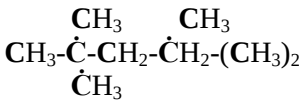
SIDS INITIAL ASSESSMENT PROFILE

Chemical Category	**C_9-C_{14} Aliphatic [≤2% aromatic] Hydrocarbon Solvents Category**
Chemical Names and CAS Registry Numbers	**Substance Name** — **CAS Number** Nonane — 111-84-2 n-Decane — 124-18-5 n-Undecane — 1120-21-4 Dodecane — 112-40-3 Tridecane — 629-50-5 Alkanes, C10-14 — 93924-07-3 Alkanes, C9-11-iso- — 68551-16-6 Alkanes, C9-12-iso- — 90622-57-4 Alkanes, C10-13-iso- — 68551-17-7 Alkanes, C12-14 — 129813-67-8 Alkanes C12-14 -iso — 68551-19-9 Alkanes, C11-15-iso- — 90622-58-5 Paraffins, petroleum, normal C5-20 — 64771-72-8 Naphtha (petroleum), hydrotreated heavy — 64742-48-9 Solvent naphtha, petroleum, medium aliph. — 64742-88-7 Naphtha, petroleum, heavy alkylate — 64741-65-7 Distillates, petroleum, hydrotreated light — 64742-47-8
Structural Formula and CAS Registry Numbers	**Structural Formula** — **CAS Number** ***n-Paraffins Subcategory*** CH_3-$(CH_2)_7$-CH_3 (linear molecule) — 111-84-2 CH_3-$(CH_2)_8$-CH_3 (linear molecule) — 124-18-5 CH_3-$(CH_2)_9$-CH_3 (linear molecule) — 1120-21-4 CH_3-$(CH_2)_{10}$-CH_3 (linear molecule) — 112-40-3 **C**H_3- (**C**H_2)$_8$-**C**H_3 to CH_3- $(CH_2)_{12}$-CH_3 — 64771-72-8 CH_3-$(CH_2)_{11}$-CH_3 (linear molecule) — 629-50-5 Various isomers of primarily C_{12}, C_{13}, and C_{14} alkyl-normal hydrocarbons — 129813-67-8[†] Various isomers of primarily C_{10}, C_{11}, C_{12}, C_{13}, and C_{14} alkyl-normal hydrocarbons — 93924-07-3[†]

Iso-Paraffins Subcategory



Various isomers of primarily C_{10}, C_{11}, C_{12}, and C_{13} alkyl-branched hydrocarbons	68551-16-6†
Various isomers of primarily C_9, C_{10}, C_{11}, and C_{12} alkyl-branched hydrocarbons	90622-57-4†
Various isomers of primarily C_{10}, C_{11}, C_{12}, and C_{13} alkyl-branched hydrocarbons	68551-17-7†
Various isomers of primarily C_{12}, C_{13}, and C_{14} alkyl-branched hydrocarbons	68551-19-9†
Various isomers of primarily C_{12}, C_{13}, C_{14}, and C_{15} alkyl-branched hydrocarbons	90622-58-5†

Multi-constituent Subcategory

UVCB substances containing aliphatic (linear, branched, and/or cyclic paraffins) molecules of carbon and hydrogen, predominantly in the C_9 to C_{14} range	64742-48-9† 64742-88-7† 64741-65-7† 64742-47-8†

Description of Substances in Category

Individual category member substances are comprised of aliphatic hydrocarbon molecules with carbon numbers between C_9 and C_{14}; approximately 80% of the aliphatic constituents for a given substance fall within the C_9-C_{14} carbon range and <100 ppmV benzene. The distinguishing characteristics of this category are the limitation on carbon range (C9-C14) and the limitation of aromatic constituents to < 2% (although as shown in table 1, in most cases the levels of aromatics are well below 2%) of the total hydrocarbons present.

In some instances, the carbon range of a test substance is provided in the test protocol or report. In these instances, the specific carbon range (e.g. C8-C10, C9-C10, etc.) will be given in the SIAP.

* It should be noted that other substances defined by the same CAS RNs may have boiling ranges outside the range of 142.9 – 253.5 ° C and that these substances are not covered by the category.

†Denotes a UVCB substance. UVCBs are defined as chemical substances of unknown or variable composition, complex reaction products or biological materials.

The category has been defined for members with specific constituents/component profiles or composition as outlined in the full SIDS Initial Assessment Report and the SIDS Dossiers.

The substances in the C_9-C_{14} Aliphatic [≤ 2% aromatic] Hydrocarbon Solvents Category contain >98% hydrocarbons. Several category members are described as UVCBs (Unknown or Variable Composition, Complex Reaction Products and Biological Materials) because they are composed of a defined, progressive carbon number range that includes various types of hydrocarbons: aliphatic molecules (linear, branched, and cyclic) and less than 2% aromatic molecules (generally one-ring alkylbenzenes), predominantly in the C_9 to C_{14} range. The benzene and sulphur contents of substances in this category are low; benzene levels for example are typically <3 ppm.

Some of the category members are complex hydrocarbon substances described by CAS RNs which can also be used to describe petroleum process streams and other complex substances. Thus, there are substances which are described by the same CAS numbers used by category members which are not included in the category because they do not meet the category definition (C_9-C_{14} aliphatic hydrocarbons, ≤2% aromatics).

The present assessment only applies to substances with the constituent profiles and compositions described within this assessment, i.e., C_9-C_{14} aliphatic hydrocarbons < 2% aromatics. As noted above, the conclusions of this assessment do not necessarily apply to petroleum process streams with the same CAS number as those belonging to the C_9-C_{14} Aliphatic [≤ 2% aromatic] Hydrocarbon Solvents Category or to other substances that do not meet the category definition because they have different carbon number ranges and/or higher levels of aromatics. In particular it should be noted that production of hydrocarbon solvents is differentiated from other refinery substances with similar boiling ranges such as gasoline and diesel fuel by additional processing steps leading to finished hydrocarbon solvents with relatively narrow distillation ranges, defined aromatic content, and low color (indicative of relatively low levels of benzene, other aromatics and sulfur-containing compounds).

