii) C9-C15 cycloparaffins

A C9-C11 naphthenic solvent was tested in a repeated inhalation toxicity study by Carrillo *et al*. (2018). Rats were exposed to the solvent at levels of 1500, 3000 or 6000 mg/m^3 for 90 days. At study termination the rats were examined for adverse effects. The only effects observed were significantly increased liver weights and kidney effects in male rats. As these effects are not toxicologically important or relevant to humans, the overall NOAEL for this study was 6000 mg/m^3. Similar results were reported by Carpenter *et al*. (1977).

C9-C15 aliphatic hydrocarbon solvent constituents - Overall Summary

Results of repeated dose studies of C9-C15 aliphatic hydrocarbon solvent constituents indicated that normal paraffins did not cause any systemic effects. The isoparaffinic and cycloparaffinic solvents caused liver enlargement and male rat kidney effects, and, additionally, the cycloparaffinic solvents caused small but statistically significant reductions in hemoglobin content and hematocrit. None of these effects is toxicologically important. The data also indicated that the C9-C15 aliphatic solvents are not developmental toxicants and not genotoxic and showed no evidence of effects on fertility. In sum, there is no evidence that C9-C15 aliphatic solvents and their constituents produce adverse systemic effects that are relevant to humans. Accordingly, the effects that are most relevant to occupational exposure considerations are acute CNS effects discussed in the previous section. Volunteer studies provide empirical evidence that neither acute CNS effects nor upper respiratory tract irritation are experienced at recommended occupational exposure limits. It should be noted that the potential for aerosols should be taken into consideration, and, when present, should be controlled at recommended levels for "particulates not otherwise specified".

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(3) Aromatic hydrocarbon solvent constituents (C9-C15). Group Guidance Value = 50 mg/m3

(3.1) C9-C10 Aromatic Hydrocarbon Solvents and Their Constituents

Systemic Toxicity – There have been two independently conducted, repeated inhalation toxicity tests of C9 aromatic hydrocarbon solvents in which the principal findings in rats were increased liver and kidney weights in the animals from the high exposure group which were shown to be reversible in a recovery study. The overall no effect level for all effects in the 90-day studies was approximately 200 mg/kg/day. There have also been repeated dose studies of most of the major constituents including 4-ethyltoluene (EINECS number 210-761-2; 1,2,3-trimethylbenzene (EINECS number 208-394-8; 1,2,4-trimethylbenzene (EINECS number, 202-436-9; 1,3,5- trimethylbenzene (EINECS number 203-604-4; and iso-propyl benzene (cumene, EINECS number 202-704-5). The majority of these have been by inhalation although one (1,3-5 trimethylbenzene) was by gavage. The results of most of these studies were like those of the study of the

C9 aromatic solvents, i.e., that the only systemic effects were increases in liver and/or kidney weights at doses of approximately 200 mg/kg/day. The only counter example was iso-propyl benzene (cumene) which caused α2u globulin-mediated nephropathy, a male rat-specific effect without human health significance. However, isopropyl benzene also caused liver and kidney enlargement at levels equivalent to those found in the studies of the C9 aromatic solvents and its other constituents.

More specifically, a C9 aromatic solvent containing > 99% C8-C10 constituents (EINECS number 918-668-5, Table A4) was tested for systemic toxicity in a 13-week inhalation toxicity test (OECD 413, summarized in Clark *et al*., 1989). Male and female rats were exposed by inhalation, 6 hours/day, 5 days/week for 13 weeks to the aromatic solvent at levels of 1800 mg/m^3, 3700 mg/m^3 or 7400 mg/m^3 (approximately 360, 740, or 1490 ppm, corresponding to systemic doses of approximately 209, 429, or 858 mg/kg using the relationship published by Dahl *et al*. (1988)). The principal effects were increased absolute liver and kidney weights in female rats from the high and medium exposure groups as well as increased relative liver and kidney weights in both males and females from the mid- and high-exposure groups. However, there were no pathological changes in these or other organs, or, in the case of the liver effects, elevation of marker enzymes. The authors also reported a "low grade anemia" in female rats from all exposure groups which the authors attributed to an inter-current infection, in part because there were no effects in male rats and also because the effect was not substantiated in a subsequent 12-month inhalation toxicity study. An overall no effect level for all effects was approximately 209 mg/kg in a 90-day study.

Table A4. Principal constituents of the C9 aromatic substance tested by Clark *et al*., (1989)

Constituent	Concentration in test material
Trimethyl benzene isomers	46.8%
Methylethylbenzene isomers	30.5%
Propylbenzene isomers	4.8%
Xylenes	5%

Supporting information: In a subsequent study of a C9 aromatic hydrocarbon solvent (EINECS number 918-668-5, Table 5) (Clark *et al*., 1989), male and female rats were exposed by inhalation, 6 hours/day, 5 days/week for 12 months with one group sacrificed after 6 months of exposure. One additional group was exposed for 12 months at the high exposure level and then held for an additional 4 months to assess recovery. Exposure levels were 450, 900, or 1800 mg/m^3 (corresponding to systemic doses of approximately 50, 100 or 200 mg/kg). At terminal sacrifice there were statistically significant increases in the liver and kidney weights of male rats from the high exposure group, but there were no pathological findings suggestive of systemic toxicity. There were also some small but statistically significant changes in chemistry and/or hematological values but these were considered incidental and not toxicologically relevant. The elevated liver and kidney weights were not observed in animals sacrificed at the end of the recovery period providing evidence that these effects were physiological adaptations and not pathological changes. The overall no effect level for all systemic effects was approximately 100 mg/kg for a 12-month study.

