# Special Report No. 13

# Occupational Exposure Limits for Hydrocarbon Solvents

August 1997

ISSN-0773-8072-13

Brussels, August 1997

# ECETOC Special Report No. 13

# ECETOC SPECIAL REPORT No. 13

# on

# Occupational Exposure Limits for Hydrocarbon Solvents

## CONTENTS


SUMMARY ..... 1

1. INTRODUCTION ..... 2

1.1 HYDROCARBON SOLVENTS, PRODUCT DESCRIPTION ..... 2

1.2 OCCUPATIONAL EXPOSURE LIMITS (OELs) ..... 3

1.3 BLENDING AND PROCESSING ..... 3

2. PROCEDURES FOR ASSIGNING OELS TO COMPLEX HYDROCARBON SOLVENTS ..... 5

2.1 GENERAL ..... 5

2.2 TYPICAL HYDROCARBON SOLVENTS AND BLENDS ..... 7

2.3 CHARACTERISTICS OF HYDROCARBON SOLVENTS IN RELATION TO ASSIGNING OELs ..... 9

2.4 EXISTING METHODOLOGIES FOR ASSIGNING OELs TO MIXTURES ..... 14

2.5 COMPARISONS OF GENERIC APPROACHES ..... 20

2.6 CRITERIA FOR SELECTION ..... 25

3. EXPOSURE MONITORING ..... 28

3.1 INTRODUCTION ..... 28

3.2 SAMPLING AND ANALYSIS ..... 28

3.3 ANALYTICAL METHOD STANDARDISATION ..... 29

3.4 WORKPLACE MONITORING METHODS ..... 29

4. TOXICOLOGICAL OVERVIEW ..... 33

4.1 INTRODUCTION ..... 33

4.2 CENTRAL NERVOUS SYSTEM EFFECTS ..... 34

4.3 NEPHROTOXICITY ..... 37

4.4 TOXICITY OF SPECIFIC HYDROCARBONS ..... 40

4.5 SUMMARY OF THE TOXICOLOGY INFORMATION ..... 42

4.6 UNDERLYING ASSUMPTIONS FOR THE JUSTIFICATION OF THE APPLICATION OF THE RCP ..... 42

4.7 CONCLUSION ..... 44

5. CONCLUSIONS ..... 45

BIBLIOGRAPHY ..... 47

APPENDIX I. THRESHOLD LIMIT VALUES FOR MIXTURES ..... 52

APPENDIX II. CHROMATOGRAPHIC ANALYSIS OF A STANDARD WHITE SPIRIT ..... 56

MEMBERS OF THE TASK FORCE ..... 58

MEMBERS OF THE SCIENTIFIC COMMITTEE ..... 60

# SUMMARY

The objectives of this work were to review the generic methods currently available for deriving occupational exposure limits (OELs) for complex hydrocarbon solvents and to determine the most scientifically-acceptable procedure.

To accomplish that objective the Task Force has defined hydrocarbon solvents, identified their important physical and chemical properties and reviewed the existing approaches for setting OELs. A critical review of monitoring methods and the toxicological and epidemiological information was also carried out. Criteria were set by which the merits of the available approaches could be judged. This process led to the conclusion that the best available method was a reciprocal calculation procedure (RCP), following the general guidance provided by the American Conference of Governmental Industrial Hygienists (ACGIH). It was noted that, of the procedures currently being used in Europe, the one recommended by the UK Health and Safety Executive (UK-HSE) is the most consistent with the views of the ECETOC Task Force. It was agreed that the assignment of OELs to groups of constituents as recommended by the UK-HSE, a prerequisite for the application of a RCP, was reasonable and pragmatic and makes the best use of the available information. Thus the Task Force recommends that, for calculating an OEL of a mixture or a blend of hydrocarbons, the most appropriate procedure is to use a RCP and to take account of all constituents.

The use of the RCP is only justified if the various constituents of hydrocarbon solvents have similar toxicity and act in an additive manner. A review of the toxicology of hydrocarbons concluded that, with the exception of n-hexane, the molecules which comprise hydrocarbon solvents are toxicologically similar and act in an additive manner. For hydrocarbons in general it was found that the most sensitive health effect is central nervous system (CNS) depression, and it was concluded that this effect could be a basis for setting OELs. The peripheral neurotoxicity of n-hexane is unique and not additive, but n-hexane has its own OEL to protect from this effect. If the OEL for n-hexane is used in a RCP with OELs for other constituents, the resulting OEL for the solvent will assure that exposure to n-hexane would not exceed its own OEL. Thus the exceptional character of n-hexane does not invalidate the use of the RCP approach.

The method does not apply if the ratios of the vapour concentrations of the constituents are significantly different from those of the constituents in the liquid. In the exceptional case where this occurs the RCP should be applied to the vapour composition. The RCP method should not be applied to high-boiling solvents, as at boiling points above 220° C a RCP method could produce a calculated OEL, which exceeds the saturated vapour concentration.

# 1. INTRODUCTION

## 1.1 HYDROCARBON SOLVENTS, PRODUCT DESCRIPTION

Hydrocarbon solvents are produced by the distillation of petroleum feedstock, sometimes followed by additional processing steps, such as solvent extraction, hydrodesulphurisation or hydrotreatment, and by blending. They contain a large number of individual hydrocarbons of between 5 and 15 carbon atoms and boil within the range of 35-320° C. Altogether they could contain over 5,000 different molecular species. They are generally described as being either "aliphatic" (normal- and iso-paraffinic or alkanes), "alicyclic" ("naphthenic" or cycloalkanes) or "aromatic" but in practice they are often mixtures of these three types of molecules. Hydrocarbon solvents are manufactured according to specification depending on the solvent properties required and consequently differ in composition. Many different substances and preparations (blends) are marketed, and health and safety properties may differ depending on chemical composition.

Hydrocarbon solvents manufactured directly from feedstock are considered to be substances under present regulations and appropriate CAS/EINECS numbers (further indicated as CAS) have been assigned. During the preparation of the inventories of existing substances for the US Toxic Substances Control Act (TSCA) and the European Directive 67/548/EC, all refinery streams were characterised on the basis of their refining history and given unique CAS numbers in order to include them in the inventories of existing substances. These definitions indicate carbon range, preferential type of hydrocarbon molecules and the last refinery step. Currently there are at least 52 CAS numbers which could be used to describe hydrocarbon solvents as substances. It is anticipated that the majority of products in commerce in Europe are described by 30. Blends of those substances are considered as 'preparations' for regulatory purposes.

Hydrocarbon solvents* form a group of products clearly distinguished from other petroleum derived mixtures such as fuels and lubricants as they are produced specifically for solvent purposes and are highly refined. Contamination with molecules of molecular weights over 250 Daltons (e.g. carcinogenic

---

* The following defintions from R.J. Lewis (Ed.), Hawley's Condensed Chemical Dictionary (12th Ed. Van Nostrand Reinhold Co. 1993) are relevant to the terms used in this report:

| | |
|---|---|
| 1. Solvent: | A substance capable of dissolving another substance to form a uniform dispersed mixture at the molecular or ionic-size level. |
| 2. Organic Solvent: | An organic (carbon) based substance capable of dissolving another substance. |
| 3. Hydrocarbon: | An organic compound consisting exclusively of the elements carbon and hydrogen. |
| 4. Hydrocarbon Solvent: | Chemical compounds composed of carbon and hydrogen capable of dissolving another substance. |
| 5. Gasoline: | A mixture of volatile hydrocarbons suitable for use in a spark-ignition internal combustion engine having an octane number of at least 60. |

polyclic aromatic hydrocarbon species) is excluded through the manufacturing process. Furthermore other problematic hydrocarbon molecules that may influence the health and safety properties of hydrocarbon solvents are removed (e.g. benzene) during manufacturing, or controlled (e.g. n-hexane, aromatics fraction) to reduce health hazards.

Hydrocarbon solvents have to be distinguished from other organic solvents such as oxygenated solvents and halogenated solvents which are not covered by this report. For the toxicological assessment of organic solvents the reader is referred to the ECETOC report on the Chronic Neurotoxicity of Solvents (ECETOC, 1996). The main elements of the toxicity of hydrocarbon solvents are reviewed in Section 4.

## 1.2 OCCUPATIONAL EXPOSURE LIMITS (OELs)

This report reviews the methods currently in use to derive OELs for complex hydrocarbon mixtures. There are two procedures which can be used for this purpose; OELs can be derived either from an assessment of the toxicology data on the complex solvent, or, by calculation, from data on its constituents. Because of the large number of products and the way in which the existing toxicology data have been obtained, there are only a few solvents for which sufficient data are available to produce OELs based solely on the assessment of toxicological data. Therefore the second approach seems more pragmatic as a general methodology. However, there may be situations in which sufficient data are available for a particular hydrocarbon solvent. In such situations these data take precedence over the results of a calculation method.

As will be further described below, the methodology for developing OELs is based on a reciprocal calculation procedure (RCP) which takes into account the properties of the individual constituents. However, as there are hundreds if not thousands of these constituents, it is necessary for these to be grouped in some reasonable way. The grouping and the use of the RCP to calculate OELs, require assumptions about similarity in physico/chemical and toxicological properties and that the individual constituents act in an additive manner. As will be shown, these assumptions are satisfied for the constituents of hydrocarbon solvents. Thus the use of the RCP is valid for these products.

## 1.3 BLENDING AND PROCESSING

In principle the recommended approach, discussed in this report, is applicable to hydrocarbon solvents in general, whether they are called substances or preparations (blends) for regulatory purposes, as long as all of the constituents are of the types described in Section 1.1.

When hydrocarbon solvents are blended with other solvents, the RCP as described by the American Conference of Governmental Industrial Hygienists (ACGIH, see Appendix 1) can be used for calculating OELs if the underlying assumptions of additivity (i.e. substances act on the same organ systems with similar toxicity) are legitimate. Additivity is addressed and supported for hydrocarbon solvents, but it is beyond the scope of this report to carry out this assessment for other solvents.

The assumption of additivity is not justified for all organic solvents. For example methyl ethyl ketone may potentiate the neurotoxic effects of n-hexane. In the case of blends of hydrocarbon solvents with other substances which are not additive, the OELs may need to be assessed independently for the different components in the blend. For example gasoline blending stocks contain a range of hydrocarbon constituents including benzene. Benzene has its own OEL and is not additive with other hydrocarbons. For such products the OEL of benzene needs to be separated from that of the other hydrocarbon constituents and independently met.

# 2. PROCEDURES FOR ASSIGNING OELs TO COMPLEX HYDROCARBON SOLVENTS

## 2.1 GENERAL

The most widely acknowledged view on the application of individual OELs of the components in a mixture to determine an overall OEL is expressed by ACGIH (Appendix 1). ACGIH recommends that effects of components with similar toxicological properties be considered as additive, and a RCP be used to calculate the overall OEL. This approach is inappropriate when there is information showing the effects may be synergistic, potentiating or antagonistic. No reference to the scientific basis for the introduction of the formula by the ACGIH has been found although the approach may be explained by accepting that the individual effects of the components may be summed in the form of effective doses with respect to their OELs. The German MAK Commission (Henschler, 1991) acknowledges the scientific weaknesses of the method but accepts its usefulness and practicability. Similar principles are adopted in other areas including the evaluation of the toxic hazards of gaseous emissions from fires (ISO, 1993). The approach has been recommended by ACGIH since 1940 without amendment although there does not appear to be any published record of its application to complex hydrocarbon mixtures prior to 1976 (Farmer, 1992).

A number of authors have commented on technical aspects of applying the RCP approach to simple mixtures with a small number of components. There is evidence that this method can be improved by recognising the non-ideal behaviour of some components in the mixture (Bishop *et al*, 1982). Scheffers *et al* (1985) suggested exposure indices based on the sum of the ratios of the air concentrations and the corresponding effect-specific limit values for the components. Findings by Sokal and Korsak (1990) suggest that the RCP approach may require modification to fit interactive effects of toluene and xylenes. Mutti *et al* (1982) questioned the importance of synergism for n-hexane and cyclohexane based on electroneurographic abnormalities. An alternative approach has been suggested by Blinova (1990) linking substance ratios to toxicological parameters. However, application of the suggested approaches to hydrocarbon solvents would be extremely complex due to the number of components in the product.

Since 1976, the Solvents Industry Association (formerly the UK Hydrocarbon Solvents Association) has applied the RCP to complex mixtures of hydrocarbons producing a table of OELs for the major hydrocarbon solvents, based on assumed values for components. These figures have been circulated to the solvents and user industries as guidance.

Toxicological studies carried out on hydrocarbon solvents, and related materials, provide data on a broad range of materials covering both the different distillation ranges and molecular types represented by these products (Cavender, 1994a; 1994b; 1994c). These studies showed that hydrocarbon molecules as described in Section 1.1 are of relatively low toxicity and molecules of similar structure have similar toxic properties. There are a few notable exceptions, e.g. benzene and n-hexane. In most cases recommendations were made for OELs based on the potential to produce discomfort or central nervous system (CNS) depression.

Since the majority of the studies have been on commercial mixtures or surrogates of generic composition, rather than on pure substances, they only provide sufficient information to enable a limited

**Table 1: Typical Compositions of Volatile Hydrocarbon Solvents**

| SOLVENT | b.p. Range °C | Main Carbon Number Range | Average MW | % w/w n-hexane | % w/w aliphatic | % w/w alicyclic | % w/w aromatic |
|---|---|---|---|---|---|---|---|
| 1. Pentane fraction | 35-38 | 5 | 72 | <1 | 99 | 1 | 0.01 |
| 2. Commercial hexane | 65-70 | 6 | 86 | 50 | 88 | 12 | <0.1 |
| 3. SBP 60/95 | 62-95 | 5-8 | 94 | 2 | 68 | 32 | <0.1 |
| 4. SBP 80/110 | 86-106 | 6-8 | 100 | <5 | 64 | 36 | <0.1 |
| 5. SBP 100/140 | 103-136 | 7-9 | 112 | <1 | 64 | 36 | <0.1 |
| 6. Rubber Solvent | 104-150 | 7-10 | 112 | <1 | 62 | 38 | <0.1 |
| 7. SBP 140/165 | 141-161 | 8-11 | 130 | <1 | 63 | 37 | <0.1 |
| 8. Standard White Spirit | 150-200 | 8-12 | 141 | neg. | 57 | 22 | 21 |
| 9. Dearomatised White Spirit | 155-200 | 8-12 | 142 | neg. | 51 | 49 | <0.1 |
| 10. High flash point White Spirit | 180-215 | 10-13 | 159 | neg. | 56 | 23 | 21 |
| 11. Aromatic naphtha 160/180 | 163-180 | 8-10 | 124 | neg. | neg. | neg. | >99.5 |
| 12. Aromatic naphtha 180/215 | 181-215 | 9-11 | 130 | neg. | neg. | neg. | >99.5 |

b.p. = Boiling Point
neg. = Negligible
MW = Molecular Weight
SBP = Special Boiling Point solvent

number of OELs to be set either for individual substances or for typical commercially available complex hydrocarbon solvents .

To enable OELs to be assigned to the broad range of complex hydrocarbon solvents, a generic approach is required.

## 2.2 TYPICAL HYDROCARBON SOLVENTS AND BLENDS

### 2.2.1 Standard Product Types

Hydrocarbon solvents span a boiling point range of 35-320° C, pentane fractions and printing ink distillates being illustrative of the extremes. Complex hydrocarbon solvents may contain 100-200 components. Normally only solvents boiling below 220° C are considered when assigning OELs, as those boiling above this temperature have low vapour pressures under ambient conditions (Section 2.3.3). Table 1 summarises the basic compositions of 12 volatile and commonly-employed hydrocarbon solvents.