Table 1 - Typical compositional data for representative commercial C_9-C_{14} aliphatic [≤ 2% aromatic] hydrocarbon solvents

CAS No.	Carbon Number *	Aliphatics* (%)			Aromatics*	Ethyl-benzene*	Naphthalene*	Benzene*
	(range)	% total	% n-, iso-	% cyclo	% total	%	%	ppmv
111-84-2	9	100	100	-	<0.01	0	0	0
124-18-5	10	100	100	-	<0.01	nd	nd	0
1120-21-4	11	100	100	-	<0.01	0	0	0
112-40-3	12	100	100	-	<0.01	0	0	0
629-50-5	13	100	100	-	<0.01	0	0	0
68551-16-6	9-11	100	100	-	0.007	0	0	0
90622-57-4	9-12	100	96-100	0-4	<0.01	na	na	<1

68551-17-7	10-13	100	100	-	0.007	0	0	0
93924-07-3	10-14	>99.98	>99.98	-	<0.02	na	na	-
129813-67-8	12-14	99.4	97.8	1.6	0.6	na	na	-
68551-19-9	12-14	99.9	99.9	-	<0.1	na	na	na
90622-58-5	11-15	100	88-100	0-12	<1	na	na	<1
64742-48-9	9-13	>99	43-97	3-57	<1	<1ppm	<1ppm	<1
64742-88-7	9-13	>98	46-52	47-54	<1.5	na	na	na
64741-65-7	9-14	99.9	37-62.9	37-62.9	<0.1	na	na	<1
64742-47-8	8-15	>99	30-60	40-70	<1	na	na	na
64771-72-8	10-14	100	100	-	<0.1	<10ppm	<10ppm	<1

* The values in this table were provided by manufacturers from analyses of commercial products and are examples, not specifications.
< Less than detection limit (detection limit reported)
nd not detected
na not available

Table 2 - Typical Carbon Number Range for the Aliphatic Molecules in the C_9-C_{14} aliphatic [≤2% aromatic] hydrocarbon solvents category

Identification of chemicals defined by processing procedures	**Typical Carbon Number Range for the Aliphatic Molecules (%) of substances in the C_9-C_{14} aliphatic (≤2% aromatic) category**									
	< C8	**C8**	**C9**	**C10**	**C11**	**C12**	**C13**	**C14**	**C15 to C16**	**Total Aromatics**
Nonane 111-84-2			100							
Decane 124-18-5				>99.9						<0.01

Undecane 1120-21-4					>99.9					<0.01
Dodecane 112-40-3						>99.9				<0.01
Tridecane 629-50-5							>99.9			<0.01
Alkanes, C10-14 93924-07-3			~3	~16	~20	~23	~18	~12	~6	<2.0
Alkanes, C9-11-iso- 68551-16-6		~1	~31	~35	~31	~3	~1			<0.05
Alkanes, C9-12-iso- 90622-57-4			~2.5	~23	~36	~20	~18	~0.5		<0.05
Alkanes, C10-13-iso- 68551-17-7			~2	~11	~34	~37	~10	~5	~1	<0.05
Alkanes, C12-14 129813-67-8				~3	~23	~34	~24	~11	~3	<2.0
Alkanes C12-14 –iso 68551-19-9					~14	~38	~31	~17		<0.05
Alkanes, C11-15-iso- 90622-58-5					~21.5	~27.5	~20.5	~17.5	~13	<0.05
Paraffins, petroleum, normal C5-20 64771-72-8	~2	~5	~11	~15	~18	~19	~13	~9	~6	<2.0
Naphtha (petroleum), hydrotreated heavy 64742-48-9		~1.1	~5	~13	~32	~33	~13	~2.2		<0.7
Solvent naphtha, petroleum, medium aliphatic 64742-88-7		~1.5	~18	~27	~35	~10	~6.5			<2.0
Naphtha, petroleum, heavy alkylate 64741-65-7				~0.5	~13	~23	~30	~19	~14	<0.5
Distillates, petroleum, hydrotreated light 64742-47-8		~3	~26	~36	~31	~2				<2.0

SUMMARY CONCLUSIONS OF THE SIAR

Category Definition

The C_9-C_{14} Aliphatic [≤ 2% Aromatic] Hydrocarbon Solvents Category is comprised of complex aliphatic hydrocarbon solvents that contain >98% aliphatic constituents with carbon numbers in the range of C_9-C_{14} and less than 2% aromatic constituents. These hydrocarbon solvents which are defined by boiling range and/or flash point have carbon numbers within the range of C_9 to C_{14} (approximately 80%). The chemical constituents in these complex UVCB substances may include straight chain (n-), branched (iso-) and cyclic aliphatic hydrocarbons but must have less than 2% aromatic hydrocarbons (generally one-ring aromatics). These products may be sold under a variety of brand, commercial and trade names and they may be associated with one or more of the Chemical Abstract Services (CAS) Registry Numbers (RN) for this category. It should be noted that the CAS registry numbers assigned to these substances are generic and can also be used to describe substances that do not meet the category description and are not included in this assessment.

Assignment of CAS RNs for complex hydrocarbon products is generally based on a hierarchy of considerations including hydrocarbon type(s), carbon number range, distillation range, and last processing step. One documented source of criteria for assignment of CAS RNs for complex hydrocarbons is provided by the U.S. EPA on proceedings for development of the TSCA inventory for U.S. chemicals. Because these CAS RN are broadly defined to encompass UVCBs, they can be applied to both hydrocarbon solvents and other petroleum-derived substances with somewhat different composition and applications (e.g., solvents, fuels, lubricants, etc.). However, because hydrocarbon solvents are manufactured to meet specific industrial needs, they tend to be more compositionally defined than other petroleum-derived materials with more narrow boiling ranges and, often, lower levels of benzene as well as sulfur- and nitrogen-containing constituents.

Category Justification

For substances in the C_9-C_{14} Aliphatic [≤ 2% Aromatics] Hydrocarbon Solvents Category, the CAS RNs listed here are all applied to compositionally similar and generally commercially interchangeable hydrocarbon solvents. This similarity of composition is the primary justification for evaluating these substances in a category. Further, the existing toxicology and environmental effects data shows that substances in this category have a similar order of toxicity which further supports the grouping of these substances as a category.

The underlying hypothesis that justifies this category is that aliphatic hydrocarbons of similar carbon number range have similar properties. As above, the substances in this category are comprised of aliphatic constituents (normal paraffins, iso-paraffins and cycloparaffins) with carbon numbers ranging from C9-C14. One distinguishing characteristic of this category is that the substances have very low levels of aromatic constituents.