Table A5 –Compositional data for the C9 aromatic hydrocarbon solvent tested by Clark *et al*. (1989) in a 12-month study

Component	Percent of test material
Non-aromatics	0.46
Benzene	Not detected
o-xylene	2.27%
n-propylbenzene	4.05%
1-methyl-3-ethylbenzene	7.14%
1-methyl-4-ethylbenzene	16.60%
1,3,5-trimethylbenzene	9.35%
1-methyl-2-ethylbenzene	7.22%
1,2,4-trimethylbenzene	32.70%
1,2,3-trimethylbenzene	2.76%
1-methyl-3-n-propylbenzene 1.2-diethylbenzene	6.54%
1-ethyl-3,5-dimethylbenzene	1.77%

Another study of a C9 aromatic solvent (EINECS number 918-668-5) was reported by Carpenter *et al*. (1975) in which male rats and beagle dogs were exposed to vapors of "70 solvent", an aromatic solvent described as containing primarily C9 (40%) and C10 (20% alkylbenzenes). The authors reported small but statistically significant reductions in body weight gains in animals exposed at the highest level (2000 mg/m^3, equivalent to a systemic dose of approximately 470 mg/kg), but body weight differences were not observed in the 1000 mg/m^3 (equivalent to a systemic dose of approximately 230 mg/kg) group. No toxicologically important differences in blood chemistry or hematology values were reported, and no pathological changes were noted. The overall no effect level in a 90-day study was 1000 mg/m^3, equivalent to a systemic dose of approximately 230 mg/kg.

Studies of C9-C10 aromatic solvent constituents: There have also been at least 5 repeated exposure studies of constituents of C9 aromatic solvents including:

4-ethyltoluene (EINECS number 210-761-2; Swiercz *et al*., 2000) - Rats were exposed to 4-ethyltoluene at levels of 95 or 467 ppm (corresponding to systemic doses of approximately 55 or 271 mg/kg), 5 days/week for 4 weeks. All animals survived, and there were no statistically significant differences in body weight gain. The pathological investigation did not reveal any toxicologically important findings. The overall no effect level was the highest concentration tested, 467 ppm (or approximately 271 mg/kg).

1,2,3-trimethylbenzene (TMB, EINECS number 208-394-8; Korsak *et al*., 2000a) - Rats were exposed 6 hours/day, 5 days/week for 3 months to 1,2,3-TMB at levels of 25, 100, or 250 ppm (corresponding to systemic doses of 14, 58, or 145 mg/kg). The authors reported an approximately 10% increase in liver weights in male rats from the high dose group and an approximately 10% reduction in spleen weights in female rats from the same group. In the absence of any pathological findings the authors considered 250 ppm (equivalent to a systemic dose of approximately 145 mg/kg) to be the no effect level.

1,2,4-trimethylbenzene (EINECS number, 202-436-9; Korsak *et al*., 2000b) - Rats were exposed 6 hours/day, 5 days/week for 3 months to 1,2,4-trimethylbenzene at levels of 25, 100, or 250 ppm (corresponding to systemic doses of approximately 14, 58, or 145 mg/kg). There were no unscheduled deaths and no toxicologically important findings were reported. The authors considered that the highest exposure level tested, 250 ppm (equivalent to a systemic dose of approximately 145 mg/kg) was the overall no effect level.

1,3,5- trimethylbenzene (EINECS number 203-604-4, Adenuga *et al*., 2014). This was an oral toxicity study in which male and female rats were given 1,3,5 TMB by oral gavage at levels of 50, 200, or 600 mg/kg/day (equivalent to systemic doses of approximately 40, 158, or 474 mg/kg/day). An additional group of animals was held without treatment for an additional 4 weeks to assess recovery. The only effects reported were increased liver weights in males and females from the high dose group and increased kidney weights in high dose group males. There were no organ weight differences between treated and control rats at the end of the recovery period. The overall no effect level for all systemic effects was approximately 158 mg/kg/day.

iso-propyl benzene (cumene, EINECS number 202-704-5; Cushman *et al*., 1995; NTP, 2009). Male and female Fischer 344 rats were exposed by inhalation, 6 hours/day, 5 days/week for 13 weeks at levels of 50, 100, 500 or 1200 ppm (corresponding to systemic doses of approximately 29, 58, 290, or 696 mg/kg). At terminal sacrifice there was evidence of increased liver, kidney, and adrenal weights in animals from the 500 and 1200 ppm groups. The only histological change was evidence of α2u globulin-mediated nephropathy in male rats. It is thought that cumene may cause male rat nephropathy because its alkyl side chain is larger and more branched than those of other aromatic hydrocarbon solvent constituents. The overall no effect level for all effects was a systemic dose equivalent to approximately 290 mg/kg.