Hydrocarbon solvents may be classified as 'aliphatic' ('n-paraffinic' or 'isoparaffinic'), 'alicyclic' ('naphthenic') or 'aromatic' according to the type of molecule predominantly present. Many solvents contain more than one of the above classes, e.g. standard White Spirit typically is a mixture of 80% aliphatic/naphthenic and 20% aromatic molecules. Special Boiling Point solvents (SBPs) are almost pure 'aliphatic' solvents; the aromatic naphthas are examples of the 'aromatic' grades.

Many hydrocarbon solvents are produced as discrete streams within the refinery. Different feedstocks and differences in manufacturing lead to slight variations in composition. Overall there have been few attempts to establish standard product specifications for these solvents other than to describe the product performance. Hydrocarbon solvents are considered as 'substances' for regulatory purposes and have been assigned CAS numbers (EEC, 1990). The product definitions relating to these CAS numbers tend to be very broad and consequently CAS numbers are not a good basis for assigning OELs. Frequently, the same CAS number is allotted to several products as illustrated in Table 2.

Hydrocarbon solvents which can be generically described as "White Spirit" are given CAS numbers which relate to petroleum refinery processes, i.e. hydrotreatment, hydrodesulphurisation or straight run. In the USA the equivalent to "White Spirit" is called Stoddard Solvent; it is assigned a different CAS number and a description which does not refer to its mode of manufacture.

**Table 2: CAS Numbers Associated with Hydrocarbon Solvents**

| TYPE | CAS No. | EINECS No. | SOLVENTS |
|---|---|---|---|
| HT | 64742-49-0 | 265-151-9 | SBPs 60/95, 80/110, 100/140, 140/165 |
| STR | 64742-89-8 | 265-192-2 | SBPs 60/95, 80/110, 100/140 |
| HT | 64742-48-9 | 265-150-3 | SBP 140/165, dearomatised White Spirit |
| HDS | 64742-82-1 | 265-185-4 | Standard White Spirit,<br>High flash point White Spirit |
| STR | 64742-88-7 | 265-191-7 | Standard White Spirit,<br>High flash point White Spirit |
| REFD | 64742-95-6 | 265-199-0 | Aromatic naphtha 160/180 |
| REFD | 64742-94-5 | 265-198-5 | Aromatic naphtha 180/215 |

HT = Hydrotreated HDS = Hydrodesulphurised SBP = Special Boiling Point solvent
STR = Straight run REFD = Reformed

### 2.2.2 Blends

Solvent blends may be produced from two or more solvents of different CAS numbers. The resulting products are called 'preparations' in regulatory terms and, as such, do not receive CAS numbers. Examples of blends employed in user industries are given in Table 3.

**Table 3: Examples of Concentrations of Aromatics and n-Hexane in Hydrocarbon Solvent Blends**

| PRODUCT | n-Hexane % | Aromatic % |
|---|---|---|
| 90% SBP 140/165, 6% aromatic naphtha 160/180, 4% toluene | - | 30 |
| 20% Aromatic naphtha, 80% standard White Spirit | - | 38 |
| 95% High flash point White Spirit, 5% aromatic naphtha 180/215 | - | 27 |
| 90% Heptane, 10% toluene | - | 10 |
| 80% SBP 140/165, 20% xylene | - | 20 |
| 38% Aromatic naphtha 160/180, 62% standard White Spirit | - | 49 |
| 99% Heptane, 1% toluene | - | 1 |
| 75% Heptane, 25% toluene | - | 25 |
| 74% Heptane, 26% toluene | - | 26 |
| 8% Aromatic naphtha 160/180, 92% standard White Spirit | - | 24 |
| 50% Isohexane, 50% n-hexane | 50 | - |
| 90% Isohexane, 10% n-hexane | 10 | - |
| 94% Isohexane, 6% n-hexane | 6 | - |

## 2.3 CHARACTERISTICS OF HYDROCARBON SOLVENTS IN RELATION TO ASSIGNING OELs

### 2.3.1 Theoretical Considerations

In theory the toxic effects of substances may be independent, additive, synergistic or may exhibit antagonism or potentiation. In the absence of any evidence to support synergism, potentiation or antagonism, which is the case for hydrocarbon solvents as is shown in Section 4, only 'independent' and 'additive' effects have to be considered.

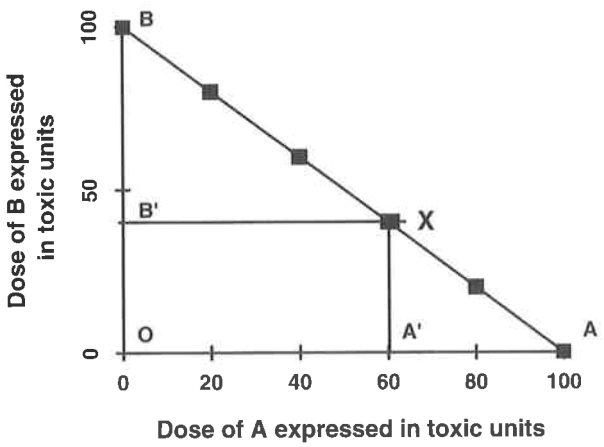
Where components act independently in the vapour exposure situation, the exposure limit of any single component should not be exceeded. Hence the permissible exposures are given by the individual component exposure limits and the total permissible exposure by the sum of these OELs, e.g. for components A, B, C...with exposure limits of $OEL_a$, $OEL_b$, $OEL_c$...and concentrations in air of a, b, c... the ratios

$$\frac{a}{OEL_a}, \frac{b}{OEL_b}, \frac{c}{OEL_c}, \ldots$$

individually must not exceed 1. In practice, the differences in the volatilities of the components, or in the OELs, will ensure that the OEL of one component is reached before those of the remaining components; the OEL for this component would become the limiting OEL for exposure to the mixture.

The constituents of hydrocarbon solvents have similar toxicological properties with the exception of n-hexane (Section 4.4.1). It is therefore reasonable to assume that the components act in an additive fashion. The mathematical implications of additivity are derived from Niessink *et al* (1995) and are illustrated in Figure 1.

**Figure 1: Graphic presentation of additivity of toxic effects**




OA and OB represent the respective 'doses' expressed in toxic units of components A and B which produce the same toxicological effect and the line AB describes the 'additivity situation'. The mixture represented by point X relates to concentrations of OA' (60) of component A plus OB' (40) of component B, and produces the same effect as any mixture derived by a point on the line AB.

For a multi-component mixture, accepting that the 'effective dose' of any substance is directly proportional to its concentration and indirectly to its OEL, the following equation applies:

$$\frac{K_1.Fr_a.C_s}{OEL_a} + \frac{K_2.Fr_b.C_s}{OEL_b} + \cdots = \frac{K_s.C_s}{OEL_s}$$

where $C_s$ is the concentration of the mixture in mass units and $Fr_a$, $Fr_b$ are the fractions of components a, b... in the mixture and $K_1$, $K_2$, . . . are constants. $K_1$, $K_2$, . . will be the same for all components if similar criteria have been used in the assignment of $OEL_a$, $OEL_b$, . ., the equation then reduces to:

$$\frac{Fr_a}{OEL_a} + \frac{Fr_b}{OEL_b} + \cdots = \frac{1}{OEL_s}$$

the numerators and denominators being in mass units. This principle is applied in the RCP developed by ACGIH (ACGIH, 1996). This procedure is reproduced in full in Appendix I to this report.

### 2.3.2 Workplace Situations to be Considered

In practice, exposures to solvent vapours arise basically from three situations:

***Vapours evaporating from a 'pool' of liquid solvent***

In this situation, which is the most common, vapour arises directly from the solvent in use. The vapour composition may differ from that of the liquid. The worst case is represented by equilibrium conditions where the vapour concentration may be higher than the OEL. (This will not be the case for less volatile products, see Section 2.3.3).

***Fugitive emissions from closed systems***

These tend to arise from equipment such as faulty valves leaking minute amounts of the liquid. In this case the vapour is likely to have the same composition as the liquid solvent. When high boiling solvents are involved the escape may give rise to the formation of a mist at ambient temperature.

***Vapour arising from a 'drying film'***

In this situation the composition of the vapour may vary with time although with narrow boiling range mixtures the differences are not of practical significance.

### 2.3.3 High Boiling Solvents

Hydrocarbon solvents with boiling points above 220°C have low vapour pressures and present a special case in OEL setting. The OEL for these products, derived from the methods described in the following paragraphs, may exceed the saturated vapour concentration. Table 4 illustrates the relationships between vapour pressure at 25°C and the calculated OEL for a number of hydrocarbon solvent components. The ratios of the calculated OEL to the saturated vapour concentrations (both in $mg/m^3$), i.e. B/A, indicate clearly that at boiling points of greater than approximately 220°C the vapour concentration at ambient temperature is less than the calculated OEL; e.g. for n-pentadecane the 'calculated OEL' is approx. 18 times the hydrocarbon vapour pressure at 25°C. Hence, with solvents boiling above 220°C vapour concentrations equivalent to the calculated OELs cannot be achieved and mists can develop.

The health consequences of hydrocarbon solvent mists have not been specifically considered as part of this report. However, it seems reasonable, by analogy to the ACGIH TLV for oil mist, to control hydrocarbon mist exposure to less than of 5 $mg/m^3$ to avoid possible irritant effects.

This general advice appears to raise the difficult sampling/analytical question of separating vapours and mists: however, in this situation the problem can be obviated by a pragmatic solution. Consider for example, n-pentadecane (the worst-case situation based on the assumption that solvents range from C5 to C15). The maximum attainable vapour concentration at 25°C is 68 $mg/m^3$ (Table 4). Thus, if the measured concentration exceeds 68 $mg/m^3$, mist must also be present. If 5 $mg/m^3$ of hydrocarbon mist is also present, then the airborne concentration of hydrocarbon would be 73 $mg/m^3$. The contribution by the mist to the total exposure is less than 10%, and the potential for CNS effects due to the combined exposure to vapour and mist seems insignificant. If the total hydrocarbon levels are higher, then the mist concentration must exceed 5 $mg/m^3$. In this situation additional effects such as irritation relating to the mist itself may occur and should be addressed separately.

A value approximating the saturated vapour concentration at the prevailing ambient temperature could be adopted as the OEL for control purposes, unless the OEL derived by the adopted RCP is lower. This should prevent CNS effects due to vapour exposure and any irritant effects on the respiratory tract due to mist exposure.

**Table 4: Relationship Between Calculated OEL* and Vapour Pressure at 20°C for some n-Alkanes and Typical Hydrocarbon Solvents**

| SUBSTANCE / SOLVENT | i.b.p. °C | v.p. at 25°C (M/M) | A vap.conc. at 25°C (in mg/m$^3$) | B OEL* listed or calc. (in mg/m$^3$) | Ratio B/A |
|---|---|---|---|---|---|
| 1. n-Pentane | 36 | 520 | $2.01 \times 10^6$ | 1,800 | 0.0009 |
| 2. n-Hexane | 69 | 153 | $708 \times 10^3$ | 70 | 0.0001 |
| 3. n-Heptane | 98 | 47 | $253 \times 10^3$ | 1,200 | 0.005 |
| 4. SBP 100/120 | 100 | 43 | $257 \times 10^3$ | 1,010 | 0.004 |
| 5. n-Octane | 126 | 16 | $98 \times 10^3$ | 1,200 | 0.012 |
| 6. SBP 140 /165 | 140 | 7 | $56 \times 10^3$ | 680 | 0.012 |
| 7. n-Nonane | 151 | 4.5 | $31 \times 10^3$ | 1,200 | 0.039 |
| 8. White Spirit | 150 | 5.0 | $40 \times 10^3$ | 660 | 0.017 |
| 9. n-Decane | 174 | 1.3 | $10 \times 10^3$ | 1,200 | 0.12 |
| 10. High f.p. White Spirit | 180 | 1.0 | $7.6 \times 10^3$ | 820 | 0.11 |
| 11. n-Undecane | 196 | 0.42 | $3.5 \times 10^3$ | 1,200 | 0.35 |
| 12. Aliphatic 195/240 FR. | 195 | 0.44 | $4.2 \times 10^3$ | 960 | 0.23 |
| 13. n-Dodecane | 216 | 0.16 | $1.5 \times 10^3$ | 1,200 | 0.8 |
| 14. n-Tridecane | 235 | 0.055 | 545 | 1,200 | 2.2 |
| 15. Distillate 240/260 | 240 | 0.037 | 408 | 770 | 1.9 |
| 16. n-Tetradecane | 253 | 0.019 | 202 | 1,200 | 5.9 |
| 17. n-Pentadecane | 271 | 0.006 | 68 | 1,200 | 17.6 |
| 18. Distillate 260/290 | 260 | 0.012 | 143 | 780 | 5.5 |
| 19. iso-Heptadecane | 294 | 0.0015 | 20 | 1,200 | 60 |
| 20. Distillate 280/310 | 280 | 0.003 | 39 | 790 | 20 |
| 21. iso-Octadecane | 309 | 0.0008 | 11 | 1,200 | 109 |

* UK-HSE (UK EH 40/96) used to calculate OELs.

i.b.p. = Initial Boiling Point
SBP = Special Boiling Point solvent
M/M = Mass/Mass
v.p. = Vapour Pressure
f.p. = Flash Point

## 2.4 EXISTING METHODOLOGIES FOR ASSIGNING OELs TO MIXTURES

As hydrocarbon solvents include both substances and preparations (Section 1.1), any method to be considered for the allocation of OELs should be applicable to both. The methodologies discussed below relate to the determination of OELs for complex hydrocarbon solvents and to preparations (blends) based on these solvents.

### 2.4.1 Existing Limit Values

There are only a few OELs assigned to complex hydrocarbon solvents. Table 5 summarises OELs for individual components and complex hydrocarbon mixtures from a number of published lists. The one or two exceptional cases of OELs for complex and variable composition solvents, such as White Spirit and Stoddard Solvent are included. It is known that in some cases the RCP has been employed in deriving these figures for complex hydrocarbon solvents. In other cases it is not clear how the OELs have been assigned. In general, OELs are given in ppm although some countries do employ $mg/m^3$ units for polyalkylbenzenes and $C_{10}$ and $C_{10+}$ alkanes.