There are a number of unifying considerations which together justify the inclusion of substances within the C9-C14 Aliphatic [< 2% aromatics] Hydrocarbon Solvents Category. These include:

1. Similarity of Composition – Constituents of solvents in this category can include n-alkanes, iso-alkanes, or cycloalkanes or combinations thereof with carbon numbers ranging from approximately C9-C14. However, the aromatic content of these solvents does not exceed 2%.

2. Similarity of Functional Groups – The substances in this class are comprised almost entirely of aliphatic constituents. The only functional groups are alkyl side chains, which are found on most if not all constituents other than the n-alkanes.

3. Similarity of Physical / Chemical Properties – All category members have a boiling point range from 142.9 to 253.5°C, vapour pressure values in a range from 0.007 to 8.28 hPa, water solubility values range from 0.009 to 6.45 mg/L, measured log Pow values for category member constituents range from 5.0 – 7.2 (at 25°C).

4. Similarity of Metabolism – Hydrocarbon molecules in this range are absorbed from the intestinal tract but very poorly absorbed through the skin. However, once absorbed, these molecules are relatively rapidly metabolized and excreted.

5. Similarity of Mammalian Toxicity – The constituents of this class have similar toxicological properties. They are not acutely toxic, not irritating to the eyes and not sensitizing. They have differing skin irritant properties but all can produce severe irritant dermatitis due to defatting. They do not produce systemic effects (other than male rat-specific kidney changes) in repeated dose studies. They are not mutagenic. They do not produce developmental toxicity, and there is no evidence that they are toxic to the reproductive system.

6. Similarity of Environmental Toxicity – The substances in this category have similar environmental effects properties. The environmental effects data are similar for most category members in that most members do not exhibit acute aquatic toxicity due to their low water solubility. However some members do exhibit acute and chronic aquatic toxicity. Category members and their constituents are neutral organic hydrocarbons whose toxic mode of action is nonpolar narcosis. The mechanism of short-term toxicity for these chemicals is disruption of biological membrane function, and the differences between their toxicities can be explained by the differences in target tissue-partitioning behaviors of the individual hydrocarbons.

7. Similarity in Health Effects and Mechanism of Toxic Action – There are two general potential health effects associated with substances in this category, acute central nervous system (CNS) depression and, if taken into the lung in a liquid state (i.e. aspiration), chemical pneumonitis. Both of these are common effects shared by all hydrocarbon solvents. It should be noted, however, that the vapor pressures of hydrocarbons with more than 9 carbons are so low that acute effects on the central nervous system are not produced even at saturated vapor concentrations.

8. Similarity of Production Methods – Hydrocarbon solvents in this category can be produced in several ways, but in each case the manufacturing process leads to aliphatic solvents within a relatively narrow range of carbon numbers and with an overall low (<2%) aromatic hydrocarbon content.

9. Similarity of Use – Substances in this category are liquids at room temperature and are produced for use as solvents. The technical properties for which these solvents are intended require that the constituents have well defined rates of evaporation which is related to the carbon number distribution, to limit the aromatic content, and to also have very low levels of sulphur- and nitrogen-containing constituents.

Category Member Conventional Naming

The naming convention used to identify category members is based on their general compositions (predominant carbon number range and hydrocarbon type, specifically aromatics) and is intended to identify hydrocarbon solvent substances manufactured by various companies that are sufficiently similar with regard to composition such that their physical and biological properties would exhibit similar properties. The naming convention as applied to hydrocarbon solvents was seen as a means to provide more precise information on the type of solvent and its composition than is obtained from the CAS description and allows for an accurate grouping of hydrocarbon substances within categories. As UVCBs, some of the hydrocarbon solvent category members share CAS RNs with some petroleum process streams which have broader boiling ranges and consequently are compositionally more complex.

Category members (CAS RN 64771-72-8, 129813-67-8, 68551-16-6, 90622-57-4, 68551-17-7, 93924-07-3, 68551-19-9, 90622-58-5, 64742-48-9, 64742-88-7, 64741-65-7, and 64742-47-8) meet the criteria for UVCB substances because they contain a relatively large number of discrete chemical constituents and the identities of all of the constituent chemicals may be unknown. The general naming convention guidance was developed and used for category members as follows:

"Hydrocarbons", the first part of the name, recognizes the specific chemical class.

The carbon number range typically identifies at least 80% of the chemical constituents in the substance.

The structures are identified by the types of hydrocarbons present: n-paraffins (n-alkanes), iso-paraffins (isoalkanes), cyclic-paraffins or naphthenic (cyclics), and aromatics. The first three structural types of hydrocarbons are mentioned when present in the substance at a level between approximately 10 and 80%. Levels of total Aromatics are below 2% for all category members.

Read-Across Substance Identification

In addition to the available physical and biological data for substances in the C_9-C_{14} Aliphatic [$\leq$ 2% aromatic] Hydrocarbon Solvents category, data for the following analogues are also presented, as necessary, to support the characterization of selected endpoints:

JP-8, a commercial jet fuel (having a carbon number range of 8-16 and ~25% aromatics, but not described by CAS RN)
Hydrodesulfurized kerosene (CAS RN 64742-81-0, having a carbon number range of C_9-C_{16} and ~ 20% aromatics)
CAS RN 8052-41-3; Stoddard Solvent; White Spirit (C_9-C_{14}, ~25% aromatics)
CAS RN 90622-58-5; Hydrocarbons, C_{11}-C_{13}, isoalkanes, <2% aromatics
CAS RN 64742-47-8; Hydrocarbons, C_{13}-C_{16}, n-alkanes, isoalkanes, cyclics,<2% aromatics
CAS RN 109-66-0; n-Pentane
CAS RN 629-59-4; n-Tetradecane

Tetramethylcyclohexane, mixed isomers (no CAS number available)

Jet fuel (JP-8), a U.S. military fuel, is a complex hydrocarbon substance (UVCB) with a carbon number range of C_8-C_{16}, a boiling range of approximately 150 – 290°C, an aromatic content of approximately 25% and approximates the physical/chemical properties of the C_9-C_{14} Aliphatic [≤ 2% aromatic] Hydrocarbon Solvents. Since JP-8 contains substantially higher levels of aromatic constituents than the C_9-C_{14} Aliphatic [≤ 2% aromatic] Hydrocarbon Solvents, test results from JP-8 could be considered as "worst-case" when used as read-across to the C_9-C_{14} Aliphatic [≤ 2% aromatic] Hydrocarbon Solvents. The same logic applies to hydrodesulfurized kerosene (CAS RN 64742-81-0) and Stoddard solvent (CAS RN 8052-41-3) which contain approximately 80% aliphatic constituents with carbon numbers that overlap those found in the C9-C14 aliphatic, ≤2% aromatics category but differ in that these other analogue substances contain aromatic (primarily alkylated single ring aromatics) at levels ranging from approximately 15-25%.