Summary – There have been several independently conducted repeated dose studies of C9 aromatic solvents as well as most of their constituents. Effects reported included liver weight increases (without pathological changes), reductions in hematological parameters, and, in one case, male rat kidney effects. None of these differences is considered relevant to humans. The overall no adverse effect levels varied due to differences in study design but overall were approximately 200 mg/kg/day.

Genotoxicity - A C9 aromatic solvent (EINECS number 918-668-5, compositional information shown in Table A6) was tested in a battery of genotoxicity tests including *Salmonella* (OECD 471), reverse mutation in CHO cells (OECD 476), *in vitro* chromosome aberration (OECD 473), *in vitro* sister chromatid exchange (OECD 479), and *in vivo* chromosome aberration (OECD 473) tests (Schreiner *et al*., 1989). All tests produced negative results, providing evidence that C9 aromatic solvents are not genotoxic.

Table A6. Compositional Information for C9 aromatic solvent (EINECS number 918-668-5) used in tests for genotoxicity (described above), developmental toxicity and reproductive toxicity

Constituent	Percentage of Tested Substance
o-xylene	3.20%
Isopropyl benzene (cumene)	2.74%
n-propyl benzene	3.97%
4-ethyltoluene	7.05%
3-ethyltoluene	15.1%
2-ethyltoluene	5.44%
1,3,5-trimethylbenzene	8.37%
1,2,4-trimethylbenzene	40.5%
1,2,3-trimethylbenzene	6.18%
➢ **C10 constituents**	6.19%
Total identified constituents	98.74%

Supporting studies

C9 aromatic solvents – A C9 aromatic hydrocarbon solvent, reported to contain 46% trimethylbenzene isomers and 40% ethyltoluene isomers was tested for reverse mutation in *Salmonella* (OECD 471), sister chromatid exchange under *in vitro* conditions (OECD 479) and *in vivo* for micronucleus induction (OECD 474). The *Salmonella* and micronucleus tests were reported as negative, whereas small but statistically significant increases in sister chromatid exchange were observed (Janik-Spiechowicz *et al*. 1998b).

C9 aromatic solvent constituents – A number of C9 aromatic solvent constituents have been tested for genotoxic activity. Among those reported to have been tested for reverse mutation in *Salmonella* (OECD 471), 1,2,4-TMB, 1,3,5-TMB and 4-ET were reported as inactive whereas 1,2,3-TMB was reported as active without metabolic activation (Janik-Spiechowicz *et al*., 1998a;b). Cumene was also reported as inactive in a *Salmonella* test (NTP, 2009). In other *in vivo* tests, all TMB isomers and 4-ET isomer were reported as inactive in *in vivo* micronucleus tests (Janik-Spiechowicz, *et al*., 1998a; b). Cumene was reported to have produced a small but statistically significant increase in micronuclei following intraperitoneal administration but did not increase micronucleus frequency after inhalation exposure.

Developmental Toxicity

Developmental and developmental neurotoxicity studies were conducted by Ungvary and co-workers using "Aromatol", a C9 aromatic hydrocarbon solvent (EINECS number 918-668-5) (Ungvary *et al*., 1983; Ungvary and Tatrai, 1985). In the developmental toxicity study pregnant female CFY rats were exposed continuously (*i.e*., 24 hours/day) to aromatic hydrocarbon solvent vapors at levels of 120, 200 or 400 ppm (corresponding to absorbed doses of approximately 282, 470, or 940 mg/kg) on gestational days 7-15. The dams were sacrificed on gestational day 21 and the uterine contents were examined as described in the previous section. An additional group of dams was allowed to deliver litters, and the offspring were then held for an additional 90 days before they were sacrificed and examined. Developmental delays along

with maternal toxicity were observed in the intermediate and high exposure groups, but there was no evidence of fetal mortality or major malformations. There were no differences in the offspring sacrificed at post-natal day 90 providing evidence that the developmental delays were reversible effects. The overall no effect level was approximately 282 mg/kg for all effects. Additionally, the offspring were tested for potential effects on neurological system development. There were no significant differences in functional observations (tests administered on post-natal days 23, 36 or 90), on amphetamine sensitivity, or in tests of learning ability. The authors concluded that pre-natal exposure to C9 aromatic solvent vapors at levels up to 400 ppm (approximately 940 mg/kg/day) had no effects on post-natal development or on nervous system development.

Supporting Studies – A developmental toxicity test in mice (OECD 414) was conducted using a C9 aromatic solvent (EINECS number 918-668-5) discussed above (McKee *et al*., 1990). Female CD-1 mice, confirmed to have mated, were exposed to C9 aromatic hydrocarbon vapors, 6 hours/day from gestational days (GD) 6-15. The exposure levels were 100, 500, or 1500 ppm. The mice were sacrificed on GD 18 and the uterine contents were examined. The number and location of viable and non-viable fetuses and early and late resorptions were recorded and then the uteri were excised and weighed. Fetuses were removed and examined for external malformations. The fetuses were then divided into two groups with half being dissected to examine visceral malformations and the remainder preserved for skeletal examinations. There was substantial maternal toxicity in the high exposure group, slight maternal toxicity in the intermediate exposure group, and no maternal toxicity in the low exposure group. The fetal examination revealed significant reductions in live fetuses/litter and fetal body weight in the high dose group, and there were also significant elevations in the number of fetuses with delayed ossification and an increased incidence of cleft palate (a stress response in mice). There was a reduction in fetal body weight in the intermediate exposure group, but survival was unaffected, and there was no increase in frequency of malformations. The low exposure group (100 ppm) group was a no effect level for both maternal and fetal effects.