**Table 5: OELs in Use in 1994** (in ppm unless otherwise stated)

| Substance | ACGIH | UK | France | Germany | Sweden | Norway | Denmark |
|---|---|---|---|---|---|---|---|
| n-Butane | 800 | 600 | 800 | 1000 | | | |
| n-Pentane | 600 | 600 * | 600 | 1000 * | 600 * | 250 * | 500* |
| Cyclopentane | 600 | | 600 | | | | |
| n-Hexane | 50 | 20 | 50 | 50 | 25 | 25 | 50(25)* |
| Other hexanes | 500 * | 500 * | 500 | 200 * | 200 * | 250 * | 300(200)** |
| Cyclohexane | 300 | 100 | 300 | 300 | 300 | 150 | 300(200)** |
| n-Heptane | 400 | 400 | 400 | 500 * | 200 * | 200 * | 400(200)** |
| Methylcyclohexane | 400 | 400 | 400 | 500 | | | |
| n-Octane | 300 | 300 | 300 | 500 * | 200 * | 150 * | 300(200)** |
| Toluene | 50 | 50 | 100 | 100 | 50 | 40 | 50(25)** |
| Ethyl benzene | 100 | 100 | 100 | 100 | 50 | 50 | 50 |
| Xylenes | 100 | 100 * | 100 | 100 | 50 * | 40 * | 50(25) ** |
| n-Nonane | 200 | | 200 | | 150 * | 100 * | 200 |
| Trimethylbenzenes | 25 * | 25 * | 25 * | | 25 * | 20 * | |
| Cumene | 50 | 25 | 50 | 50 | 25 | | |
| p-tert.Butyltoluene | 10 | | 10 | 10 | | | |
| Naphthalene | 10 | 10 | 10 | 10 | | 10 | 10 |
| Polyakylbenzenes | | | | | 120 $mg/m^3$ | | |
| Alkanes $C_8$-$C_{10}$ | | | | | | | 300 |
| Decanes & $C_{10+}$ | | | 1,000 $mg/m^3$ | | 350 $mg/m^3$ | | |
| Aromatic $C_9$ | | | | | | | 25 * |
| Aromatic $C_{10}$ | | | | | | | 45 * |
| Aromatic $C_{11-13}$ | | | | | | | 45 * |
| Stoddard Solvent | 100 | | | | | | |
| White Spirit (22% Arom.) | | | | | ± 50 | | |
| White Spirit (< 22% Arom.) | | | | | | 50 | |
| White Spirit (> 22% Arom.) | | | | | | 25 | 100(25) ** |
| White Spirit | | 100 | | | | | |
| VM & P Naphtha *** | 300 | | | | | | |
| Rubber Solvent | 400 | | | | | | |
| $C_9$-$C_{14}$ (< 5% Arom.) | | | 150 $mg/m^3$ | | | | 100 |
| Use RCP | ✓ | ✓ | | ✓partly | ✓ | ✓ | |

* Underlining indicates "all isomers" (Note - Some product names are ambiguous e.g. Rubber Solvent)

** Anticipated changes are given in brackets

*** VM & P: Varnish Makers & Painters

### 2.4.2 Generic Approaches

Generic approaches are considered to be those which can be applied to the full range of hydrocarbon solvents, including blends. Such approaches need to take account of all constituents of the solvents and their additive effects. The simplest generic approach is to assign a single OEL to all hydrocarbon solvents. In practice this OEL would have to be the value assigned to the most hazardous common constituent, n-hexane. However, as the toxicity of n-hexane is unlike that of any other hydrocarbon solvent constituent, its use as a surrogate to set OELs for all hydrocarbon solvents cannot be justified scientifically, nor would such an approach be consistent with historical practice or experience.

Establishing OELs for all the possible constituents of hydrocarbon solvents and using these to calculate the solvent OELs via a RCP is theoretically possible. However, as only a few individual constituents have been assigned OELs, and for many there is a limited toxicological data base, this approach is impractical at present.

A simpler approach, but one which still takes account of the constituents of each solvent, is required. Two possible methods emerge. In the first the OEL for the solvent is defined by the percentage of the specific constituents which have been assigned OELs, e.g. n-hexane, aromatics. In the second all constituents of the solvent are taken into account via a group approach and an overall OEL is calculated using a RCP.

The first approach results in the selection of a small number of distinct OELs which cover the whole range of hydrocarbon solvents, but may give significantly different OELs to products of very similar composition. The second results in OELs which change continuously as the composition of the solvent changes. As a way of examining the relative strengths and weaknesses of these two approaches the remainder of this section compares the experiences in two European countries in which the approaches have been applied.

For purposes of comparison the underlying principles of these approaches have been described. These principles have then been critically evaluated to determine which of them can best be utilised as a common approach to the assignment of OELs to complex hydrocarbon solvents. For the purpose of this report the approaches are described as “selective’ and “constitutional” respectively.

#### *The Selective Approach*

The selective approach assigns OELs to groups of solvents on the basis of concentration of selected constituents.

The German Technical Guidance for Hazardous Substances (TRGS 404, 1992) applies a RCP, employing ppm values, to produce OELs for 4 groups of complex hydrocarbon solvents based on their n-hexane and aromatic hydrocarbon content (Table 6). For regulatory purposes, should exposure to hydrocarbon solvents be related to more than one group, the lowest value of the relevant groups is applied. Values are given in ppm and are intended to be applied at the workplace. The conversion from ppm to $mg/m^3$ is based on "octane equivalents": 1 ppm = $(114/24.1)(mg/m^3) = 4.74\ mg/m^3$.

Graphical representation of this approach as applied to hydrocarbon solvents with different compositions are presented in Figures 2 and 3 (Section 2.5).

(Note that here and in the discussion to follow, particularly Section 2.5, the assumptions and recommended values given in TRGS 404 (1992) were used to calculate the various examples. This was done only as a convenience; other assumptions could have been made and would have produced somewhat different numerical results, but the overall conclusions would be the same.)

**TABLE 6: Group OEL Values from TRGS 404**

| | | |
|---|---|---|
| **GROUP 1** | **OEL 350 ppm** | Dearomatised hydrocarbon mixtures containing less than 1% aromatic hydrocarbons and less than 5% n-hexane; |
| **GROUP 2** | **OEL 200 ppm** | Aromatic-deficient hydrocarbon mixtures containing from 1 to 25% aromatic hydrocarbons and less than 5% n-hexane; |
| **GROUP 3** | **OEL 50 ppm** | Hydrocarbon mixtures rich in aromatic substances containing greater than 25% aromatic hydrocarbons; |
| **GROUP 4** | **OEL 50 ppm** | Other hydrocarbon mixtures containing greater than 5% n-hexane; |

***The Constitutional Approach***

The constitutional approach takes into account the different properties of the constituents as it calculates an OEL for each complex hydrocarbon solvent in accordance with its composition.

The UK Health and Safety Executive (UK-HSE, 1996) produced guidance (UK-HSE-EH40/96) for the calculation of OELs for complex hydrocarbon solvents based on the RCP developed by the ACGIH. This guidance document also lists individual OELs and guidance values for groups of unlisted alkanes, cycloalkanes and aromatics. n-Hexane can be included in the method to ensure that is OEL will not be exceeded as long as the vapour composition is similar to the liquid composition.

The constituents included in the list are indicated in Table 7.

**Table 7: UK OELs and Guidance Values**

| | |
|---|---|
| Alkanes $C_5$-$C_6$ (except n-hexane) | 1800 mg/m$^3$ |
| n-Hexane | 70 mg/m$^3$ |
| Alkanes > $C_7$ | 1200 mg/m$^3$ |
| Cycloalkanes $C_5$ - $C_6$ (except cyclohexane) | 1800 mg/m$^3$ |
| Cyclohexane | 340 mg/m$^3$ |
| Cycloalkanes > $C_7$ | 800 mg/m$^3$ |
| Aromatics (except where listed in EH40) | 500 mg/m$^3$ |
| Toluene | 188 mg/m$^3$ |
| Ethyl benzene | 435 mg/m$^3$ |
| Xylene isomers | 435 mg/m$^3$ |
| Cumene | 125 mg/m$^3$ |
| Trimethyl benzene | 125 mg/m$^3$ |

The results of the application of this method are presented in Figures 2 and 3 (Section 2.5). An example of the use of the constitutional approach to calculate an OEL for standard White Spirit is given in Table 8. For a few volatile solvents which contain a high proportion of n-hexane, e.g. SBP 2 (boiling range 70-90ºC), the RCP should be applied to the vapour composition as this may vary from the liquid composition. However, in most situations, the vapour and liquid compositions are sufficiently similar that the RCP can be directly applied to the liquid composition.

**Table 8: Application of the Constitutional Approach to Standard White Spirit**

| Composition | Guidance Value or OEL |
|---|---|
| 52% alkanes ≥ $C_7$ | guidance value = 1200 mg/m$^3$ |
| 27% cycloalkanes ≥ $C_7$ | guidance value = 800 mg/m$^3$ |
| 10% aromatics | guidance value = 500 mg/m$^3$ |
| 1% $C_8$ aromatics (xylene isomers) | OEL = 435 mg/m$^3$ |
| 10% trimethylbenzenes | OEL = 125 mg/m$^3$ |

Calculation of OEL

$$\frac{1}{OEL_{Solvent}} = \frac{0.52}{1200} + \frac{0.27}{800} + \frac{0.10}{500} + \frac{0.01}{435} + \frac{0.10}{125}$$

$$= 0.000433 + 0.000338 + 0.0002 + 0.000023 + 0.0008$$

$$= 0.001794$$

$$OEL_{Solvent} = \frac{1}{0.001794}$$

$$= 557 \text{ mg/m}^3,$$

$$= 550 \text{ mg/m}^3 \text{ (rounded to the nearest 50)}$$

Conversion from the calculated OEL in mg/m$^3$ to a value in ppm at 25°C, under standard pressure conditions is effected by use of the relationship:

$$\text{OEL in ppm} = \frac{\text{OEL in mg / m}^3 \text{ x } 24.45}{\text{Mean MW of solvent}}$$

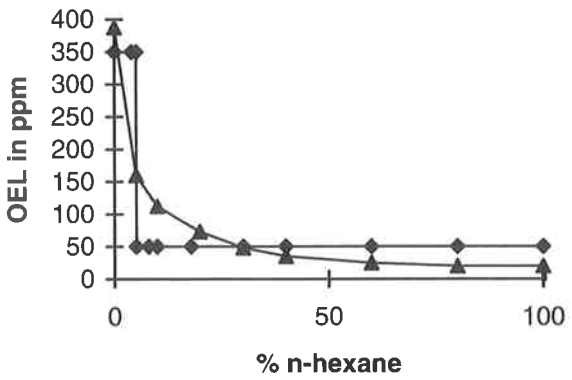
(The calculated figures will be rounded up or down to conform with a series of preferred values: Calculated value < 100 mg/m$^3$ rounded to nearest 25, between 100 - 600 mg/m$^3$ to the nearest 50 and > 600 mg/m$^3$ to the nearest 200 mg/m$^3$)

## 2.5 COMPARISONS OF GENERIC APPROACHES

Comparisons for mixtures with increasing n-hexane content are shown in Figure 2. Two mixtures are used for the selective approach which meet the descriptions of Group 1 and Group 4 respectively (Table 6, Section 2.4.2). The mixture used for the constitutional approach contains unlisted non n-hexane-C6-alkanes with an OEL of 1800 mg/m$^3$, and a variable percentage of n-hexane.

The selective approach gives a constant OEL (50 ppm) over the range of 5-100% n-hexane and a dramatic change at 5%, whereas the constitutional approach yields a smooth curve with OELs decreasing as the n-hexane content increases.

**Figure 2: Comparison of OELs, derived by the application of the different approaches, for solvents with varying contents of n-hexane**

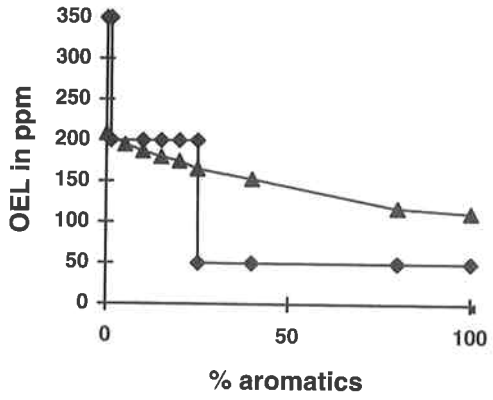



◆ — ◆ Selective approach (Group 1: 350 ppm, Group 4: 50 ppm)
▲ — ▲ Constitutional approach (unlisted non n-hexane-C6-alkanes 1800 mg/m$^3$, n-hexane 70 mg/m$^3$).

Conversion mg/m$^3$ to ppm is based on a MW of 114

Comparisons for mixtures with increasing aromatics content are shown in Figure 3. The mixture used for the constitutional approach contains a fixed amount of alkanes with an OEL of 1200 mg/m$^3$ and a fixed amount of cycloalkanes with an OEL of 800 mg/m$^3$; n-hexane is less than 5%. The content of aromatics varies. Three mixtures are used for the selective approach: one meets the description of Group 1, the others meet the descriptions of Group 2 and 3 respectively (Table 6, Section 2.4.2). Utilisation of the constitutional approach produces a smooth curve, whereas the selective approach produces a three stepped plot. The diagram shows clearly the dramatic effects produced by some small compositional changes when the selective approach is applied.

**Figure 3: Comparison of OELs, derived by the application of the different approaches, for solvents with varying contents of aromatics**

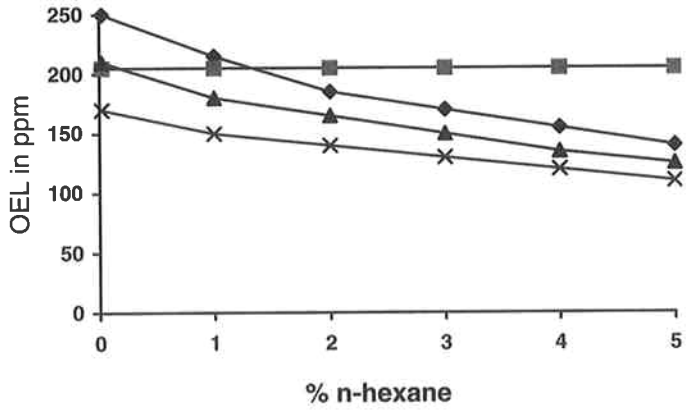



◆ — ◆ Selective approach (Group 1: 350 ppm, Group 2: 200 ppm, Group 3: 50 ppm)
▲ — ▲ Constitutional approach (alkanes 1200 mg/m$^3$, cycloalkanes 800 mg/m$^3$, aromatics 500 mg/m$^3$)

Conversion mg/m$^3$ to ppm is based on a MW of 114.

Differences in OELs resulting from the different procedures are presented in Figure 4 for solvents containing less than 1% aromatics and 5% n-hexane. Three plots for the constitutional approach are introduced to show aliphatic and alicyclic mixtures of different carbon numbers In this case the guidance values developed by the UK (EH-40/96) were used to carry out the calculations. When the constitutional method is used, the resulting OELs have continuous values over a range of constituent concentrations. Constant OELs for solvents in this range result from the selective approach (using TRGS 404 values as an example). The selective approach does not recognise differences between the aliphatic and alicyclic components or differences due to carbon numbers.

**Figure 4: Comparison of OELs by applying the different approaches to Group 1 (TRGS) solvents with < 1% aromatics and up to 5% n-hexane**




■ — ■ Selective approach

◆ — ◆ Constitutional approach for mixtures with C7-C15 alkanes

▲ — ▲ Constitutional approach for mixtures with 50/50 C7-C15alkanes/C7-C15 cycloalkanes.

× — × Constitutional approach for mixtures with C7-C15 cycloalkanes.

Conversion mg/m$^3$ to ppm is based on a MW of 114.

### *Conversion Complications*

The process stipulated in TRGS 404 specifies that the molecular weight of n-octane be used to convert from ppm to mass units. This simplification introduces an inaccuracy which becomes greater for solvents at the upper and lower ends of the range (i.e $C_{12}$ and $C_5$). Table 9 which provides a comparison of the OELs in mg/m$^3$ for the main groups of hydrocarbon solvents calculated with the two generic approaches, illustrates clearly that this simplification results in OELs (mg/m$^3$) which rise steadily with carbon number.