Table 3 (SIAR Table 4) – Data for the following analogues for the C9-C14 aliphatic (≤2% aromatics) category are provided to support the characterization of relevant endpoints.

Analogue (CAS RN)	**Composition**	**Endpoint(s) Characterized**
Commercial product not described by a CAS RN	JP-8 (a commercial fuel containing approximatley 80% C_8-C_{16} aliphatic constituents and 20% aromatics , most of which are alkylated benzenes).	Dermal Absorption Reproductive Toxicity
8052-41-3	Stoddard Solvent; White Spirit – A commercial hydrocarbon solvent which contains 15-20% aromatic constituents, primarily alkylated benzene, with the remainder being aliphatic constituents with carbon numbers predominantly in the range of C_9-C_{11}.	Toxicokinetics
64742-81-0	Hydrodesulfurised kerosene, a hydrocarbon fuel consisting of hydrocarbons in the range of C_9-C_{16} and a boiling range of approximately 150-290°C. Hydrodesulfurised kerosene contains approximately 80% aliphatic constituents (C_{10}-C_{16}) and 20% aromatics (mostly alkylated single ring compounds). The manufacturing process includes a hydrogenation step with removes sulfur and nitrogen.	Developmental Toxicity Reproductive Toxicity
A CAS RN for the mixed isomers is not available	Mixed Tetramethylcyclohexane (C_{10} cycloparaffins) isomers	Acute Toxicity Repeated Dose Toxicity
90622-58-5	Hydrocarbons, C_{11}-C_{13}, isoalkanes, <2% aromatics	Biodegradation Chronic Aquatic Toxicity
64742-47-8	Hydrocarbons, C_{13}-C_{16}, n-alkanes, isoalkanes, cyclics,<2% aromatics	Biodegradation Chronic Aquatic Toxicity
109-66-0	n-Pentane	Biodegradation
629-59-4	n-Tetradecane	Biodegradation Acute Aquatic Toxicity

Substances in the C_9-C_{14} Aliphatic [≤2% Aromatic] Hydrocarbon Solvents Category are composed of paraffinic hydrocarbons that fall within a carbon number (C) range of 9 to 14 but with the levels of aromatic constituents limited to 2%. As a result, many of the category member physicochemical properties are characterized by a range of values as a function of composition because a single value is not possible. For example, complex hydrocarbon solvents do not have single P_{ow} values, but rather a range of values based on the properties of the constituents. This would be the case regardless of whether the data were measured using a standard testing procedure or calculated based on the individual constituent chemicals.

For several of the physical-chemical properties, the value range is based on a series of representative hydrocarbons that were selected by industry, based on hydrocarbon process (distillation) knowledge, to accurately characterize category members. The hydrocarbons selected to characterize the C_9-C_{14} aliphatic (≤2% aromatic) category include paraffins (normal, iso-, cyclic) from C_9 to C_{14}.

Table 4: List of Representative Hydrocarbon Constituents used to characterize the physical/chemical and environmental properties of C9-C19 aliphatic [≤ 2% aromatics] category

Chemical Name	CAS RN
n-nonane	111-84-2
2-methyloctane	3221-61-2
1,2,4-trimethylcyclohexane	2234-75-5
n-decane	124-18-5
1,2,4,5-tetramethylcyclohexane	2090-38-2
decahydronaphthalene	91-17-8
n-undecane	1120-21-4
2,5-dimethyl-nonane	17302-27-1
n-dodecane	112-40-3
n-tridecane	629-50-5
2,3-dimethyl-undecane	17312-77-5
1,3,4,5-tetramethylnonane	n/a
n-tetradecane	629-59-4
2,6,10-trimethylundecane	6864-53-5
2,3,6,7-tetramethyldecalin	n/a

n/a = not available

Physicochemical Properties

The members of the C_9-C_{14} Aliphatic [≤2% Aromatic] Hydrocarbon Solvents Category are liquids at room temperature. The measured melting point values for constituents range from <-83.5 to 5.8°C. The boiling points range from approximately 142.9 to 253.5°C. The measured vapour pressure values for constituents range from 0.007 to 8.28 hPa at 20° to 25°C and cover the full carbon range (C_9 to C_{14}) . The calculated water solubility values range from 0.009 to 6.45 mg/L (at 25°C) for constituents, with a relative density range of 0.718 to 0.815 g/cm^3 (at 20° C). The measured log Pow values for category member constituents range from 5.0 – 7.2 (at 25°C). Based on estimated values, the log Pow may range from 4.0 to >7.0.

Human Health

Category members represent a wide variety of structures. Unless otherwise indicated all structural constituents (linear, branched and cyclic) of the category members have been tested for all of the individual endpoints.

Toxicokinetics, Metabolism, and Distribution

Much of the toxicokinetics data comes from studies of substances in another category, C_9-C_{14} Aliphatic [2-25% Aromatic] Hydrocarbon Solvents and from studies of jet fuel (JP-8) constituents. However, for purposes of this document, the data on the aliphatic constituents of these other substances is directly relevant as there are similarities between the aliphatic constituents in the C_9-C_{14} Aliphatic [≤ 2% Aromatic] Hydrocarbon Solvents Category and the C_9-C_{14} Aliphatic [2-25% Aromatic] Hydrocarbon Solvents Category. Because these solvents are complex, the toxicokinetic studies are usually based on marker compounds such as decane. The toxicokinetic behavior of aromatic constituents can be ignored for purposes of this evaluation because (as shown in table 1), aromatic constituents are only present at low levels. Nevertheless, information on the aromatic constituents can be found in the summarized information for the C_9-C_{14} aliphatic [2-25%] category document if it is of interest. It should also be noted that the aromatic constituents induce their own metabolism, so the rate of metabolism and excretion of both aliphatic and aromatic constituents can be enhanced in studies involving extended periods of high exposure to solvents containing aromatics; however, as the levels of aromatics are limited to a maximum of 2% for substances in this category, the contributions of aromatics to metabolic rates would probably be negligible.