In addition to the above, there have also been developmental toxicity tests of 1,2,4- and 1,3,5-TMB (Saillenfait *et al*., 2005) and iso-propyl benzene (Darmer *et al*., 1997). In the Saillenfait *et al*. studies, rats were exposed at levels of 100, 300, 600, and either 900 or 1200 ppm. In the 1,3,5-TMB study maternal body weights were significantly reduced among dams exposed to levels of 300 ppm (approximately 174 mg/kg) and above, but there were no effects on fetal survival and frequencies of malformation were not increased at that level. In the 1,2,4-TMB study there was no evidence of either maternal or fetal toxicity in the 300 ppm group. Accordingly, the overall no effect level for fetal effects was 300 ppm, or approximately 174 mg/kg with the next highest level, 600 ppm (or 348 mg/kg) as the low effect level.

In the isopropyl benzene (cumene) study, Darmer *et al*. (1997) tested both rats and rabbits. In the rat study pregnant dams were exposed by inhalation on GD 6-15 to cumene vapor at levels of 100, 500, or 1500 ppm (approximately 58, 290, or 870 mg/kg). Pregnant female rabbits were exposed on gestational days 6-18 at exposure levels of 500, 1200 or 2300 ppm. There was some evidence of maternal body weights of both rats and rabbits during the exposure period, but there were no maternal or fetal effects at termination. Thus, in these studies, the no effect level for both maternal and fetal effects for cumene in the rat was 870 mg/kg.

Reproductive Toxicity Studies

A 3-generation reproductive toxicity test (OECD 416) was conducted on the same C9 aromatic hydrocarbon solvent (EINECS number 918-668-5) used in the genetic toxicity and mouse developmental toxicity test described above (McKee *et al*., 1990). Briefly, male and female rats, 30/sex, were exposed to C9 aromatic hydrocarbon solvent vapors at levels of 100, 500, or 1500 ppm (equivalent to systemic doses of approximately 58, 290, or 870 mg/kg). Exposures were 6 hours/day, 7 days/week starting at the initiation of a 14-day mating period. Once mating had been confirmed, exposure of the mated females continued to gestational day 20, at which point exposures were discontinued to allow the dams time to deliver their litters. Exposures were re-initiated on post-natal day (PND) 5 and continued to the end of weaning (PND 21). At that point the dams were sacrificed, and exposures were continued for all offspring scheduled to be used to produce the second generation. Exposures of male and female offspring continued for 10 weeks, and they were then mated to produce a second generation. This procedure was then repeated to assess potential effects on fertility through a 3rd generation. There were some effects on body weight gain in the high exposure group dams, but there were no effects on reproductive parameters. Similarly, there were no effects on offspring (e.g., litter size, mean birth weight, survival or growth in the post-natal period). The most notable observation in this study was in the 3rd generation when all offspring were re-introduced to the exposure chambers on PND 21, and many of the offspring exposed to the high dose died during the first week of exposure. Among the survivors, body weight gain was substantially reduced. Nevertheless, there were no differences in reproductive parameters. This study provided evidence that exposure to C9 aromatic hydrocarbon solvents did not influence reproductive parameters.

Neurotoxicity

(a) Developmental neurotoxicity

Lehotzky *et al*. (1985a, b) reported a developmental neurotoxicity test in which pregnant rats were exposed to a C9 aromatic solvent at levels of 600, 1000, or 2000 mg/m^3, 24 hours/day on gestational days 7-15. The dams were allowed to give birth and the offspring were held to terminal sacrifice on post-natal day 90. No significant differences were observed in any of the neurological tests conducted on the offspring. Accordingly, it was concluded that continuous exposures of fetuses to C9 aromatic solvents at levels up to 2000 mg/m^3 had no effects on nervous system development.

(b) Chronic neurotoxicity

In a study to assess the potential for C9 aromatic solvents to cause chronic neurological effects, adult male rats were exposed to a C9 aromatic solvent at levels of 500, 2500, or 7500 mg/m^3, 6 hours/day, 5 days/week for 13 weeks (Douglas *et al*., 1993). Neurological investigations were conducted at intervals during the exposure period and at termination, and, after sacrifice, nervous system tissue was examined for pathological changes. No neurological effects were observed, and, similarly, there were no pathological observations of note. The no effect level for neurological effects was the highest level tested, 7500 mg/m^3.