**Table 9: Comparison of OELs ($mg/m^3$) calculated with the Constitutional Approach (EH40/96) and the Selective Approach (TRGS 404)**

| Product | EH 40/95 | | | TRGS 404 | | |
|---|---|---|---|---|---|---|
| Carbon No. | Alkane* | Cycloalkane* | Aromatic* | Alkane | Cycloalkane | Aromatic |
| C5 | 1,800 | 1,800 | | 1,470 | 1,430 | |
| C6 | 1,800 | 1,800 | ** | 1,760 | 1,720 | ** |
| C7 | 1,200 | 800 | | 2,040 | 2,000 | 376 |
| C8 | 1,200 | 800 | | 2,330 | 2,290 | 434 |
| C9 | 1,200 | 800 | 500 | 2,620 | 2,580 | 245 |
| C10 | 1,200 | 800 | 500 | 2,900 | 2,860 | 274 |
| C11 | 1,200 | 800 | 500 | 3,190 | 3,150 | 303 |
| C12 | 1,200 | 800 | 500 | 3,480 | 3,440 | 331 |
| C13 | 1,200 | 800 | 500 | 3,760 | 3,720 | 360 |
| C14 | 1,200 | 800 | 500 | 4,050 | 4,010 | 389 |
| C15 | 1,200 | 800 | 500 | 4,340 | 4,290 | 417 |
| C16 | | 800 | 500 | | 4,580 | 446 |
| **Excluded from the above are** | | | | | | |
| n-Hexane | 70 | | | 176 | | |
| Cyclohexane | | 340 | | | 300 | |
| Toluene | | | 188 | | | 100 |
| Xylenes | | | 435 | | | 100 |
| Ethyl-benzene | | | 435 | | | 100 |
| Cumene | | | 120 | | | 245 |
| Trimethyl benzenes | | | 123 | | | No MAK |

* UK-HSE (UK EH 40/96) used to calculate OELs

** Although benzene is excluded it does appear in national lists. However, only trace quantities are present in commercially available hydrocarbon solvents.

To overcome this inaccuracy the formula needs to be modified so that the numerators of each constituent ratio become molecular fractions,

$$\frac{1}{OEL_s} = \frac{Mol.Fr_a}{OEL_a} + \frac{Mol.Fr_b}{OEL_b} + \text{etc.}$$

i.e. where $OEL_s$, $OEL_a$, $OEL_b$,... (of solvent, component a, component b, etc.) are the respective OELs of the solvent and the components a, b, etc. in ppm. The OELs obtained with the amended formula are shown and compared with the original values in ppm (Table 10). It can be seen that significantly different OELs are obtained if the revised formula is used, in particular, for the higher molecular weight fractions.

**Table 10: Comparison of OELs Calculated by the TRGS 404 and TRGS 404 (Revised) Procedure**

| | Calculated OEL | |
|---|---|---|
| Solvent | TRGS 404 | TRGS 404 (Revised) |
| Group 1 | | |
| C5 fraction | 350 ppm | 350 ppm |
| C12 fraction | 350 ppm | 260 ppm |
| Group 2 | | |
| C7 fraction | 200 ppm | 200 ppm |
| C12 fraction | 200 ppm | 160 ppm |

***Adjustment to changes in OELs***

Because of the rigid selection criteria, the selective method requires formal amendment to comply with changes in constituent OELs. Using the TRGS 404 procedure (as published in 1992) as an example, the constituents which determine limits for Groups 1 and 2 solvents are:

| | |
|---|---|
| 'aliphatic' hydrocarbons | 500 ppm |
| 'aromatic' hydrocarbons | 100 ppm |
| toluene/xylene | their respective OELs (100 ppm) |
| n-hexane | 50 ppm |

in which the value for 'aliphatic' hydrocarbons (500 ppm) was the MAK value for n-heptane and the value for 'aromatic' hydrocarbons (100 ppm) was the MAK value for toluene at that time.

However, since the method was published, MAK values for iso-hexane and cyclohexane have been developed and the MAK value for toluene reduced, thus requiring the method to be updated. Further changes in TRGS 404 may be necessitated by proposals from the EC Scientific Committee on Occupational Exposure Limits (SCOEL) to establish indicative limit values (ILVs) for a number of relevant substances including n-hexane, toluene, cyclohexane, heptane, pentane and several isomers of trimethylbenzene. Each time a new regulatory value is developed the OEL calculation needs to be changed to assure that the regulatory limits for the individual constituents are respected.

## 2.6 CRITERIA FOR SELECTION

***Key issues***

In reviewing the available approaches a number of conclusions emerged which encompass the various issues related to the assignment of OELs to hydrocarbon solvents, specifically:

1. Hydrocarbon solvents are products with complex and variable composition which have a wide variety of application including their use in blends or as components of other products.

2. Generally the constituents of hydrocarbon solvents have similar toxicity and are additive in effect (Section 4).

3. No airborne constituent of any complex solvent should exceed its individual OEL if the OEL for the solvent is complied with.

4. n-Hexane has specific toxicological properties and is a component of some solvents.

5. OELs which have been assigned to constituents of hydrocarbon solvents should be taken into account.

6. Small changes in composition are of minor toxicological importance and should have only minor consequences for the OEL of the complex hydrocarbon solvent, whether substance or blend.

7. The underlying scientific assumptions should be amenable to test and/or verification.

8. Component OELs may change as a result of regulatory decisions and these changes need to be accommodated readily.

***Selection criteria***

These principles have led to the development of the following criteria for a comparative analysis of the approaches. The procedure should:

a) be universally applicable to any hydrocarbon solvent;
b) take into consideration the contributions of all constituents;
c) ensure that the OEL of no constituent is exceeded, assuming the vapour composition equates to the liquid composition;
d) recognise the specific problem of n-hexane;
e) recognise the specific problems of certain aromatic constituents (e.g. trimethylbenzenes);
f) produce changes in OEL which are proportional to the changes in composition;
g) have underlying scientific assumptions that are sound and transparent;
h) be readily adaptable to changes in the OEL of the costituents;

Table 11 compares the selective and constitutional approaches according to the above criteria. The constitutional approach meets all the criteria whereas the selective approach has significant disadvantages as previously described. Therefore the constitutional approach, using the RCP, is recommended for assigning OELs to complex hydrocarbon solvents. To make this practicable, OELs for groups of similar constituents are required to make up for the lack of individual hydrocarbon OELs.

**Table 11: A Comparison of the Selective and Constitutional Procedures**

| | CRITERION | SELECTIVE | CONSTITUTIONAL |
|---|---|---|---|
| a) | Universally applicable to any hydrocarbon solvent | ✓ | ✓ |
| b) | All constituents of the hydrocarbon solvent are adequately recognised | X | ✓ |
| c) | The OEL of no component can be exceeded assuming vapour and liquid compositions are similar | X | ✓ |
| d) | Specific problems of n-hexane are recognised | ✓ | ✓ |
| e) | Specific problems of aromatics (e.g. trimethylbenzenes) are recognised | X | ✓ |
| f) | Produces changes in OELs which are proportional to small changes in composition | X | ✓ |
| g) | Has underlying transparent assumptions | ✓ | ✓ |
| h) | Has methodology which readily takes account of changes in constituent OELs | X | ✓ |

✓ meets criteria
X does not meet criteria

# 3. EXPOSURE MONITORING

## 3.1 INTRODUCTION

In the workplace there is a need for simple, inexpensive, repetitive measurements of the concentration of solvent vapours in the air to determine if excursions above accepted limits occur. These simplified methods need to be standardised against known airborne concentrations of the respective solvents which have been evaluated quantitatively with the appropriate degree of specificity and accuracy.
These aspects are addressed below as Sampling and Analysis, Analytical Method Standardisation and Workplace Monitoring Methods.

## 3.2 SAMPLING AND ANALYSIS

The hydrocarbon solvents which are commonly used can be classified in terms of their complexity as:

A) Simple solvents consisting of a few well-defined constituents, such as toluene, xylene and hexane.

B) Complex solvents consisting of a large number of components, some ill-defined, for example petroleum ether, White Spirit, naphtha. These are usually petroleum fractions containing aliphatic, alicyclic and/or aromatic hydrocarbons with up to 200 distinguishable components.

C) Complex solvents consisting of a combination of types A and B.

The requirements for measuring airborne concentrations of these solvents are:

- Short-term or spot-reading measurements.
  Available methods generally indicate the average concentration at a single position over a short period of time (< 5 min) and provide instantaneous indication with a specified time constant. They are useful for deciding whether or not it is safe to enter a particular area and for giving a rough indication of concentration levels. However, a statistically meaningful number of such readings would normally be required to determine whether or not an OEL is being met.

- Measurements of average concentration levels over a given time period.
  These measurements will give average concentration levels for part or all of a work shift up to 8 or 12 h. They are particularly useful for measuring personal exposure by mounting the equipment in the breathing zone of a worker.

- Continuous measurement of concentration levels at a fixed point.
  These provide a continuous measure of the concentration levels at a particular point in the workplace to show trends and, less commonly, to provide alarms if inadvertent emission occurs. Data can be integrated to give average concentrations.

The pragmatic methodology for setting OELs for such hydrocarbon solvents needs to be supported by practical methods, which provide simple, inexpensive, repeatable measurements, indicating deviations from the compliance level. Generally there is a high degree of experience, skill and resource in this area amongst the producers but much less in the small users. Methods of evaluation need to fit in with these constraints.

## 3.3 ANALYTICAL METHOD STANDARDISATION

For calibration of analytical instruments under standard laboratory conditions known concentrations of a specified hydrocarbon solvent can be generated following the procedure of the UK-HSE Methods for the Determination of Hazardous Substances (MDHS). Such standardisation would need to be undertaken by laboratories operating to the standards of such schemes as the UK National Measurement Accreditation Service (NAMAS, 1989), with acceptable performance in external quality assessment schemes such as the Workplace Analysis Scheme for Proficiency (WASP) or the Proficiency Analytical Testing Program (PAT).

The instruments most commonly employed for calibration are the capillary gas chromatograph and the infra-red spectrophotometer. The former, if used with a flame ionisation detector, and the latter, if used at the 3.4 µm hydrocarbon wavelength, respond to a range of hydrocarbons with more or less equal sensitivity per weight of hydrocarbon sampled.

Generally, when more than one constituent is present, calibration would be expressed in $mg/m^3$. Acceptable levels of performance for use with complex substances or preparations have also been standardised.

## 3.4 WORKPLACE MONITORING METHODS

Workplace methods which are applicable to hydrocarbon solvents are described under the headings of Direct Reading and Analytical Methods and Continuous Monitoring.

### 3.4.1 Direct Reading Methods

These range from the simple gas indicator tube to instrumental methods based on infra-red, flame ionisation, semiconductors and photo-ionisation.

***Gas indicator tubes***

Gas indicator tubes provide a rapid, inexpensive and simple method for evaluating the level of complex hydrocarbons in some circumstances. They are available for several specific hydrocarbon molecules and some solvents. The length of the stain produced in the tube is related to the concentration of the solvent being measured in the test atmosphere.

Type A solvents (Section 3.2) may often be assessed by using agent-specific tubes, for example Draeger toluene 5/a. Type B solvents may often be evaluated by validated chemical indicator tubes for hydrocarbons which are available from a number of manufacturers. The sensitivity of these tubes is low (detection limit about 100 ppm) and the response varies greatly with the hydrocarbons present. Detector tubes are less suitable for the determination of type C solvents, although a qualitative estimate may be obtained from, for example, a Draeger polytest tube.

The validity of use of any one indicator tube for a single hydrocarbon or multiple hydrocarbons must be determined as described in the section on Method Standardisation.

***Instrumental methods***

Infra-red spectrophotometers, equipped with long path length (c. 0.5-20m) gas cells, are available for monitoring complex hydrocarbon vapours. A precision of ± 5% or better with a measurable concentration range from less than 1-100 ppm is achievable with such instrumentation.

For many Type B solvents, the spectrophotometer may be calibrated for "total hydrocarbons" against a suitable reference compound, e.g. hexane or the petroleum hydrocarbon fraction in use.

For highest accuracy, the infra-red spectrophotometer is calibrated for a well-defined set of constituents using a single wavelength. Alternatively measurement can be made at several specific wavelengths.

Portable, direct reading, flame ionisation analysers, can be used to obtain on-site data on concentrations in air. This type of instrument is most useful for type B solvents, calibrated for "total hydrocarbons" against a suitable reference compound, e.g. hexane or the petroleum hydrocarbon fraction in use.

Gas analysers based on semiconductors are available for obtaining short-term readings (1-3 sec) of complex materials. These instruments have a precision of about ± 1% and measure over the approximate range 20-100 ppm. They are non-specific and are most useful for type B mixtures. Calibration for "total hydrocarbons" is made against a suitable reference compound, e.g. hexane or the petroleum hydrocarbon fraction in use.

Photo-ionisation analysers provide a range of measurement within the range 1 to 1000 ppm with a response time of about 2 seconds. This method, like the semiconductor gas analyser, lacks specificity. It is also applicable to type B solvents. The sensitivity of the analyser to aromatic hydrocarbons is approximately 10 times greater than that for aliphatic hydrocarbons, so the response is heavily influenced by the aromatic content of a solvent.

### 3.4.2 Analytical Methods

Pumped or diffusive sampling can be used in combination with thermal desorption and capillary gas chromatography.

The technique is appropriate for all types of hydrocarbon solvents. The technique is suitable for the separation of individual components (e.g. n-hexane) from a series of constituents.

Experience with gasoline has led to the adoption of a particular method based on pumped sampling which has general application for hydrocarbon solvents (CONCAWE, 1987; UK-HSE, MDHS 60).

Protocols for the validation of methods are given for on-site use in MDHS 5, for pumped samplers in MDHS 54 and European Standards EN 1076 and 1232, and for diffusive samplers in MDHS 27 and European Standards EN 482 and 838.

Pumped charcoal tube and diffusive sampling can be used in combination with solvent desorption and a packed column method. This method is described in MDHS 66, for toluene. The method is most useful for type A solvents; for type B solvents, the method gives only a crude chromatogram, which is best analysed as total peaks measured against the closest-matching solvent mixture available. For type B solvents, considerable error is introduced both by the crudity of the calculation and in the extent of mismatch between sample and standard. The ratio of peaks present may not be the same in bulk sample and airborne vapours because of differing volatilities. The advantage of the method is that it is relatively quick, reliable and inexpensive.

Alternatives, using diffusive badges and thermal desorption tubes with infra-red spectrophotometry or thermal desorption with detector tube are adaptable to specific situations.

### 3.4.3 Continuous Monitoring

The methods described above can be adapted to continuously monitor complex hydrocarbon vapours in the work room air. The measurements can be single or multipoint depending on the construction of the equipment.

The most useful mode of operation is in estimating "total hydrocarbons" in a solvent type B. In all cases, the response to individual hydrocarbons will vary, and be subject to error if alcohols, ketones, esters or chlorinated hydrocarbons are present. Most-accurate results will be obtained by calibration against specific group of constituents.

# 4. TOXICOLOGICAL OVERVIEW

## 4.1 INTRODUCTION

In general the types of hydrocarbon compounds present in hydrocarbon solvents have very similar toxicological properties; they may produce skin irritation or dermatitis through defatting; eye and respiratory tract irritation as well as central nervous system depression if inhaled at high levels.
They may also cause chemical pneumonitis if taken into the lung in liquid state (aspiration). Some of these hydrocarbons may produce persistent neurological problems and/or cardiac sensitisation if abused, but not when used responsibly and in accordance with recommended procedures. There are some exceptions to these general rules, but many of the more problematic hydrocarbons including benzene, 1,3 butadiene, and the carcinogenic polycyclic aromatic hydrocarbon (PAH) species (certain PAHs containing more than 3 aromatic rings) are not found in significant quantities in hydrocarbon solvents. Except as described below, these are not relevant and will not be discussed further.