Absorption

Inhalation - When inhaled, white spirit constituents were readily absorbed. The absorption of inhaled substances in this category depends on several factors including concentration in the inspired air, blood partition coefficient, pulmonary ventilation, and pulmonary flow. Generally speaking, however, studies have shown by the inhalation route that materials in this category are readily absorbed through the lungs. After a 30-minute exposure at rest to approximately

1040 mg/m3 of the aliphatic components, the concentration in alveolar air was 255 mg/m3 (25 % of the concentration in the inspiratory air). The corresponding arterial blood concentration was 1.7 mg/kg. When alveolar ventilation tripled (50 W exercise), the alveolar concentration increased to 515 mg/ m3 (50 % of the concentration in inspiratory air), whereas the arterial concentration rose to 3.5 mg/kg. When alveolar ventilation was raised to 60 L/min (150 W exercise), the alveolar concentration rose to about 60 % of the concentration in inspiratory air. Thirty minutes following exposure, alveolar concentration was ~180 mg/m3 and arterial concentration was near 0 mg/kg.

Oral - It is estimated that 61% - 81% of a C_9-C_{14} hydrocarbon solvent would be absorbed when ingested. C_9-C_{14} aliphatic, $\leq$ 2% aromatic hydrocarbon solvents are metabolized by side chain oxidation to alcohol and carboxylic acid derivatives. These metabolites can be glucuronidated and excreted in the urine or further metabolized before being excreted. The majority of the metabolites are expected to be excreted in the urine and to a lower extent, in the feces. Any unabsorbed material would be excreted in the feces. Most of the excretion is expected to occur within the first 24 hours of exposure.

Dermal Absorption

There have not been any in vivo dermal absorption studies of C9-C14 aliphatic, < 2% aromatic hydrocarbon solvents, but there have been in percutaneous absorption studies of jet fuel, a C9-C16 aliphatic hydrocarbon substance with approximately 20% aromatics. Both *in vivo* and *in vitro* studies to assess the percutaneous absorption of aliphatic and aromatic jet fuel constituents have been conducted. Dermal flux values (ug/cm2/hr) for C9-C14 aliphatic constituents ranged from less than 1.0 to 2.5 ug/cm2/hr. Based on the data from a human volunteer study, percutaneous absorption of C9-C14 aliphatic constituents would be in the range of 0.01%/hr to 0.1%/hr and that of aromatic constituents (which constitute <2% of the total hydrocarbon constituents) would be approximately 0.2%/hr.

Distribution

Studies in rats have shown that following absorption, members of the C_9-C_{14} Aliphatic [2-25% Aromatic] Hydrocarbon Solvents Category are widely distributed throughout the body of both humans and animals and preferentially accumulate in the adipose tissues due to the lipophilic nature of the solvents.

A toxicokinetic study on the distributions of C_9 to C_{10} alkanes, aromatics and cycloalkanes in blood, brain, liver, kidney and perirenal fat demonstrated that aromatics generally showed higher blood concentrations than alkanes and cycloalkanes. C_9 cycloalkanes showed higher brain concentrations than the corresponding aromatics and alkanes, while brain concentrations of C_{10} alkanes were slightly greater than C_{10} cycloalkane concentrations, which in turn were greater than C_{10} aromatic concentrations. Fat contained the highest concentrations of each of the hydrocarbons examined; concentrations of aromatics and cycloalkanes in fat were higher than concentrations of alkanes. Brain/blood ratios of 11.4, 2.0 and 11.4, and fat/blood ratios of 113, 63 and 135 were found for n-nonane, trimethylbenzene and trimethylcyclohexane, respectively. A marked decrease in biological concentrations of trimethylbenzene and trimethylcyclohexane during the initial phase of exposure indicates that when exposure levels are sufficiently high, these hydrocarbons are capable of inducing their own metabolic conversion resulting in lower steady state levels.

Metabolism

Information on the metabolic fate of the C_9-C_{14} Aliphatic [2-25% Aromatic] Hydrocarbon Solvents Category constituents comes mostly from studies of hydrocarbon solvent constituents and not with complex hydrocarbon substances themselves. Aliphatic hydrocarbons undergo oxidative conversion, catalyzed by monooxygenases, to alcohols. The cytochrome P-450 dependent monooxygenases, located mainly in the endoplasmic reticulum of liver cells, are responsible for this first metabolic transition.

Excretion

Most of the information concerning the elimination and excretion of aliphatic and aromatic hydrocarbons has been derived from studies in rats involving exposure to single substances including constituents of the C_9-C_{14} Aliphatic [2-25% Aromatic] Hydrocarbon Solvents. Generally speaking, it is expected that components or metabolites of complex hydrocarbon solvents such as Stoddard solvent/white spirit that have low solubility in the blood, would be rapidly exhaled from the lungs. As for pulmonary absorption, this process is governed by blood/gas solubility ratios. Components with low blood/gas ratios would be most rapidly excreted from the lungs because of their low blood solubility, while those with high blood/gas solubility ratios would be eliminated less efficiently by the lungs due to their high blood solubility; this situation is exactly the reverse of that for inhalation absorption. One study conducted reported that ten minutes after exposure had ceased, the expiratory concentration levels of aliphatics and aromatics were found to be about 12% of the initial exposure level for both fractions. Sixteen hours later, the levels in expiratory air had fallen to 2% (aliphatics) and 4% (aromatics) of the initial exposure level.