Supporting Information – In addition to the above, there have also been studies of the potential of C9 aromatic solvent constituents to cause neurological effects. Constituents tested included various trimethylbenzene isomers (Gralewicz *et al*., 1997; Gralewicz and Wiaderna, 2001; Wiaderna *et al*., 2002) as well as iso-propyl benzene (Cushman *et al*., 1995). None of these studies provided evidence that exposure to C9 aromatic solvents or their constituents could cause pathological changes in nervous system tissue or neurobehavioral effects.

In summary, the potential for systemic effects from exposure to C9-C10 aromatic hydrocarbon studies has been extensively studied. Across a range of studies of both C9-C10 aromatic hydrocarbon solvents and their constituents, the systemic findings have been increased liver and kidney weights and, in some cases, reductions in hematological values. These changes were shown to be reversible in recovery studies, and, further, were not toxicologically important. The overall no effect levels were in the range of approximately 1800 mg/m^3 in the 90-day studies. Additional studies have provided evidence that these solvents were not selective developmental toxicants, did not affect fertility, did not cause adult or developmental neurotoxicity and were not genotoxic. These findings supported the practice of basing occupational exposure level recommendations on acute central nervous system effects and upper respiratory tract irritation.

(3.2) C10-C15 Aromatic Hydrocarbon Solvents

A C10-C13 aromatic solvent was tested for repeated dose effects in an oral gavage study in rats (see McKee *et al*., 2015). Dose levels were 300, 600, or 1000 mg/kg/day. Most of the rats were sacrificed after 13 weeks of treatment, but one group was given 1000 mg/kg for 13 weeks and then held for an additional 4 weeks without treatment to assess recovery. There was evidence of increased liver and kidney weights but no pathological changes were reported. There were reductions in hematological values in both male and females with the differences being statistically significant in the 600 and 1000 mg/kg/day groups. All the differences were reversed in the recovery group. The overall no effect level was reported as 300 mg/kg/day based on the hematological effects.

Developmental toxicity – A developmental toxicity study was conducted using a C10-C13 aromatic solvent as the test substance (summarized in McKee *et al*., 2015). The aromatic solvent was administered by gavage to pregnant female rats at daily doses of 75, 150, or 450 mg/kg/day on gestational days 6 to 15. The rats were sacrificed on gestational day 21, and the uterine contents were examined. Although maternal body weight gain was reduced in dams from the high dose group, there were no statistically different findings in the fetal observations. The no observed effect level was 450 mg/kg.

Genetic toxicity – A C10-C13 aromatic solvent was tested for genotoxic potential in *Salmonella* and in an *in vivo* micronucleus test using mouse bone marrow. The test material was not mutagenic and did not increase micronucleus frequency (summarized in McKee *et al*., 2015). The available information indicated that naphthalene was not genotoxic (Schreiner, 2003).

Summary – Aromatic hydrocarbon solvents covering carbon numbers ranging from C10-C13 have been tested for repeated dose effects in oral gavage studies at levels up to 450 mg/kg without evidence of toxicologically relevant systemic effects. Further, these solvents were not developmental toxicants, did not affect fertility, did not cause non-acute effects in the nervous system and were not genotoxic.

Overall Summary - The Group Guidance Value for this group of solvents is 50 mg/m^3, based on the ACGIH® TLV of 50 mg/m^3 for trimethylbenzene isomers. This GGV can normally be used for all C9-C15 constituents of multi-constituent aromatic solvents although there are several aromatic solvent constituents which have their own occupational exposure levels including iso-propyl benzene (cumene), indene, bi-phenyl, di- and triethylbenzenes, and methylnaphthalenes as described in more detail below.

Historical Information from Volunteer Studies and Occupational Experience Supporting the Occupational Exposure Recommendations – The earliest occupational exposure limits for multi-constituent trimethylbenzene (TMB) solvents were in the range of 35-50 ppm (approximately 175-250 mg/m^3) based on suggestive evidence of acute central nervous system (CNS depression), respiratory problems, and hematological effects in occupationally exposed humans (Battig *et al*., 1956). Subsequent toxicological studies in animals (Battig *et al*., 1958; Nau *et al*., 1966; Carpenter *et al.,* 1975) failed to replicate the hematological findings, leading to speculation that the hematological effects may have been due to benzene which may have been present in the aromatic solvents used at that time (Gerarde, 1960). Nau *et al*. (1966) recommended an occupational exposure limit of 250 mg/m^3 based on a volunteer study. Based primarily on this historical information, currently recommended occupational exposure limits are in the range of 50 (ACGIH®) - 100 (SCOEL) mg/m^3. The recommended GGV is based on the occupational exposure recommendations for trimethylbenzenes from ACGIH®.

Acute Central Nervous System Depression and Upper Respiratory Tract Irritation – A study to systematically characterize the acute CNS effects of aromatic hydrocarbon solvents and their constituents, provided no evidence for effects at levels below 1000 mg/m^3 (McKee *et al*., 2010). Based on pharmacokinetic analysis using a model validated with human data it was predicted that brain concentrations of humans would be approximately twice those of rats exposed to equivalent levels of aromatic solvents (Hissink *et al.,* 2007), supporting a theoretical no effect level of 500 mg/m^3. In volunteer studies, over periods ranging from 4-8 hours, there were no abnormal findings in routine clinical or hematological investigations (Jarnberg *et al*., 1996; 1997; Jones *et al*., 2006; Krostrzewski *et al*. 1997). In summary, 50 mg/m^3 is well supported as a protective level for acute CNS effects and respiratory irritation associated with exposure to C9-C15 aromatic hydrocarbon solvents and their constituents.