Inasmuch as the intent of this document is to recommend a method of establishing responsible guidelines for the establishment of OELs applicable for normal use, solvent abuse issues are not directly relevant and will not be taken up further.

Excluding the specific molecules listed above, the data from animal studies indicate that hydrocarbon solvents are low in acute toxicity, produce skin and eye irritation only under conditions of extreme exposure, and do not produce skin sensitisation. Additionally they have shown no evidence of selective developmental or reproductive toxicity, and there is no evidence that they are mutagenic. None of the hydrocarbon solvents is considered to be carcinogenic (IARC, 1989), although as noted above, certain hydrocarbon species which are not found in hydrocarbon solvents may be carcinogenic. In the group of hydrocarbon solvents there is one substance, n-hexane, which produces clinically important changes in the peripheral nervous system. However, aside from this example, none of the hydrocarbons found in solvents is associated with irreversible pathological changes in the central nervous system, at least at occupationally-relevant exposure levels. n-Hexane represents an exception, not only to the generalisations about toxicity, but also the assumptions about additivity and physical and chemical behaviour that are required by the method for setting occupational exposure limits proposed herein. For those reasons n-hexane (and a few other specific hydrocarbon species) are discussed below in more detail.

In addition to the animal studies, there are a number of human volunteers studies (Carpenter *et al*, 1975 b-h; 1976 a-e; 1977 a-c; 1979), which show that the acute effects in humans are limited. These studies have formed the basis for many of the current occupational exposure recommendations. The toxicities of specific hydrocarbon molecules and mixtures have recently been reviewed by Cavender (Cavender

1994a; 1994b; 1994c) and are considered low and non-specific. The reader is referred to these publications for more-detailed information on the subject in general or on any specific molecular type covered by this review. It should also be noted that the range of products encompassed by this review includes several hundred molecular species. Some of these may produce effects under certain experimental conditions. However, other than n-hexane, none is known to produce effects other than irritation and/or acute CNS depression in man under occupationally-relevant conditions.

Warranting further discussion is the possible association of chronic exposure to hydrocarbon solvents with persistent and clinically important changes in the central nervous system or the kidneys. These questions have arisen largely from epidemiological investigations which, in part due to their nature, have been neither completely clear nor entirely consistent. The sections which follow provide a review of the human and animal data which have bearing on that debate.

## 4.2 CENTRAL NERVOUS SYSTEM EFFECTS

### 4.2.1 Background

As stated previously, all hydrocarbons can produce CNS depression if exposure occurs at sufficiently high levels. This is normally a transient effect and rapidly reversible after cessation of exposure.

A more controversial issue is the question of whether repeated exposure to hydrocarbons over prolonged periods can produce more profound and persistent changes in the CNS.

### 4.2.2 Animal Data

The effects of a number of hydrocarbons on the nervous system have been assessed in animal studies. Many of these substances were tested in a series of toxicology studies conducted between approximately 1975 and 1978. A common protocol which involved repeated exposure of several animal species for periods of up to 90 days to exposure levels which were often the maximally-attainable vapour concentrations was used in all cases. The animals were observed during the in-life period, and after sacrifice, an extensive pathological examination was carried out (Carpenter *et al*, 1975a). Other than signs of CNS depression in some of these studies, there was no evidence of persistent neurological effects and no evidence of pathological changes in the central or peripheral nervous system (Carpenter, 1975 b-h; 1976 a-e; 1977 a-c; 1979).

Exposure to hydrocarbons may also produce eye and/or respiratory tract irritation along with signs of CNS depression. In general, levels judged to be intolerable on the basis of comfort exceeded approximately 400 ppm although lower levels were found for some "alkylbenzene-rich" materials. When human data are used, OELs are generally set either to protect against CNS depression or on the basis of comfort.

More recently there has been renewed interest in neurological effects, and techniques have been developed to assess more subtle parameters. Of particular relevance are studies conducted in accordance with protocols developed by the US Environmental Protection Agency and now under discussion within the OECD. In these tests adult rats are exposed repeatedly for up to 90 days with periodic examination for clinical changes, behavioural effects and changes in motor activity. Following exposure the nervous tissue is examined microscopically for evidence of pathologic changes in either the central or peripheral nervous system. One substance tested under this protocol was high flash aromatic naphtha, an aromatic solvent composed primarily of ethyl toluene and trimethylbenzene isomers (Douglas *et al*, 1993). White Spirit (ECETOC, 1996; Ostergaard *et al*, 1993) and toluene (Ladefoged *et al*, 1991) were also tested under similar protocols. None of these substances produced overt neurotoxicological effects as defined by pathological and neurobehavioural studies.

There are also studies of the effects of toluene, xylenes and gasoline (ECETOC, 1996; CONCAWE, 1992) which examined the potential of the test material to produce pathological changes in the nervous system, but did not directly assess functional changes. Repeated exposure to hydrocarbons produced no changes which could be identified by microscopic examination. In this regard, gasoline could be considered "worst case" since it contains hydrocarbon constituents similar to those in solvents but has a wider boiling range, is normally less-well refined, and also contains certain constituents which are toxicologically important in themselves and are not found in the solvents products. Thus it is particularly noteworthy that gasoline produced negative results in these studies.

In summary, studies in animals provide no support for the view that repeated exposure to hydrocarbons at less than acutely toxic levels produces clinically important changes in the CNS.

### 4.2.3 Human Data

Several studies emanating mainly from Scandinavian countries, which can be traced back to the beginning and middle of the 1970s, have reported on solvent-exposed cases with a symptomatology that could be summarised as a psycho-organic or neurasthenic syndrome (Arlien-Soborg, 1992; Hogstedt, 1994).

The typical symptoms reported included memory disturbances, excessive tiredness, personality changes (including depression), irritability and affects on lability, sometimes intellectual reduction, and problems in maintaining a job and other social functions. In addition, several cross-sectional studies reported excess neuropsychiatric symptoms and impaired neuropsychological performance among various populations exposed to solvents at work.

These studies are limited, in particular with respect to exposure information. In many cases it has been difficult to draw any conclusions about the materials to which individuals might have been exposed, and levels of exposure were seldom recorded. In addition, the diagnoses were often based on subjective judgement, and, at least prior to 1985, were not assessed by a standard methodology. Further, many of these studies have been criticised. Among the issues raised are that potentially confounding variables including solvent abuse, ethanol consumption. Additionally, other substances to which the individuals might have been exposed, and intellectual levels of the individuals were not taken into account.

In more recent studies (Fidler *et al*, 1987; Treibig *et al*, 1988; Hooisma *et al*, 1993; Bleeker *et al*, 1991; Spurgeon *et al*, 1992) there have either been no decrements in neurobehavioural test performance (Fidler *et al*, 1987 and Treibig *et al*, 1988) or much less-marked effects than those reported in earlier studies (Hooisma *et al*, 1993; Bleeker *et al,* 1991; Spurgeon *et al*, 1992). The failure to confirm earlier reports may reflect either improvements in study design in terms, for example of control of potential confounders and selection of control group, or the general reduction in exposure levels which has occurred during the last 30 years.

Based on these data, it is apparent that hydrocarbon solvents, as they are currently used in industry, do not produce serious neurological or neurobehavioural deficits (ECETOC, 1996). Whether they produce subtle effects or none at all cannot be discerned. Nevertheless, there is good reason to believe that long-term exposure at relatively low levels (i.e., approximating current OELs) does not result in clinically important damage to the CNS (Baker, 1994; Spurgeon *et al*, 1994). It should be noted in this regard that long-term chronic disorders are less likely to develop if the regular occurrence of acute reversible effects (i.e., acute CNS depression) is prevented (World Health Organization, 1985). Thus, in principle, if occupational exposure is maintained at levels below those which produce acute CNS depression, chronic disorders should not occur.

## 4.3 NEPHROTOXICITY

### 4.3.1 Background

There have also been allegations, based primarily on epidemiology studies, that repeated exposure to hydrocarbon solvents produces kidney damage in humans. This issue has been confounded by an unfortunate use of incorrect terminology. In the first paper on this subject (Bierne and Brennan, 1972) the term "hydrocarbon" was used as a synonym for "organic solvent", and the use of this terminology has continued. However, in many of the reports, actual case studies were described. Often the effects resulted from exposure to other substances, for instance carbon tetrachloride, which has specific toxic effects and is a halogenated solvent and not a hydrocarbon solvent.

It is beyond the scope of this report to discuss whether exposure to *any* organic solvent can produce nephrotoxic effects in humans. Rather, this report will be confined to a discussion of whether hydrocarbon solvents produce such effects.

### 4.3.2 Animal Studies

#### *(a) General Toxicity Studies*

There are a large number of studies in which laboratory animals, primarily rats, are repeatedly exposed to hydrocarbon solvents at various levels for extended periods of time and then subjected to pathological examination. Many of these studies are represented in the same data base discussed previously in the neurotoxicity section (For a more complete listing see Cavender 1994a). In the initial reports it was concluded that no effects were seen, that is, repeated exposure to hydrocarbon solvents of various types did not produce any toxicologically-significant effects in the kidneys (or any other organ examined). There were some situations in which a mild microscopic lesion was noted in the kidneys of male rats, but not female rats. This was considered to have been a typical "old age" lesion in male rats. In subsequent studies it was found that some hydrocarbon mixtures, most notably gasoline, and other unrelated substances produce characteristic microscopic changes in male rat kidneys. This is now most commonly referred to as hyaline-droplet nephropathy but is also called light-hydrocarbon nephropathy in the older literature. A particular characteristic of this nephropathy is its relationship to $\alpha_{2\mu}$-globulin. The male rat liver produces large amounts of this protein (male rats excrete 100-300 times the amount of this protein compared to females). It is degraded slowly in the proximal tubules. Substances, or their metabolites, inducing hyaline droplet nephropathy, bind to $\alpha_{2u}$-globulin which further reduces the catabolic

rate in tubule cells. This leads to the accumulation of protein, the formation of hyaline droplets and cell death forming the appearance of the characteristic kidney lesion.

Some substances which produce hyaline droplet nephropathy have also been found to induce kidney tumours when tested in chronic studies. The US Environmental Protection Agency (EPA) has reviewed the mechanistic data associated with this tumour type and concluded that it cannot occur in man and, therefore, is not relevant for purposes of human risk assessment (US EPA, 1991).

***(b) Mechanistic Studies***

Based on the above, it is clear that general toxicology studies in laboratory animals have not revealed any renal effects of clinical importance to man. An alternative question is "can these effects be reproduced in rats?" It should be noted that several possible mechanisms have been suggested for hydrocarbon-induced kidney damage in humans. Of particular note are suggestions, originating with Bierne (1972) that the process is immunologically mediated. The question of whether gasoline exposure produces a "Goodpasture-like" syndrome† in humans has been examined in animal studies. (As stated previously, gasoline contains hydrocarbon constituents similar to those in hydrocarbon solvents but has a broader boiling range, is normally less well refined, and contains higher levels of several toxicologically more important compounds. Thus it represents a "worst-case" situation by comparison to solvents).

The first of these studies involved a subchronic inhalation exposure of rats and monkeys to wholly vapourised gasoline. Animals were exposed 6 h/d 5 d/w for 90 d to either 384 or 1552 ppm. The pathological examination after sacrifice involved an assessment of IgG in the renal glomerulus. There was no evidence of the accumulation of this material in the lungs or kidneys of either species (Kuna and Ulrich, 1984).

A second study also involved an examination of the immune complex in rat kidney after subchronic exposure to gasoline but used antibody techniques and may, therefore have been more sensitive. Rats were repeatedly exposed to levels of gasoline (the levels were not measured but were sufficient to produce anaesthesia). After treatment the rats were injected with anti-glomerular basement membrane (anti-GBM) antibody. No evidence of antibody binding was found. The negative immunofluorescent studies were interpreted as evidence that gasoline exposure does not cause Goodpasture's syndrome (O'Regan and Turgeon, 1986).

† Goodpasture's Syndrome: A condition marked by proliferative and usually progressive glomerulonephritis and a necrotising hemorrhagic interstitial pneumonitis. This is the consequence of antibodies evoked by antigens common to the glomerular and pulmonary basement membranes. Robbins S and Cotran R, 1979; Pathologic Basis of Disease, 2nd Ed. , p859; WB Saunders, London.

In summary it seems evident that exposure to hydrocarbon solvents does not produce a Goodpasture's syndrome in animals.

### 4.3.3 Human Data

As previously stated, it has been alleged that exposure to hydrocarbon solvents can induce kidney damage in humans. In many instances, however, the offending agents were not hydrocarbon solvents. Thus, the evidence for effects in humans is both confusing and contentious. In general the exposure levels at which such effects have been reported are poorly defined, particularly in the occupational setting, and when kidney damage has been noted, it has most often followed accidental exposure at high levels.

In recent years various studies have been performed using different approaches to address whether exposure to hydrocarbon solvents in the workplace is associated with effects on the kidneys. The two main experimental approaches have been to assess biochemical markers of kidney integrity and function in populations exposed to hydrocarbon solvents and to undertake questionnaire studies of people already suffering from kidney damage as a means of evaluating (usually in a qualitative way) their previous exposure to hydrocarbons.

The biochemical studies have, in general, produced both conflicting and controversial results. In some but not all studies, there was evidence that specific markers were elevated but with no clinical signs of renal disease. Thus these findings may be early, sub-clinical signs of kidney disease or they may not. It is not possible to draw a conclusion from the present data (Yacoob *et al*, 1992).

The questionnaire studies have suffered from limitations in study design; recall bias being a particular problem with studies of this type. However, to the extent that conclusions can be drawn, it seems that more often than not, patients suffering from renal disease are more likely to have been exposed to hydrocarbon solvents than the control groups (Yacoob *et al*, 1992).

In summary, therefore, there are now a group of studies available using different approaches that would seem to indicate that chronic (e.g. in the workplace) exposure to hydrocarbon solvents or "solvents" (including oxygenated and halogenated solvents) may induce damage to the kidney in humans. However, even if the data that do exist are taken to be meaningful, it would not be possible, using the current information to identify those substances particularly likely to be active in this respect, or to identify dose-response relationships for such effects.

## 4.4 TOXICITY OF SPECIFIC HYDROCARBONS

There are several specific hydrocarbon substances including n-hexane, toluene and xylenes which are described in more detail below. As noted above n-hexane is toxicologically distinct from other hydrocarbons and represents a special case. Toluene and xylenes are well-studied substances which are often considered to be uniquely toxic; however, if the data are critically evaluated, there is little evidence that these substances produce unusual effects, at least under normal conditions of occupational exposure. The remainder of the data base is comprised of studies on both individual molecules and mixtures of molecules, most of which are commercial products. These studies provide little evidence that, other than n-hexane, any molecule which is found in hydrocarbon solvents at anything above trace levels has toxicological properties substantially different from the generalised properties previously described.

### 4.4.1 n-Hexane

n-Hexane has a low acute toxicity (although like other hydrocarbons it can cause CNS depression if inhaled at high levels). Of greater concern is that long-term exposure causes a form of peripheral neuropathy which involves loss of sensation and function in the limbs. Pathologically this condition is characterised by axonal degeneration in long and large fibre tracts in the CNS as well as the peripheral nervous system (PNS) (Spencer *et al*, 1980). It has been hypothesised that this neuropathy results from the interruption of axoplasmic flow. Several elegant experiments have demonstrated that the neuropathy is actually produced by a metabolite, 2,5-hexanedione. Chemical entities which cannot be metabolised to 2,5-hexanedione do not produce this type of effect. In this regard it should be noted that no other hexane isomer or any other hydrocarbon are known to form this particular metabolite, although 2,5-hexanedione is a metabolite of methyl n-butyl ketone, an oxygenated solvent. (For a general review see Spencer *et al*, 1980).