A 3-week inhalation study conducted in rats exposed for 6 hours/day, 5 days/week at levels of 2290 and 4580 mg/m3 found white spirit (20% aromatics) concentration in the brain of 3.4 and 10.2 mg/kg wet weight, respectively immediately preceding exposure cessation. These concentrations represented the steady state concentration during continuous exposure of these components rather than accumulation. In a follow up study to assess whether the measured concentrations did, in fact, reflect a steady state condition, male rats were exposed by inhalation to 0, 400 (2290 mg/m3) or 800 ppm (4580 mg/m3) of dearomatised white spirit (CAS 64742-48-9) for 6 hr/day, 5 day/week for 3 weeks. Five rats from each group were sacrificed immediately after the exposure duration of 1, 2, or 3 weeks and 2, 4, 6, or 24 hr after the end of 3 weeks' exposure. Immediately following the end of the 3 weeks of exposure, the concentration of total white spirit was 1.5 and 5.6 mg/kg in blood; 7.1 and 17.1 mg/kg in brain; 432 and 1452 mg/kg in fat tissue at the exposure levels of 400 and 800 ppm, respectively. Two hours after the end of exposure the white spirit concentration decreased to about 25% in blood and 50% in brain. The authors calculated that the post-exposure half-life in blood could be separated into two phases with half-lives of approximately 1 and 8 hr; in brain tissue two slopes with half-lives of 2 and 15 hr were identified. In adipose tissue, only one slope with half-life of about 30 hr was identified.

Acute Toxicity Summary

The acute toxicity data demonstrate that hydrocarbon solvent substances tested in the C_9- C_{14} Aliphatic [≤2% Aromatic] Hydrocarbon Solvents Category not acutely toxicity when tested at limit doses by the oral, dermal, and inhalation routes of exposure. It should be noted that the summary information (summarized in the SIAR) includes examples of acute oral and dermal toxicity studies of normal paraffins, isoparaffins, and cycloparaffins as well as solvents of mixed aliphatic constituents to show that none of these types of molecules is acutely toxic under these test conditions. The full range of constituents was covered by samples tested but as none of the studies indicated acute toxicity, the remaining studies were not considered to provide additional useful information and not included in the data compilation. The summarized information on the acute inhalation toxicity studies did include results of all tests conducted. This set of information did not cover C14 constituents, but as constituents with lower carbon numbers (C10-C13) were tested and found to be not toxic by inhalation, it was judged that the C14 constituents which are less volatile would similarily not be toxic at the maximally achievable vapor concentrations.

It should be noted, however, that these C_9-C_{14} Aliphatic Hydrocarbon Solvents [≤ 2% Aromatics] substances present aspiration hazards if taken into the lung in the liquid state due to their physical and chemical properties, particularly viscosity.

Acute Inhalation Toxicity

Acute inhalation studies conducted according to, or similar to OECD TG 403 on commercial C_9-C_{14} Aliphatic Hydrocarbon Solvents (≤ 2% Aromatics) (CAS RN 111-84-2, 124-18-5, 1120-21-4, 112-40-3, 629-50-5, 68551-16-6, 90622-57-4, 90622-58-5 and 64742-48-9) as well as a number of hydrocarbon solvent constituents demonstrated that the LC_{50} value for nonane was 23775 mg/m3 but for the constituents with higher carbon numbers as well as for the mixed aliphatic solvents the LC_{50} values were greater than the maximally attainable vapour concentrations. Solvents containing C14 constituents were not tested for acute inhalation toxicity; however, based on the low vapor pressures of C14 aliphatics (the maximally attainable vapor concentration for normal tetradecane is 202 mg/m^3), acutely toxic effects would not be expected. The inhalation LC_{50} data indicated that the C_9-C_{14} Aliphatic Hydrocarbon Solvents (≤ 2% Aromatics) were not acutely toxic by inhalation.

Acute Dermal Toxicity

Acute, single application, 14-day dermal toxicity studies were conducted according to, or similar to OECD TG 402 in rabbits or rats on commercial C_9-C_{14} Aliphatic Hydrocarbon Solvents (≤ 2% Aromatics) (CAS RN 64771-72-8, 90622-57-4, 64742-48-9, and 64742-47-8). All hydrocarbon solvent constituents were subsumed within substances shown as examples. The dermal LD_{50} results, greater than the limit doses of 2.0 g/kg, indicate that C_9-C_{14} Aliphatic Hydrocarbon Solvents (≤ 2% Aromatics) were not acutely toxic by dermal administration.

Acute Oral Toxicity (gavage administration)

Acute 14-day, single dose, oral gavage, toxicity studies were conducted according to, or similar to OECD TG 401 in rats on commercial C_9-C_{14} Aliphatic Hydrocarbon Solvents [≤ 2% Aromatics] (CAS RN 64771-72-8, 90622-57-4, 64742-48-9, and 64742-47-8) and constituents (4306-65-4). All hydrocarbon solvent constituents were subsumed within substances shown as examples. The examples shown did not encompass C9 aliphatic constituents; however, as the higher molecular weight aliphatic constituents are not acutely toxic by oral administration, it is expected that the C9 aliphatic constituents would be similarly non-toxic. The LD_{50} results of the oral studies in rats ranged from >5.0 to >15.8 g/kg, providing evidence that C_9-C_{14} Aliphatic Hydrocarbon Solvents [≤ 2% Aromatics] are not acutely toxic by oral administration.

Irritation and Sensitisation Summary

The members of the C9-C14 aliphatic (<2% aromatics) category produced minimal to slight eye irritation when tested in rabbits. Similarly, the isoparaffinic, normal paraffinic, and mixed aliphatic category members produced minimal to slight skin irritation when tested in rabbits and are also not normally irritating to human skin but can produce irritant responses if evaporation is inhibited or prevented. However, cycloparaffinic hydrocarbon fluids are considered to be dermal irritants to rabbits and to humans. It should also be noted that prolonged or repeated exposure to hydrocarbon solvents can lead to severe irritant dermatitis due to defatting of the skin. The C_9-C_{14} aliphatic (≤2% aromatics) Category members do not cause skin sensitization.

Repeated Dose Toxicity (Inhalation)

There were six repeated inhalation toxicity studies in rats, 2 with mixed aliphatic solvents, and 4 with isoparaffinic solvents. These six studies subsumed all of the constituents (C9-C14 n-paraffins, isoparaffins, cycloparaffins) in this category of solvents. There were no treatment-related mortalities, and, with one exception, no significant reductions in body weight gain. There were some reports of small but statistically significant reductions in hematological parameters but these were within the normal range and not considered toxicologically important. There were some significant changes in clinical chemistry parameters but these were small and not consistent across the studies. Of particular importance was that liver enzyme markers were not significantly elevated in any study. There were observations of liver weight increases in either male or female rats in most of the studies as well as increased kidney weights in male rats. There were no pathological changes in the liver or evidence of elevated liver enzyme markers in any of the studies. Many of the study reports drew attention to kidney effects in male rats. The pathological observations and male-rat specificity were consistent with an alpha 2u-globulin-mediated response, although the studies were conducted before the α2u-globulin-mediated process was understood. However, later studies with solvents of this type have documented an increase in alpha 2u-globulin in response to exposure, providing more direct evidence that this was in fact an alpha 2u-globulin-mediated process and not relevant to humans. For comparative purposes there was also a 28 day inhalation toxicity in primates in which no significant effects were reported following exposure to 4200 mg/m3. In summary, excluding the liver weight changes as being adaptive responses and the kidney changes in male rats as being alpha 2u-globulin mediated and not relevant to humans, the overall NOAECs were the highest concentrations tested in most of the studies although there were significant reductions in body weight gain in female rats in the highest exposure group (1800 ppm) of the inhalation study using C12 isoparaffins (<2% aromatics).