Non-Acute Effects of C9-C15 Aromatic Hydrocarbon Solvents and their Constituents – As described in detail above, the aromatic solvents and most of their constituents do not cause toxicologically important systemic toxicity, selective developmental toxicity, or reproductive toxicity, and they are not genotoxic. More specifically, in repeated dose studies, the aromatic hydrocarbon solvents and their constituents can cause liver and kidney enlargement, but these changes are physiological adaptations, not associated with pathological changes and are reversed in recovery studies. The overall no effect level for the systemic effects is approximately 200 mg/kg/day in 90-day studies. In developmental and reproductive toxicity

tests the only effects were stress-related phenomena, most likely secondary to respiratory irritation. At any event there were no effects on fertility and no selective developmental effects. The overall no effect levels were similar to those in the repeated dose studies. Further, the aromatic hydrocarbon solvents and their constituents have been found to be inactive in tests for genetic toxicity under both *in vitro* and *in vivo* conditions.

However, in addition to the generic toxicological effects, there are a few aromatic hydrocarbon solvent constituents that can cause other effects. These include:

Cumene which also causes α2u globulin-mediated nephropathy in male rats, but this is a species-specific effect not relevant to humans. Cumene can also cause respiratory tract tumors in a manner similar to that of naphthalene as described in more detail in the following paragraph.

Naphthalene which has been shown to cause respiratory tract tumors in repeated inhalation toxicity studies in rats and mice (Abdo *et al*., 1992; Adkins *et al*., 1986; NTP, 1992; 2000). These tumors were associated with inflammation in mouse lung and rat nasal tract, suggesting that tumor induction may have been related to cytotoxic effects in the affected tissues (North *et al*., 2008). Although the underlying mode of action is controversial, it seems most likely that the tumors were the consequence of a cytotoxic process (Rhomberg *et al*., 2010; Bailey *et al*., 2016), and this view is supported by evidence that naphthalene is not genotoxic (Schreiner, 2003). More recently it was reported that cumene can produce similar effects. Although the cumene data has not received the same degree of attention as the results of the naphthalene studies, it seems reasonable to assume that the effects of cumene are also related to repeated irritation. Based on the current evidence it seems reasonable to conclude that occupational exposure limits set to protect against respiratory tract irritation from aromatic hydrocarbon solvent constituents would also protect against the potential for longer term effects.

Diethyl- and Triethylbenzene isomers which have been reported to cause neurotoxic effects in mice (Gagnaire *et al*., 1990; 1991; 1992). Although the published data provides a good basis for hazard characterization, dose-response relationships have not been well defined. Based on unpublished information the AIHA (2005) developed a WEEL of 28 mg/m^3 which is recommended herein as a basis for limiting exposure to these constituents.

Indene which has not been well characterized toxicologically. The occupational exposure recommendations are based on repeated inhalation studies published in 1939 in which laboratory animals exposed to high levels were reported to have exhibited necrosis in the liver and kidneys (NIOSH, 1989). The ACGIH TLV® for indene is 24 mg/m^3.

Biphenyl which has been reported to have caused bladder tumors in male rats and liver tumors in female mice in long-term feeding studies (Zheng et al., 2016). The ACGIH TLV® for biphenyl is 1.3 mg/m^3.

1-methyl- and 2-methylnaphthalene which are respiratory irritants and caused pulmonary alveolar proteinosis in mice in repeated exposure studies in which the test material was administered via the diet. The ACGIH TLV® for 1-, and 2-methylnaphthalene is currently 0.5 ppm (approximately 3 mg/m^3) but a reduction to 0.05 ppm has been proposed.

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Specific Substance Values:

Most of the hydrocarbon solvent constituents are isomeric structures with similar toxicological properties. As discussed above, n-paraffins other than n-hexane do not cause any non-acute effects. Iso-paraffins

and cycloparaffins cause liver enlargement and male rat-kidney effects and in some cases reductions in hematological parameters; however, these effects are not toxicologically important. The aromatic constituents cause liver enlargement. In short, most hydrocarbon solvent constituents do not cause any effects that are important in a risk assessment context. Further, as shown in the following section, the liver and kidney effects are additive, so the systemic effects of any solvent containing constituents of more than one type can be predicted based on the concentrations of the various types of constituents present. Thus, the concept of generalizing these effects and assigning group guidance values to large constituent categories is a reasonable and scientifically justifiable simplification.

However, there are some constituents that have toxicological properties that differ from the generic effects discussed above. These constituents need to be managed differently to avoid potential over-exposure. Accordingly, for these constituents, their individual occupational exposure levels (i.e., TLVs® or IOELVs) are used as specific substance values when these constituents are present at toxicologically relevant levels. Of these, the two for which SSVs have been established are n-hexane and naphthalene. However, there are other constituents that need to be considered if present in complex hydrocarbon solvents at toxicologically-relevant levels.