Exposure to n-hexane has been associated with peripheral neuropathy in humans, but generally under conditions involving either prolonged exposure at high levels or solvent abuse. With respect to industrial situations, peripheral neuropathy has been described in shoe factories in Italy, China and Japan. These particular situations involved exposure to daily levels which were extremely high with respect to current industrial practice. In addition, these workers often remained in the shops for the entire working week. Thus they may have been at greater risk due to the fact that they were not given recovery periods between exposures. In parallel, it is only possible to reproduce the hexane neuropathy in rats by exposing them continuously (i.e. nearly 24 hours/day) to high levels (e.g. 500 ppm) for long periods of time (e.g. 6 months) (Egan *et al*, 1980).

There are also reports of n-hexane-induced neuropathy in "glue-sniffers', although that situation involved mixed exposures, and the effects of n-hexane by itself may have been exacerbated by the presence of other constituents (Altenkirch *et al*, 1977). As noted previously, the conclusions and recommendations of this report pertain to responsible industrial practice rather than extreme situations or solvent abuse. Thus the experience with abuse (glue sniffers) is not considered directly relevant to the present report.

Clinically-important neurological effects have only been observed following continuous exposure at relatively-high levels. Taking note of these observations the ACGIH in the US has recommended an 8-hour Threshold Limit Value (TLV) of 50 ppm (176 mg/kg) for n-hexane. The basis for this is that clinically-important effects are not produced as long as exposure is maintained below this level (ACGIH, 1996).

It is clear that n-hexane is a special case. The effect produced, peripheral neuropathy, is toxicologically distinct from the effects produced by other hydrocarbons. Therefore, by definition, this effect cannot be considered on an additive basis with other hydrocarbons (although the CNS-depressive effects probably do follow additive behaviour). However, as there are no known hydrocarbons which potentiate the effects of n-hexane, the proposed methodology can still be extended to include products containing n-hexane. As long as the level selected for n-hexane is protective in itself, that level can be used in a RCP to determine appropriate exposure levels for hydrocarbon mixtures containing n-hexane. This is true when the vapour concentrations and liquid composition are similar. This similarity needs to be verified.

### 4.4.2 Toluene/Xylenes

These low molecular weight aromatic molecules are commonly assumed to be uniquely toxic, but a critical reading of the literature provides little evidence to support this view. In animal studies toluene and xylenes are of relatively low acute toxicity and are not mutagenic or carcinogenic. In some studies there has been evidence of developmental and/or reproductive effects, but in general these have been at or above maternally-toxic levels. There are some reports of specific organ toxicity but these are normally at extremely high exposure levels and not clearly related to the occupational situation. Toluene and xylenes do produce CNS depression at high exposure levels, but, again at least in animals, there is little evidence of clinically important effects on either the CNS or the PNS (for toluene see Rhudy *et al*, 1978; Shigeta *et al*, 1978; API, 1980; Lewis and Holdsworth, 1982; Tahti et al, 1983; Bushnell et al, 1985; Huff, 1990; Ladefoged et al, 1991; for xylenes see Carpenter et al, 1975e; Hejtmancik et al, 1985).

The human experience is similar to the animal data. These substances are irritating to the eye, nose and throat and also cause CNS depression if exposure is to sufficiently high levels. In general, various national occupational exposure limits for these substances have been set to protect against either or both of these effects. There is some evidence of more profound effects associated with long-term toluene a

buse, but there is little evidence for persistent effects following chronic exposure at current occupational exposure levels (Cherry *et al*, 1985). For the purposes of this report, it is difficult to differentiate the effects of these substances from the generalised hydrocarbon toxicity described earlier.

## 4.5 SUMMARY OF THE TOXICOLOGY INFORMATION

On the basis of available evidence it can be concluded that the hydrocarbon solvents can produce reversible acute CNS depression at high exposure levels, chemical pneumonitis if aspirated, and irritation to the skin, eyes, and respiratory tract depending on the means and levels at which they are encountered. In animals, repeated exposures even at high levels, with the exception of n-hexane, normally produce either no effects (i.e. toxic levels are higher than the maximally-attainable vapour concentrations) or relatively non-specific effects such as reduced weight gain, elevated liver weights (resulting from increased metabolic requirements) and CNS depression. There has been little evidence of persistent effects or of clinically-important pathological changes in any of the organs examined. Thus, the animal data in general suggest that hydrocarbon solvents produce only acute effects and normally only at relatively high levels of exposure. More specifically, these results provide no support for the view that repeated and prolonged exposure to hydrocarbon solvents at relatively low levels would produce clinically-important CNS or renal effects in humans.

The human evidence is less clear and more controversial. There are claims that exposure under occupational conditions has produced chronic neurological effects and renal disease. The various studies which underlie these claims are limited in a number of ways including inconsistent characterisation of the effect, inadequate study design, and often, limited exposure information. However, there is reason to believe that such effects are unlikely except under conditions of prolonged, high exposure.

## 4.6 UNDERLYING ASSUMPTIONS FOR THE JUSTIFICATION OF THE APPLICATION OF THE RCP

In principle it would seem possible to define exposure levels which would protect against the most-sensitive acute effects, i.e. CNS depression. It would also seem reasonable that occupational exposure limits based on those defined levels would also protect against chronic effects. The data base at present is not sufficient to define such levels with assurance. However, advances in experimental toxicology may have made possible more-sensitive and -relevant studies than were possible in the past. The possibility of an experimental approach is well worth exploring. In the interim, it must be recognised that the current OELs are derived from an experimental data base which is now about 20 years old.

When sufficient toxicological information is available for any substance, that information should be used to develop a product-specific OEL. However, for the substances described in this report, there is a relatively limited data base, and considerable assumptions about similarity of toxicity are necessary. A better data base would certainly be helpful, but in the absence of such information, it seems most sensible to devise a methodology for setting OELs which is as generic and pragmatic as possible. The RCP seems to be such a methodology. However, for this approach to be applied to the entire class of products herein represented, it is necessary to make two assumptions, i.e. that the toxicity of all of the substances is similar and that the adverse effects are additive.

The information summarised above suggests that, with the exception of n-hexane, the toxicities of the various molecules which constitute hydrocarbon solvents are similar. None of the molecules is highly toxic, all produce similar effects and the most prominent effect in all cases is CNS depression. Thus, with the exception of n-hexane, the first assumption is satisfied. However, since n-hexane also produces CNS depression, it can be considered similar to the other solvents. In other respects it can still be included in a RCP methodology as long as the allowable limits are set low enough to account for its particular effects.

The assumption that the toxicity of the various hydrocarbon species would be additive seems reasonable. In general, substances would be presumed to act in an additive manner unless there is contrary evidence. As originally described (Finney, 1952), chemicals are additive when the dose-response regression lines are parallel, they have similar modes of action and they act on the same organ systems. The hydrocarbons covered by this review apparently all have similar modes of action and act on the same organ system i.e. the CNS. In addition, the studies which have been conducted to assess this, directly concluded that additive behaviour is followed for acute toxicity in animals (Pozzani *et al*, 1959) and for narcotic effects in fish (Shirazi and Linder, 1991).

The question about parallelism of dose-response curves is difficult to assess; hydrocarbons have such limited toxicity that there is little dose-response information, and, in addition, work subsequent to that of Finney of showed that parallelism of dose-response curves was not required (McKee and Scala, 1994).

No toxicologically-important interactions involving solely hydrocarbon solvents have been described, although only a limited number of studies have been conducted (e.g. Dudek *et al*, 1990), and not all reports are consistent on this point (Mutti *et al*, 1982; Sokal and Korsak, 1990). Thus there is little reason to believe that the toxic behaviour would be anything other than additive. It should also be noted that a limited number of tests have assessed the principal of additivity of organic solvents with human volunteers. "Extra-additive" effects were not observed either for pharmacokinetic (Brown *et al*, 1987) or for acute CNS effects (Dick *et al*, 1984; 1988).

There have been studies of the additivity of substances in general (Jonker *et al*, 1990; 1993). The results of these studies (which did not involve hydrocarbon solvents) indicate that when combinations of chemicals were tested at less than acutely-toxic levels, the response was more likely to be less than additive than greater. Thus, additivity is not only a reasonable assumption for these specific materials, it may even be conservative. However, the effects on n-hexane may be accentuated by methyl ethyl ketone (Altenkirch *et al*, 1977; 1978); and interactions between hydrocarbons and ethanol may also occur (e.g., Pryor *et al*, 1985). Thus, the assumptions of additivity need to be tested if the model is extended to substances other than hydrocarbon solvents.

## 4.7 CONCLUSION

Inasmuch as the constituents of hydrocarbon solvents have similar structure, similar physical and chemical properties and similar toxicological properties, with the exception of n-hexane, to the extent it can be determined, they act in an additive manner. It therefore is reasonable to treat these constituents in an equivalent manner for purposes of developing occupational exposure levels. The underlying assumptions necessary for a RCP-based methodology are supported by the available toxicological information.

# 5. CONCLUSIONS

- The term hydrocarbon solvent describes a wide range of products defined by boiling range, carbon number, and types of constituents which may consist either of individual hydrocarbons or mixtures of many different hydrocarbon molecules. These substances are represented in commerce in Europe by approximately 30 CAS numbers. Additionally, hydrocarbon solvents may be blended into preparations.

- As there are not sufficient toxicological data to set OELs for all hydrocarbon solvents a generic methodology is required. In principle this generic approach should:

  - be applicable to all hydrocarbon solvents;
  - take account of all constituents;
  - ensure that the OEL for any individual constituent cannot be exceeded;
  - recognise the specific problems of n-hexane and certain aromatic constituents;
  - produce changes in OEL which are proportional to changes in composition;
  - have transparent underlying assumptions; and
  - be readily adaptable to changes in constituent OELs.

  The only identified approach which meets all these criteria uses a reciprocal calculation procedure (RCP). The guidance provided by the UK-HSE and published in UK-EH 40/96 is an example of a practical application of this approach.

- The constituents of hydrocarbon solvents generally have common toxicological properties (n-hexane being an exception) and act on the same organ systems. Thus the assumption of additivity of effect is satisfied. Additionally, hydrocarbon solvents generally span a relatively restricted carbon number range. Thus the vapour composition is usually similar to that of the liquid material. Since these assumptions are satisfied, the RCP can be used to define OELs for hydrocarbon solvents.

- In the absence of data on individual components a constitutional approach based on the RCP is recommended. This entails defining groups of hydrocarbons and assigning "group" OELs. An OEL can then be calculated using these "group" OELs in the RCP in the same way as if they were

individual hydrocarbon OELs. This approach developed by the UK-HSE (EH 40/96) ensures that all constituents of all hydrocarbon solvents are taken into account.

- The health effect which appears to be the most appropriate for developing OELs is acute CNS depression. There is a limited toxicological data base to address this effect, but data are available which provide general guidance for deriving OELs. Due to limitations in the data base the values chosen by the UK-HSE produce OELs for hydrocarbon solvents which are lower than currently recommended. This in itself seems an adequately-protective measure based on occupational experience. A further review of the concept will be useful in the light of additional data.

- There has been considerable controversy over the question of the association of chronic neurotoxic effects with long-term exposure to hydrocarbon solvents at relatively low levels. However there is growing consensus that levels which protect from acute neurobehavioural phenomena would also protect against chronic effects.

- It should be noted that a constitutional approach using the RCP is appropriate for both producers and users of hydrocarbon solvents. Occupational exposure limits for blends of other materials with hydrocarbon solvents can be derived from the recommended OELs of the respective products by the RCP provided that the assumptions listed above are satisfied. Issues related to non-additive effects (e.g. methyl ethyl ketone or n-hexane) and specific substances (e.g. benzene) are important and need to be considered but are beyond the scope of this report.

# BIBLIOGRAPHY

ACGIH, 1996. American Conference of Governmental Industrial Hygienists, 1996. Threshold Limit Values for Chemical Substances and Physical Agents and Biological Exposure Indices. ACGIH, Cincinnati, Ohio.

Altenkirch H, Mager J, Stoltenburg G, and Helmbrecht J, 1977. Toxic polyneuropathies after sniffing a glue thinner. J Neurology 214, 137-152.

Altenkirch H, Stoltenburg G and Wagner H, 1978. Experimental studies on hydrocarbon neuropathies. J Neurology 214, 137-152.

API, 1980. American Petroleum Institute, 26-Week inhalation toxicity study of toluene in the rat. API Medical Research Publication 28-31210.

Arlien-Soborg P, 1992. "White Spirit" in solvent neurotoxicity, CRC Press Inc, Boca Raton USA, 307-344.

Baker EL, 1994. A review of recent research on health effects of human occupational exposure to organic solvents. J Occup Med 86, 1079-1092.

Bierne G, 1972. Goodpature's Syndrome and exposure to solvents. J Am Med Assoc 222, 155.

Bierne G and Brennan J, 1972. Glomerulonephritis associated with hydrocarbon solvents. Arch Environ Health 25, 365-369.

Bishop EC, Popendorf W, Hanson D, and Prawnitz J, 1982, Predicting relative vapor ratios for organic solvent mixtures. Am Ind Hyg Assoc J 43, 656-661.

Bleeker ML, Bolla KL, Agnew J, Schwartz BS and Ford DP, 1991. Dose-related subclinical neurobehavioural effects of chronic exposure to low levels of organic solvents. Am J Ind Med 19, 715-728.

Blinova EA, 1990. Analysis of methodological approach to the evaluation of toxicity of complex mixtures of relatively constant composition used in industry: Review of literature. Cig Tr Prof Zabol 7, 39-42.

Brown W, Setzer J, Dick R, Phipps F and Lowrey L, 1987. Body burden profiles of single and mixed solvent exposures. J Occup Med 29, 877-883.

Bushnell PJ, Evans HL and Palmes ED, 1985. Effects of toluene inhalation on carbon dioxide production and locomotor activity in the mice. Fund Appl Toxicol 5, 971-977.

Carpenter CP, Kinkead ER, Geary DL, Sullivan LJ, and King JM, 1975a. Petroleum hydrocarbon toxicity studies. I. Methodology. Toxicol Appl Pharmacol 32, 246-262.

Carpenter CP, Kinkead ER, Geary DL, Sullivan LJ and King JM, 1975b. Petroleum hydrocarbon toxicity studies. II. Animal and human response to vapors of varnish makers' and painters' naphtha. Toxicol Appl Pharmacol 32, 268-281.

Carpenter CP, Kinkead ER, Geaty DL, Sullivan LJ and King JM, 1975c. Petroleum hydrocarbon toxicity studies. III. Animal and human response to vapors of Stoddard solvent. Toxicol Appl Pharmacol 32, 282-297.

Carpenter CP, Kinkead ER, Geary DL, Sullivan LJ and King JM, 1975d. Petroleum hydrocarbon toxicity studies. IV. Animal and human response to vapors of rubber solvent. Toxicol Appl Pharmacol 33, 526-542.

Carpenter CP, Kinkead ER, Geary DL, Sullivan LJ and King JM, 1975e. Petroleum hydrocarbon toxicity studies. V. Animal and human response to vapors of mixed xylenes. Toxicol Appl Pharmacol 33, 543-559.

Carpenter CP, Kinkead ER, Geary DL, Sullivan LJ and King JM, 1975f. Petroleum hydrocarbon toxicity studies. VI. Animal and human response to vapors of "60 solvent". Toxicol Appl Pharmacol 34, 374-394.