The specific solvents tested by inhalation and the results of these studies (assuming liver weight increases to be adaptive rather than adverse and kidney changes in male rats to be not relevant to humans) include:

(1) C10-C12 isoparaffins (< 2% aromatics) (CAS RN 64741-65-7). Tested in a 90 day inhalation toxicity study (OECD TG 413) in albino rats. The NOAEC was 10,400 mg/m3 (1444 ppm), the highest concentration tested.

(2) C9-C11 n-paraffins, isoparaffins, cyclics (<2% aromatics) (CAS RN 64742-48-9). Tested in a 90 day inhalation toxicity study (OECD TG 413) in Sprague-Dawley rats. The NOAEC was 5220 mg/m3 (900 ppm), the highest concentration tested.

(3) C10-C12 isoalkanes(<2% aromatics) (CAS RN 60742-48-9). Tested in a 90 day inhalation toxicity study (OECD TG 413) in Sprague-Dawley rats. The NOAEC was 5220 mg/m3 (900 ppm), the highest concentration tested.

(4) C11-C14 n-paraffins, isoparaffins, cyclics (CAS RN 64742-47-8). Tested in a 90 day inhalation toxicity study (OECD TG 413) in albino rats. The NOAEC was 6000 mg/m3, the highest concentration tested.

(5) C12 isoparaffins (<2% aromatics) (CAS RN 93685-81-5). Tested in a 90 day inhalation toxicity study (OECD TG 413) in Wistar rats. The NOAEC was 1390 mg/m3 (200 ppm) (based on reduced body weights in female rats).

(6) C12 isoparaffins (<2% aromatics) (CAS RN 93685-81-5). Tested in a 90 day inhalation toxicity study (OECD TG 413) in Wistar rats. The NOAEC was 6257 mg/m3 (900 ppm), the highest concentration tested.

(7) C10-C13 n-alkanes, isoalkanes, cyclics (<2% aromatics) (CAS RN 64742-48-9). Tested in a 28 day inhalation toxicity study (OECD TG 412) in Rhesus monkeys. The NOAEC was 4200 mg/m3 (615 ppm), the highest concentration tested.

Repeated Dose Toxicity (Oral)

Seven repeated oral toxicity studies in rats have been conducted, one C_{10}-C_{13} alipatic solvent, one C_{11}-C_{14} aliphatic solvent, two isoparaffinic solvents (C10-C12, C_{12}), two normal paraffinic solvents (C_{10}, C_{11}) and a study of the analogue substance tetramethylcyclohexane. In aggregate these 7 studies covered all constituents of the C9-C14 hydrocarbon (<2% aromatics). Five of these studies were essentially in accordance with OECD TG 408 but 3 of them

included "satellite" groups of animals treated for 13 weeks with the high dose of test material and then held for an additional 28 days to assess recovery. The other two studies were repeated dose/reproductive toxicity screening studies following OECD TG 422. One of these studies included an investigation in beagle dogs and reported no significant findings. In the other studies, conducted in rats, the principal finding was a treatment-related increase in liver weights. The pathology reports described the liver changes as indicative of liver cell enlargement (hypertrophy). Liver enzyme markers were not elevated, and the liver weight changes (and histologic changes) were not observed in the animals held for 28 days without treatment. There were also kidney changes in the male rats in the studies of the lower molecular weight isoparaffinic and mixed aliphatic solvents. The kidney effects were only in male rats and the histologic findings were consistent with an alpha 2u-globulin mediated response. There were also some reports of reduced weight gain. This was most likely due to the use of corn oil as a diluent in some studies. In effect the control animals were being force fed relatively high levels of corn oil and as a consequence got a higher caloric input than the treated animals in which the corn oil was replaced by increasingly higher levels of test material.

The specific solvents tested by repeated oral administration and the results of these studies (assuming liver weight increases to be adaptive rather than adverse and kidney changes in male rats to be not relevant to humans) include:

(1) Hydrocarbons C10-C11, n-alkanes, isoalkanes, cyclics (≤ 2% aromatics) (CAS RN 64742-48-9). Tested in a 90 day repeated oral toxicity test (OECD TG 408) in Sprague-Dawley rats. The study design included a 28 day recovery period for rats exposed to the highest dose (5000 mg/kg/day). The NOAEL was 5000 mg/kg/day, the highest concentration tested.

(2) Hydrocarbons C11-C14, n-alkanes, isoalkanes, cyclics (<2% aromatics) (CAS RN 64742-47-8). Tested in a 90 day repeated oral toxicity test (OECD TG 408) in Sprague Dawley rats. The study design included a 28 day recovery period for rats exposed to the highest dose (1000 mg/kg/day). The NOAEL was 1000 mg/kg/day.

(3) Hydrocarbons C10-C12 isoalkanes (<2% aromatics) (CAS RN 64742-47-8). Tested in a 90 day repeated oral toxicity test (OECD TG 408) in Sprague-Dawley rats. The study design included a 28 day recovery period for rats exposed to the highest dose (1000 mg/kg/day). The NOAEL was 1000 mg/kg/day.

(4) Hydrocarbons C12 isoalkanes (≤25 aromatics) (CAS RN 93685-81-5). Tested in a 90 day repeated oral toxicity test (OECD TG 408) in Wistar rats. The NOAEL was 1000 mg/kg/day.

(5) Hydrocarbons C10 normal paraffins (<2% aromatics) (CAS RN 124-18-5). Tested in a repeated dose/reproductive toxicity screening test (OECD TG 422) in Wistar rats. The NOAEL was 1000 mg/kg/day.