Substances for which SSVs have been established.

n-hexane – n-hexane can cause peripheral neuropathy in humans under repeated exposure conditions at relatively high levels. Accordingly, ACGIH® recommends limiting n-hexane exposure to 176 mg/m^3, and the SCOEL IOELv is 72 mg/m^3. N-hexane falls within the C5-C8 aliphatic constituents for which the GGV is 1400 mg/m^3. As a strict proportionality, this means that exposure to n-hexane could exceed the IOELV if the concentration exceeds 5% (i.e., 72/1400 = 0.05), even if n-hexane is not more volatile than other solvent constituents. Moreover, when n-hexane is more volatile than other solvent constituents, it could be over-represented in the vapor phase. Thus, particular care should be taken with n-hexane-containing solvents to avoid the potential for over-exposure as described elsewhere in this document.

Naphthalene – In the early days occupational exposure limits for naphthalene were based on the potential to cause upper respiratory tract irritation. However, more recently it was discovered that naphthalene could cause respiratory tract tumors in rats and mice following repeated irritation. The evidence suggests that the tumors are the consequence of repeated irritation and human relevance is controversial (Bailey *et al*., 2016). One consequence of these findings is that naphthalene is now considered to be a category 2 carcinogen, and complex substances and mixtures are classified if they contain naphthalene at levels > 1%. Additionally, SCOEL has withdrawn its IOELV for naphthalene, but the ACGIH® left its TLV® unchanged at 52 mg/m^3. Thus, it is reasonable to use 50 mg/m^3 as an SSV for solvents classified on the basis of naphthalene content; however, as the GGV for C9-C15 aromatic solvents is 50 mg/m^3, the use of an SSV for naphthalene has no practical significance.

Other Constituents with their own occupational exposure values

Diethyl- and triethylbenzene isomers – These constituents have been reported to cause neurological effects in rodents. In the absence of occupational advice from either ACGIH® or SCOEL, the AIHA WEEL value of 28 mg/m^3 is recommended. This value can be used in the calculations if the concentrations of diethyl- or triethylbenzene isomers are high enough that exposure to these constituents might exceed 28 mg/m^3.

Cumene – Cumene (isopropyl benzene) is a C9 alkyl benzene isomer which, until recently, had an occupational exposure limit of 246 mg/m^3. However, after it was found that exposure to cumene could cause respiratory tract tumors in rodents, SCOEL reduced the cumene value to 100 mg/m^3 and is now scheduled to further reduce the IOELv to 50 mg/m^3. The ACGIH® has reduced its TLV® to 25 mg/m^3. Since the cumene TLV® is half the GGV for aromatics, and the cumene contents of aromatic solvents is typically < 3%, it is unlikely that the presence of cumene would influence the occupational exposure recommendations – assuming a concentration of 3% cumene in an aromatic solvent, the calculated occupational exposure level (0.97/50 + 0.03/25 = 0.0194 + 0.0012 = 0.0206. 1/0.0206) = 49 mg/m^3 which rounds to 50 mg/m^3.

C7-C8 Aromatic Constituents (toluene, ethylbenzene, xylene isomers) – As discussed elsewhere in this document, these constituents are most likely to be found in C9 aromatic solvents for which the GGV is 50 mg/m^3. The TLV® values and/or IOELvs for the C7-C8 aromatic constituents are similar to the C9 aromatic GGV, so the levels of these constituents would never be high enough that their own occupational exposure limits would be exceeded.

Indene – Indene which has both TLV® and IOELv values of 24 mg/m^3, is most likely to be found in aromatic solvents which have recommended occupational exposure limits of 50 mg/m^3. It is unlikely that indene would exceed its occupational exposure limit unless current concentration levels change substantially.

Methylnaphthalene isomers – Methylnaphthalene isomers may represent a difficult situation depending on the concentrations of these constituents in the solvents and their vapor pressures relative to those of other constituents. The methylnaphthalene isomers would most likely be present in aromatic hydrocarbon solvents and/or aliphatic solvents with > 2% aromatics. The occupational exposure limits for these constituents (approximately 3 mg/m^3) are so much lower than the guidance values for other aromatic constituents with similar carbon numbers (50 mg/m^3), that care must be taken to avoid over-exposure situations. As mentioned earlier, the ACGIH® has proposed to lower the TLV for methylnaphthalenes to approximately 0.3 mg/m^3.

Biphenyl – Biphenyl has an occupational exposure limit (1.5 mg/m^3) which is well below the guidance value for other aromatic constituents with similar carbon numbers (50 mg/m^3). However, the concentrations of biphenyl in aromatic solvents may be low enough that over-exposure can be avoided without the necessity for additional adjustments.

Appendix C. Evidence that the effects of constituents of hydrocarbon solvents are additive.