Carpenter CP, Kinkead ER, Geary DL, Sullivan LJ and King JM, 1975g. Petroleum hydrocarbon toxicity studies. VII. Animal and human response to vapors of "70 solvent" Toxicol Appl Pharmacol 34, 395-412.

Carpenter CP, Kinkead ER, Geary DL, Sullivan LJ and King JM, 1975h. Petroleum hydrocarbon toxicity studies. VIII. Animal and human response to vapors of "140 flash aliphatic solvent". Toxicol Appl Pharmacol 34, 413-429.

Carpenter CP, Kinkead ER, Geary DL, Myers RC, Nachreiner DJ, Sullivan LJ and King JM, 1976a. Petroleum hydrocarbon toxicity studies IX. Animal and human responses to vapors of "80 thinner." Toxicol Appl Pharmacol 36, 409-425.

Carpenter CP, Geary DL, Myers RC, Nachreiner DJ, Sullivan LJ and King JM, 1976b. Petroleum hydrocarbon toxicity studies. X. Animal and human responses to vapors of "40 thinnner". Toxicol Appl Pharmacol 36, 427-442.

Carpenter CP, Geary DL, Myers RC, Nachreiner DJ, Sullivan LJ, and King JM, 1976c. Petroleum hydrocarbon toxicity studies. XI Animal and human response to vapors of deodorized kerosine. Toxicol Appl Pharmacol 36, 443-45.

Carpenter CP, Geary DL, Myers RC, Nachreiner DJ, Sullivan LJ, and King JM, 1976d. Petroleum hydrocarbon toxicity studies. XII. Animal and human responses to vapors of "40 thinner". Toxicol Appl Pharmacol 36, 457-472.

Carpenter CP, Geary DL, Myers RC, Nachreiner DJ, Sullivan LJ, and King JM, 1976e. Petroleum hydrocarbon toxicity studies. XIII. Animal and human response to vapors of toluene concentrate. Toxicol Appl Pharmacol 36, 473-490.

Carpenter CP, Geary DL, Myers RC, Nachreiner DJ, Sullivan LJ and King JM, 1977a. Petroleum hydrocarbon toxicity studies. XIV. Animal and human response to vapors of "high aromatic solvent". Toxicol Appl Pharmacol 41, 285-249.

Carpenter CP, Geary DL, Myers RC, Nachreiner DJ, Sullivan LJ and King JM, 1977b. Petroleum hydrocarbon toxicity studies. XV. Animal response to vapors of "high naphthenic solvent". Toxicol Appl Pharmacol 41, 251-260.

Carpenter CP, Geary DL, Myers RC, Nachreiner DJ, Sullivan LJ and King JM, 1977c. Petroleum hydrocarbon toxicity studies. XVI. Animal response to vapors of "naphthenic aromatic solvent". Toxicol Appl Pharmacol 41, 261-270.

Carpenter CP, Geary DL, Myers RC, Nachreiner DJ, Sullivan LJ and King JM, 1979. Petroleum hydrocarbon toxicity studies. XVII. Animal response to n-nonane vapor. Toxicol Appl Pharmacol 44, 153-61.

Cavender F, 1994a. "Aromatics" In: Patty's Industrial Hygiene and Toxicology. Fourth Edition, Volume 2, Part B. Edited by G Clayton and F Clayton. John Wiley and Sons. New York, 1301-1442.

Cavender F, 1994b. "Alicyclic Hydrocarbons", ibid, 1267-1299.

Cavender F, 1994c. "Aliphatic Hydrocarbons", ibid, 1221-1266.

Cherry N, Hutchins H, Pace T and Waldrop HA, 1985. Neurobehavioural effects of repeated occupational exposure to toluene in paint solvents. Brit J Ind Med, 42, 291-300.

CONCAWE, 1987. Survey of exposures to gasoline vapours, Report 4/87.

CONCAWE, 1992. Gasolines. CONCAWE Product Dossier 92/103.

Dick KG, Selzer J, Wait R, Hayden M, Taylor B, Tolos B and Putz-Anderson V, 1984. Effects of acute exposure of toluene and methyl ethyl ketone on psychomotor performance. Int Arch Occup Environ Health 54, 91-109.

Dick RB, Brown W, Setzer J, Taylor B and Shukla R, 1988. Effects of short duration exposures to acetone and methyl ethyl ketone. Toxicol Lett 48, 11-49.

Douglas J, McKee R, Cagen S, Schmitt S, Beatty P, Swanson M, Schreiner C, Ullrich C, and Cockerell B, 1993. A neurotoxicity assessment of high flash aromatic naphtha. Toxicol Ind Hyg 9, 1047-1058.

Dudek B, Gralewicz K, Jakubowski M, Kostrezewski P and Sokal J, 1990. Neurobehavioral effects of experimental exposure to toluene, xylene and their mixtures. Polish J Occup Med 3:109-116.

EEC, 1990. EINECS, European Inventory of Existing Commercial Substances, Off J Eu Comm, C146, p1, 15-06-90.

ECETOC, 1996. Chronic Neurotoxicity of Solvents, Technical report No. 70, February 1996.

Egan G, Spencer H, Schaumberg H, Murray KJ, Bischoff M and Scala R, 1980. n-Hexane-"free"-hexane mixture fails to produce nervous system damage. Neurotox 1, 515-524.

EN 482. European Standard, European Committee for Standardisation.

EN 838. European Standard, European Committee for Standardisation.

Farmer T, 1992. Petroleum Review. Solvents Industry. Occupational Exposure Limits for Hydrocarbon Solvents, 38-40

Fidler A, Baker E L and Letz R E, 1987. Neurobehavioural effects of occupational exposure to organic solvents among construction painters. Br J Ind Med 44, 292-308.

Finney D, 1952. Probit Analysis, 2nd edition, Cambridge: Cambridge University Press.

Hejtmancik M, Peters A, Persing R and Eastin W, 1985. Chronic toxicity/carcinogenicity studies on mixed xylenes in F344 rats and B6C3F1 mice. Battelle, Columbus, Ohio, and National Toxicology Program, Research Triangle Park, North Carolina.

Henschler, D, 1991. The concept of occupational exposure limits. The Science of the Total Environment 101, 9-16.

Hogstedt C, 1994. Has the Scandinavian solvent syndrome controversy been solved? Scand J Work Environ Health 20, 59-64.

Hooisma J, Hanninen H, Emmen HH, and Kulig BM, 1993. Behavioral effects of exposure to organic solvents in Dutch painters. Neurotoxicol Teratol 15, 397-406.

Huff J, 1990. Toxicology and carcinogenesis studies of toluene in F344/N rats and B6C3F1 mice (inhalation studies), National Toxicology Program, USA. NTP TR 371

IARC, 1989. IARC monographs on the evaluation of carcinogenic risks to humans: Some organic solvents, resin monomers and related compounds, pigments and occupational exposures in paint manufacture and painting. Vol 47. IARC, Lyon, France.

ISO, 1993. Technical Report on toxicity testing for fire effluents, TR 9122-5.

Jonker D, Wouterson R, van Bladeren P, Til H and Feron V, 1990. 4 Week oral toxicity study of a combination of eight chemicals in rats: Comparison with the toxicity of the individual compounds. Fd Chem Toxicol 28, 623-631.

Jonker D, Jones M, van Bladeren R, Woutersen R, Til H and Feron V, 1993. Acute (24 h) toxicity of a combination of four nephrotoxicants in rats compared with the toxicity of the individual compounds. Fd Chem Toxicol 31, 45-52.

Kuna R and Ulrich C, 1984. Subchronic inhalation toxicity of two motor fuels. J Am Col Toxicol 3, 217-229.

Ladefoged O, Strange P, Moller A, Lam HR, Ostergaard G, Larsen J-J, and Arlien-Soborg P, 1991. Irreversible effects in rats of toluene (inhalation) exposure for six month. Pharmacol Toxicol 68, 384-390.

Lewis SC and Holdsworth CE, 1982. Subchronic inhalation toxicity studies of n-heptane and toluene in the rat. Toxicologist 2, 11.

McKee R and Scala R, 1994. Interactions: The effects of chemicals on each other. Toxic Substances Journal 13, 71-84.

MDHS 5. UK-HSE Methods for the Determination of Hazardous Substances: On-site validation of sampling methods. UK, Health and Safety Executive, London.

MDHS 27. UK-HSE Methods for the Determination of Hazardous Substances: Protocol for diffusive samplers. UK, Health and Safety Executive, London.

MDHS 54 . UK-HSE Methods for the Determination of Hazardous Substances: Protocol for pumped samples. UK, Health and Safety Executive, London.

MDHS 60. UK-HSE Methods for the Determination of Hazardous Substances: Mixed hydrocarbons (C3 to C10) in air. UK, Health and Safety Executive, London.

MDHS 66. UK-HSE Methods for the Determination of Hazardous Substances: Mixed hydrocarbons (C5 to C10) in air. UK, Health and Safety Executive, London.

Mutti A, Cavatorta A, Lommi G, Lotta S, and Franchini I, 1982. Neurophysiological effects of long-term exposure to hydrocarbon mixtures. Arch Toxicol Suppl 5, 120-124.

NAMAS, 1989. National Measurement Accreditation Service, National Physical Laboratory, UK.

Niessink RJM, de Vries J and Hollinger MA,1995. Textbook; Toxicology: Principles and Applications, CRC Press Inc. Boca Raton.

Ostergaard G, Lam H, Ladefoged O, and Arlien-Soborg P, 1993. Effects of six months' White Spirit inhalation exposure in adult and old rats. Pharmacol Toxicol 72, 34-39.

O'Regan S and Turgeon C, 1986. Lack of antiglomerular basement membrane antibody binding to alveolar membranes after hydrocarbon exposure in rats. J Clinical Lab Immunol 20, 147-149.

PAT. Proficiency Analytical Testing Program. National Institute of Occupational Safety and Health Columbia Parkway, Cincinnati, USA.

Pozzani U, Weil C, Carpenter C, 1959. The toxicological basis of threshold limit values: 5. The experimental inhalation of vapor mixtures by rats, with notes on the relationship between single dose inhalation and single dose oral data. Am. Ind. Hyg. Assoc. J 20, 364-369.

Pryor GT, Howd RA, Uyeno ET and Thurber AB, 1985. Interactions between toluene and alcohol. Pharmacol Biochem Behav. 23, 401- 410.

Rhudy RL, Lindberg DC, Goode JW, Sullivan DJ and Gralla EJ, 1978. Ninety-day sub-acute inhalation study with toluene in albino rats. Toxicol Appl Pharmacol 48, 284-285.

Scheffers TML, Jongeneelen FJ, Bragt PG, 1985. Developments of effect specific limit values for solvent mixtures in paints. Ann Occup Hyg 29, 191-200.

Shigeta S, Misawa T, Aikawa H and Kondo A, 1978. Effects of repeated exposure to toluene on operant behaviour in rats. Jpn J Ind Hyg 20, 380-381.

Shirazi M and Linder G, 1991. A model of additive effects of mixtures of narcotic chemicals. Arch of Env Contam Toxicol 21, 183-189.

Sokal JA, and Korsak Z, 1990. The additivity rule in the evaluation of health effects of combined exposure to solvents - Does it hold? Polish J Occup Med 3, 333-336.

Spencer P, Schaumberg H, Sabri M and Veronisi B, 1980. The enlarging view of hexacarbon neurotoxicity. CRC Crit Rev Toxicol 7, 279-165.

Spurgeon A, Gray C, Sims NJ, Calvert I, Levy LS, Harvey PG, and Harrington JM, 1992. Neurobehavioural effects of long term occupational exposure to organic solvents. Two comparable studies. Am J Ind Med 221, 325- 335.

Spurgeon AD, Glass I, Calvert M, Cunningham-Hill J and Harrington M, 1994. Investigation of dose related neurobehavioural effects in paintmakers exposed to low levels of solvents. Occupational and Environmental Medicine 51, 626-630.

Tahti H, Aaran RK and Vapaatalo H, 1983. An inhalation method for testing the toxicity of volatile compounds in small laboratory animals. A study of short-term and long-term toluene inhalation in rats. Meth Find Exp Clin Pharmacol 5, 667-671.

Technische Regeln für Gefahrstoffe (TRGS) 404, September, 1992. Ausschuss für Gefahrstoffe.

Treibig G, Claus D, Csuzda I, Druschky KF, Holler P, Kinzel W *et al*, 1988. Cross sectional epidemiological study on neurotoxicity of solvents in paints and lacquers. Int Arch Occup Environ Health 60, 233-241.

UK-HSE, 1996. EH 40/96. Occupational Exposure Limits, 1996. UK, Health and Safety Executive.

US EPA, 1991. Report of the EPA peer review workshop on alpha 2u-globulin: Association with renal toxicity and neoplasia in the male rat. US Environmental Protection Agency.

WASP, 1994. UK Workplace Analysis Scheme for Proficiency; Health and Safety Executive, London.

World Health Organization/Commission of the European Communities, 1985. Neurobehavioral methods in occupational and environmental health. Symposium Report. WHO Regional Office for Europe, Copenhagen.

Yacoob M, Bell GM, Perey DF and Fim R, 1992. Primary glomerulonephritis and hydrocarbon exposure : a case control study and literature review. Quart J Med New Ser 83, 409-418.

## APPENDIX I. THRESHOLD LIMIT VALUES FOR MIXTURES

(Text reproduced, with permission, from the ACGIH Guidance Booklet Appendix C)

When two or more hazardous substances which act upon the same organ system are present, their combined effect, rather than that of either individually, should be given primary consideration. In the absence of information to the contrary the effects of the different hazards should be considered as additive. That is, if the sum of

$$\frac{C_1}{T_2} + \frac{C_2}{T_2} + \cdots \frac{C_n}{T_n}$$

exceeds unity, then the threshold limit of the mixture should be considered as being exceeded. C1 indicates the observed atmospheric concentration and T1 the corresponding threshold limit (see Example A.1 and B.1).

Exceptions to the above rule may be made when there is a good reason to believe that the chief effects of the different harmful substances are not in fact additive, but are independent as when purely local effects on different organs of the body are produced by the various components of the mixture. In such cases, the threshold limit ordinarily is exceeded only when at least one member of the series (C1/T1 + or + C2/T2, etc.) itself has a value exceeding unity (see Example B.1).

Synergistic action or potentiation may occur with some combinations of atmospheric contaminants. Such cases at present must be determined individually. Potentiating or synergistic agents are not necessarily harmful by themselves. Potentiating effects of exposure to such agents by routes other than that of inhalation are also possible, e.g., imbibed alcohol and inhaled narcotic (trichloroethylene). Potentiation is characteristically exhibited at high concentrations, less probably at low.

When a given operation or process characteristically emits a number of harmful dusts, fumes, vapors or gases, it will frequently be only feasible to attempt to evaluate the hazard by measurement of a single substance. In such cases, the threshold limit used for this substance should be reduced by a suitable factor, the magnitude of which will depend on the number, toxicity, and relative quantity of the other contaminants ordinarily present.

Examples of processes that are typically associated with two or more harmful atmospheric contaminants are welding, automobile repair, blasting, painting, lacquering, certain foundry operations, diesel exhausts etc.

***Examples of TLVs for Mixtures***

**A. *Additive effects.*** The following formulae apply only when the components in a mixture have similar toxicologic effects; they should not be used for mixtures with widely differing reactivities, e.g., hydrogen cyanide and sulfur dioxide. In such case, the formula for **Independent Effects** should be used.