As discussed above, most hydrocarbon solvents are composed of numerous isomers in relatively low concentrations. Additionally, with a few exceptions discussed in Appendix B, hydrocarbon solvent constituents produce common systemic effects through common mechanisms, indicating that the effects are additive and can be combined into generic groups as was done to develop the recommendations for the GGV values. The assumption of additivity is supported empirically by the absence of evidence of evidence for synergistic effects among hydrocarbon solvent, and, in a broader sense, among components of mixtures generally when constituents are at or below effect levels (Boobis *et al*., 2011). This section provides several examples of data from studies of complex hydrocarbon solvents, showing that, indeed, the outcomes of these studies are consistent with the types and amounts of their various components and the effects that these components produce.

As summarized above, some systemic effects have been observed in repeated dose studies: specifically, excepting n-hexane the normal paraffins do not produce any effects; isoparaffinic and cycloparaffinic hydrocarbons can produce male rat kidney effects with no effect levels ≤ approximately 100 mg/kg and liver enlargement with no effect levels ≤ 300 mg/kg; aromatic constituents can also can also cause liver (and kidney) enlargement at levels similar to those of the isoparaffinic and cycloparaffinic constituents, but are weak inducers of kidney effects in male rats. Increased organ weights without pathological changes are regarded as adaptive and α2u-mediated male rat kidney effects are not relevant to humans, but these changes are commonly observed in repeated dose studies in rats, are dose-responsive, and provide quantitative data. Otherwise, hydrocarbon solvents and their constituents are not developmental or reproductive toxicants, and, excepting n-hexane, hydrocarbon solvents do not produce chronic neurotoxicity. Hydrocarbon solvents and their constituents are not genotoxic and are not expected to be carcinogenic via genotoxic mechanisms although some aromatic constituents such as naphthalene may induce tumors through processes involving repeated irritation. However, as discussed above, the relevance of these tumors to humans is questionable (Rhomberg *et al*., 2010; Bailey *et al*., 2016). In short, for all practical purposes, the systemic effects of hydrocarbon solvents are liver enlargement and male rat kidney effects, which are additive but not relevant to humans.

As an illustration of the way in which data on hydrocarbon solvent composition can be used to predict liver enlargement and male rat kidney effects, two examples are compared, a C9-C11 aliphatic solvent containing 19% aromatics (Carrillo *et al*., 2014) and a corresponding "de-aromatized" aliphatic solvent in which the aromatic constituents had been converted to cycloparaffins by hydrogenation (Adenuga *et al*. 2014). The C9-C11 aliphatic solvent contained 56% n- and iso- paraffins, 25% cycloparaffins, and 19% aromatics. Since the specific concentrations of n- and iso-paraffins were not provided, it was assumed for purposes of this example that they were equally distributed. Thus, it was assumed that the sample contained 28% n-paraffins, 28% iso-paraffins, 25% cycloparaffins and 19% aromatics. The isoparaffins, cycloparaffins and aromatic constituents (approximately 70% of the total) can produce liver enlargement

at similar levels, and the iso-paraffins and cycloparaffins (53% total) can also produce male rat kidney effects.

The C9-C11 aliphatic solvent with 19% aromatics was tested by inhalation at exposure levels of 2000, 4000, or 7500 mg/m^3, 6 hours/day, 5 days/week for 13 weeks. Using the relationship from Dahl *et al*. (1988), the corresponding systemic doses were approximately 180, 360, 700 mg/kg of which the fractions corresponding to the total concentrations of aromatics, isoparaffins and cycloparaffins (and capable of causing liver enlargement) were 130, 260, and 500 mg/kg; and the fractions corresponding to the total concentrations of isoparaffins and cycloparaffins (and capable of causing male rat kidney effects) were 95, 190 and 371. From these data it would be predicted that liver weights would be significantly increased in the high dose group and that male rat kidney effects would be present at all doses. In the event, absolute liver weights were increased at all levels but were only statistically significant in the mid and high exposure groups and only when expressed as relative weights. Absolute liver weights were not increased in any of the exposure groups. Kidney effects were seen in male rats at all levels. In summary, the agreement between predicted and observed outcomes is reasonable given the uncertainties in the dose estimates and would probably have been better if the relative amounts of normal and isoparaffinic hydrocarbon solvent constituents had been established.

The de-aromatized aliphatic solvent was a C10-C13 aliphatic solvent containing 42% n- and iso-paraffins and 58% cycloparaffins. The test material was administered by gavage in daily doses of 100, 500, or 1000 mg/kg/day (corresponding to systemic doses of approximately 75, 375 or 750 mg/kg). If it is assumed that the n- and isoparaffinic constituents are equally divided, this means that 80% of the constituents could cause liver enlargement and male rat kidney effects, equivalent to systemic doses of 60, 300, or 600 mg/kg. According to the publication (Adenuga *et al*., 2014), liver weights were increased in the mid- and high dose groups but were only significantly different when expressed on a relative basis, and significant elevations in kidney weights in male rats, along with increased pathological evidence of α2u-globulin were also observed in the mid- and high dose groups. The low dose group was a no-effect level for all effects.

In short, despite the uncertainties in these analyses, the outcomes of the repeated dose studies are consistent with expectation based on their compositions and the types of effects that have been associated with the molecules with which they are composed. These observations provide empirical evidence that the RCP approach and the recommended group guidance values provide a basis for setting occupational exposure levels for complex hydrocarbon solvents that is both practical and consistent with toxicological information.

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