**1.** General case, where air is analyzed for each component, the TLV of mixture =

$$\frac{C_1}{T_1} + \frac{C_2}{T_2} + \frac{C_3}{T_3} + \cdots = 1$$

*Note*: it is essential that the atmosphere be analyzed both qualitatively and quantitatively for each component present in order to evaluate compliance or noncompliance with this calculated TLV.

***Example A.1:*** Air contains 400 ppm of acetone (TLV, 750 ppm), 150 ppm of sec-butyl acetate (TLV, 200ppm) and 100 ppm of methyl ethyl ketone (TLV, 200ppm).

Atmospheric concentration of mixture = 400 + 150 + 100 = 650 ppm of mixture.
The TLV calculated is:

$$\frac{400}{750} + \frac{150}{200} + \frac{100}{200} = 0.53 + 0.75 + 0.5 = 1.78$$

Threshold limit is exceeded.

**2.** Special case when the source of contaminant is a liquid mixture and the atmospheric composition is assumed to be similar to that of the original material, e.g., on a time-weighted average exposure basis, all of the liquid (solvent) mixture eventually evaporates. When the percent composition (by weight) of the liquid mixture is known, the TLVs of the constituents must be listed in $mg/m^3$. TLV of mixture =

$$\frac{1}{\frac{f_a}{TLV_a} + \frac{f_b}{TLV_b} + \frac{f_c}{TLV_c} + \cdots \frac{f_n}{TLV_n}}$$

*Note*: In order to evaluate compliance with this TLV, field sampling instruments should be calibrated, in the laboratory, for response to this specific quantitative and qualitative air-vapor mixture, and also to fractional concentrations of this mixture, e.g. 1/2 the TLV; 1/10 the TLV; 2x the TLV and 10x the TLV; etc.)

***Example A.2:*** Liquid contains (by weight)

50% heptane: TLV = 400 ppm or 1640 mg/m$^3$

1 mg/m$^3$ ≡ 0.24 ppm

30% methyl chloroform: TLV = 350 ppm or 1910 mg/m$^3$

1 mg/m$^3$ ≡ 0.18 ppm

20% perchloroethylene: TLV = 25 ppm or 170 mg/m$^3$

1 mg/m$^3$ ≡ 0.15 ppm

$$\text{TLV of mixture} = \frac{1}{\frac{0.5}{1640} + \frac{0.3}{1910} + \frac{0.2}{170}}$$

$$= \frac{1}{0.00030 + 0.00016 + 0.00118}$$

$$= \frac{1}{0.00164} = 610 \text{ mg/mg}^3$$

Of this mixture

50% or (610) (0.5) = 305 mg/m$^3$ is heptane;

30% or (610) (0.3) = 183 mg/m$^3$ is methyl chloroform

20% or (610) (0.2) = 122 mg/m$^3$ is perchloroethylene.

These values can be converted to ppm as follows:

heptane: 305 mg/m$^3$ x 0.24 = 73 ppm,

methyl chloroform: 183 mg/m$^3$ x 0.18 = 33 ppm

perchloroethylene: 122 mg/m$^3$ x 0.15 = 18 ppm.

TLV of mixture = 73 + 33 + 18 = 124 ppm or 610 mg/m$^3$.

**B.** ***Independent Effects.*** TLV for mixture =

$$\frac{C_1}{T_1} = 1 \; ; \frac{C_2}{T_2} = 1 \; ; \frac{C_3}{T_3} = 1 \quad \text{etc.}$$

***Example B.1:*** Air contains 0.05 mg/m$^3$ of lead (TLV, 0.05) and 0.7 mg/m$^3$ of sulfuric acid (TLV, 1).

$$\frac{0.05}{0.05} = 1 \; ; \qquad \frac{0.7}{1} = 0.7$$

Threshold limit is not exceeded.

**C.** ***TLV for mixtures of mineral dusts.*** For mixtures of biologically active mineral dusts the general formula for mixtures given in A.2 may be used.

# APPENDIX II. CHROMATOGRAPHIC ANALYSIS OF A STANDARD WHITE SPIRIT

A typical White Spirit chromatogram is compared with a similar analysis of a mixture of benzene, toluene and xylenes (BTX). Chromatography is a technique to separate molecules in the gas phase on the basis of their molecular weight and physico-chemical properties in a pattern of which the peaks represent the different molecular entities. The surface of a peak is directly proportional to the mass fraction of that molecule in the mixture.

All three analysis have been carried out according to a method described in CONCAWE (1987) and UK-HSE, MDHS60. Desorption from chromosorb W6 (80/100 mesh) was followed by a separation in a capillary (0.2 mm) coated with 0.25 µm OV1701. Detection was with a flame ionisation detector. Peaks appear after each other due to different retention time of the molecules in the capillary expressed in minutes.

**Figure II-1: BTX (Benzene, Toluene, Xylenes) Mixture**

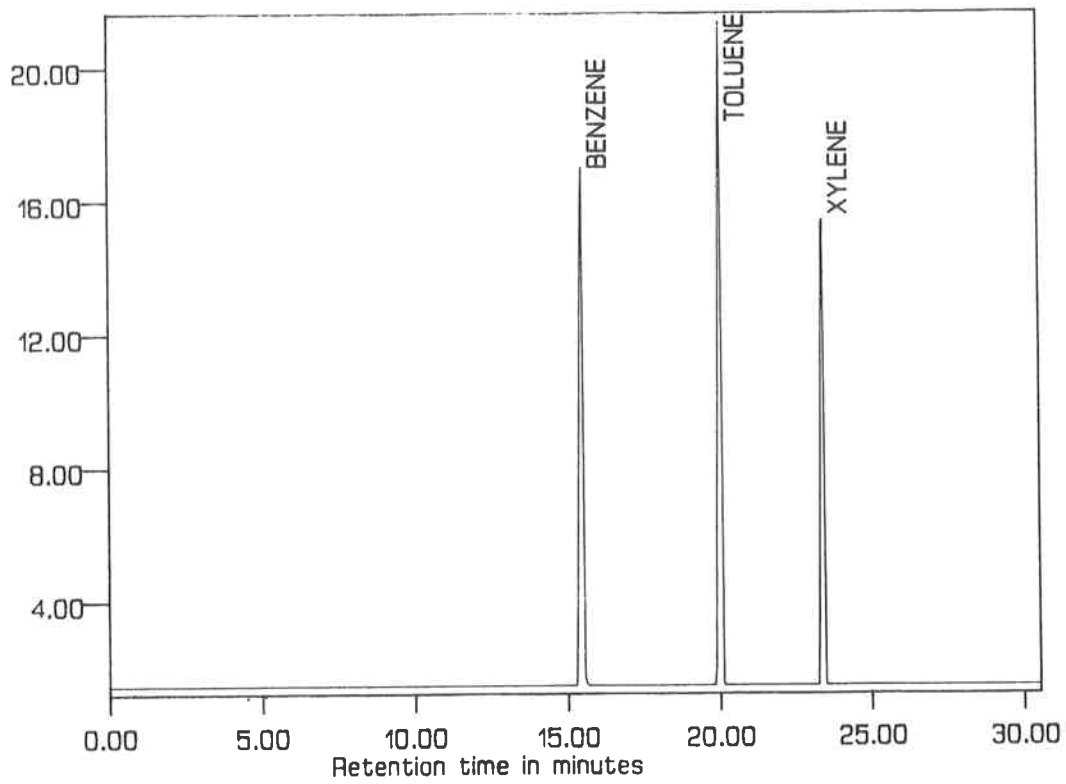


**Figure II-2: A Standard White Spirit**

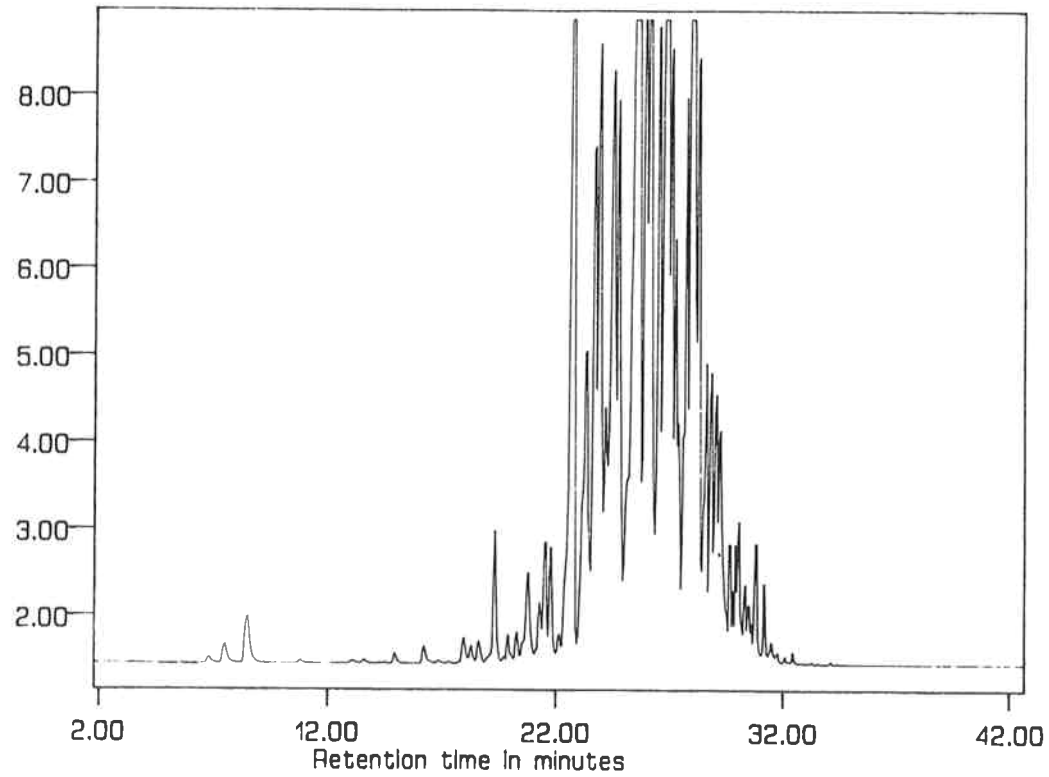
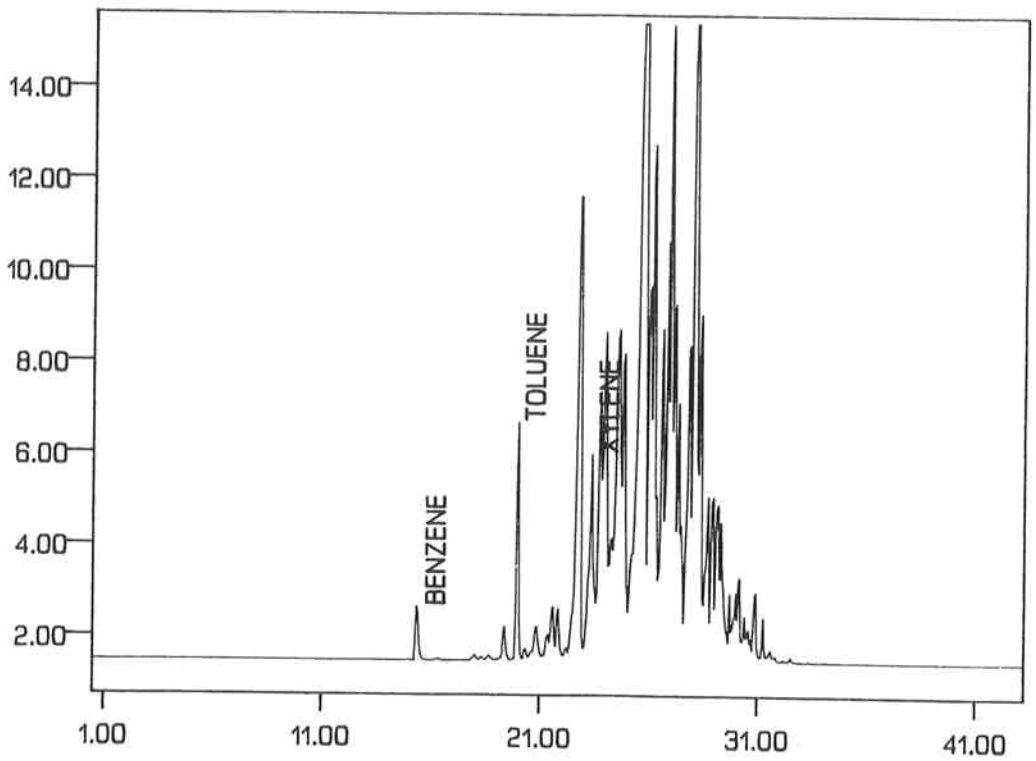



**Figure II-3: Blend of the BTX mixture and the White Spirit**



# MEMBERS OF THE TASK FORCE

| | |
|---|---|
| R. McKEE (Chairman) | EXXON CHEMICAL EUROPE<br>B - Brussels |
| P. HEXT | ZENECA<br>UK - Macclesfield |
| T.H. FARMER | Consultant<br>UK - Hatfield |
| M. MOLYNEUX | SHELL International Ltd<br>UK - London |
| J.Ph. GENNART | PETROFINA<br>B - Brussels |
| M.J. EVANS | EXXON CHEMICAL Ltd<br>UK - Southampton |
| M. BUTLER | CEFIC *<br>B - Brussels |
| W. ROZENBOOM (Secretary) | ECETOC<br>B - Brussels |

* Until 1996, ECETOC from 1996

**ACKNOWLEDGEMENT**

The Task Force acknowledges the following organisations who were consulted during the preparation of this ECETOC Special Report:

American Conference of Governmental Industrial Hygienists, USA

Institut National de recherches de Sécuritié de France (INRS), France

UK Health and Safety Executive, UK

Ausschuss für Gefahrstoffe, Germany

# MEMBERS OF THE SCIENTIFIC COMMITTEE

(Peer Review Committee)

| | |
|---|---|
| W.F. TORDOIR [1] (Chairman), Group Adviser, Environmental Health and Human Toxicology | SHELL INTERNATIONAL<br>NL - Den Haag |
| H. VERSCHUUREN (Vice-Chairman), Head, Toxicology Department | DOW EUROPE<br>CH - Horgen |
| O.C. BØCKMAN, Scientific Adviser | NORSK HYDRO<br>N - Porsgrunn |
| N.G. CARMICHAEL, Toxicology Director, Worldwide | RHÔNE-POULENC<br>F - Lyon |
| H. DE HENAU, European Technical Centre, Professional and Regulatory Services | PROCTER & GAMBLE<br>B - Brussels |
| C. d'HONDT, Head, Ecology Department, Crop Protection Division | CIBA-GEIGY<br>CH - Basel |
| A. de MORSIER, Head, Ecotoxicology | CIBA-GEIGY<br>CH - Basel |
| P.A. GILBERT, Head, Environment Division | UNILEVER<br>GB - Port Sunlight |
| B. HILDEBRAND, Director, Experimental Toxicology | BASF<br>D - Ludwigshafen |
| J. JACKSON[1], Director, Medecine and Health Science | MONSANTO EUROPE<br>B - Brussels |
| E. LÖSER, Head, Institute of Industrial Toxicology | BAYER<br>D - Wuppertal |
| R. MILLISCHER, Head, Industrial Toxicology Department | ELF ATOCHEM<br>F - Paris |
| G. RANDALL, Director, Brixham Environmental Laboratory | ZENECA<br>GB - Brixham |
| A. SARRIF, Associate Director, Toxicological Affairs - Europe | DUPONT de NEMOURS<br>D-Bad Homburg |
| H-J. WIEGAND Head, Product Safety Department | HÜLS AG<br>D- Marl |

[1] **Stewards responsible for primary review.**