(6) Hydrocarbons C11 normal paraffins (<2% aromatics) (CAS RN 1120-21-4). Tested in a repeated dose/reproductive toxicity screening test (OECD TG 422) in SD rats. The NOAEL was 1000 mg/kg/day.

(7) Tetramethylcyclohexane (C10 analogue cycloparaffinic substance, no CAS RN number provided). Tested in a 90 day dietary administration study (OECD TG 408) in rats and beagle dogs. There were no effects in either species at the highest dietary levels administered (30,000 ppm, approximately 3000 mg/kg bw/day).

Repeated Dose Toxicity (Dermal)

A 28 day dermal administration study in New Zealand white rabbits was conducted with C12-C14 normal paraffins (< 2% aromatics) (CAS RN 64771-72-8). The test material was applied daily (7 days/week) for 4 weeks to the backs of the rabbits and maintained in contact with the skin for 6 hours. Treatment levels were 0, 100, 500, or 2000 mg/kg/day. The protocol was equivalent to OECD TG 410. At the end of the treatment period the animals were examined and then sacrificed to assess the potential for target organ effects. The repeated dermal treatment under the occlusive patch conditions utilized caused severe dermal irritation in the highest treatment group (2000 mg/kg/day), leading to early termination. There was no evidence of systemic effects in animals from the highest dose group, but, because of the early terminations of some animals, conclusions based on this experimental group were considered unreliable. Accordingly, the overall NOAEL for hydrocarbons C12-C14 n-paraffins (<2% aromatics) was judged to be 500 mg/kg/day.

Repeat Dose Toxicity, overall conclusion

In summary, the members of the C_9-C_{14} Aliphatic [< 2% aromatics] Hydrocarbon Solvents Category did not appear to produce significant systemic toxicity. Repeated dose studies have been conducted on a number of category members using inhalation as well as oral and dermal administration as routes of exposure. The studies were conducted following standard guidelines and the data were judged adequate for assessing the health hazard from exposure. The principal findings in these studies were increased liver weights in males and females and kidney changes in male rats. There were no pathologic changes, levels of liver enzyme markers were not elevated, and the weight differences were reversed when the rats were held without treatment for 28 days. The kidney changes were found only in male rats and were

consistent with effects mediated by alpha 2u-globulin, an effect that has been determined to be not relevant to humans. In addition to the studies in rats there was one inhalation toxicity study in Rhesus monkeys and a dietary study in beagle dogs. There were no reported findings in these studies.

Mutagenicity

In vitro Studies

C_9-C_{14} aliphatic, < 2% aromatic hydrocarbons fluids are not mutagenic using *in vitro* genotoxicity assays. In bacterial tests, C_9-C_{14} aliphatic, < 2% aromatic hydrocarbons fluids were not mutagenic in Salmonella strains tested in the presence or absence of metabolic activation. C_9 -C_{14} aliphatic, <2% aromatic hydrocarbon fluids did not induce mutations in an *in vitro* mammalian cell gene mutation assay. In sister chromatid exchange and in chromosomal aberration studies conducted under *in vitro* conditions, C_9-C_{14} aliphatic, < 2% aromatic hydrocarbons fluids did not produce effects.

All *in vitro* genetic toxicity tests listed below had negative results for C_9-C_{14} aliphatic, < 2% aromatic hydrocarbons solvents.

Genetic Toxicity *in vitro* – Bacterial reverse mutation assay (OECD TG 471) (CAS RN 64771-72-8, 90622-57-4, 64742-48-9; 64742-88-7). Samples tested included C10-C13 n-alkanes, C10-C13 n-alkanes, C11 n-alkanes, C10-C12 isoalkanes, C10-C13 n-alkanes, isoalkanes, cyclics.

Genetic Toxicity *in vitro* – *In vitro* Mammalian Chromosome Aberration Test (OECD TG 473) (CAS RN 64742-47-8, C11n-paraffins)

Genetic Toxicity *in vitro* - *In vitro* Mammalian Cell Gene Mutation Test (OECD TG 476) (CAS RN 64771-72-8, 31807-55-3). Samples tested were C12 isoparaffins, C11-C14 n-alkanes, isoalkanes, cyclics.

Genetic Toxicity *in vitro* – In Vitro Sister Chromatid Exchange Assay in Mammalian Cells (OECD TG 479) (CAS RN 90622-57-4). The sample tested was C10-C12 isoalkanes.

In vivo Studies

C_9-C_{14} aliphatic, < 2% aromatic hydrocarbons fluids were not genotoxic when tested by gavage in an *in vivo* mouse bone marrow micronucleus assay, when tested by inhalation in a mouse micronucleus test, and when tested in dominant lethal studies utilizing an inhalation route of exposure**.**

All genetic toxicity tests listed below had negative results for C_9-C_{14} aliphatic, < 2% aromatic hydrocarbons solvents.

Genetic Toxicity *in vivo* – Micronucleus Assay in Mouse Bone Marrow, oral (OECD TG 474) (CAS RN 64771-72-8). The sample tested was C10-C13 n-alkanes, isoalkanes, cyclics.

Genetic Toxicity *in vivo* – Micronucleus Assay in Mouse Bone Marrow, inhalation (OECD TG 474 (CAS number 64742-88-7). The sample tested was C10-C13 n-alkanes, isoalkanes, cyclics.

Genetic Toxicity *in vivo* – Genetic Toxicology: Rodent Dominant Lethal Test (OECD TG 478) (CAS RN 64771-72-8 and 90622-57-4). Samples tested were C10-C12 isoalkanes, C9-C11 n-alkanes, isoalkanes, cyclics.

Mutagenicity Overall Conclusions

Members of the C_9-C_{14} Aliphatic [$\leq$ 2% Aromatic] Hydrocarbon Solvents Category have shown no mutagenic activity in a number of *in vitro* bacterial, mammalian cell mutagenicity tests and were not active when tested in *in vitro* tests for chromosome aberration and sister chromatic exchange. These substances were not genotoxic when tested under *in vivo* conditions in bone marrow assays for chromosome damage and in dominant lethal tests.

Carcinogenicity

Carcinogenicity Summary

Male and Female F-344 rats and B6C3F1 mice were exposed for two years to vapors of Stoddard solvent IIC (CAS RN 64742-88-7). Exposure levels were 0, 138 (male rats only), 550, 1100 mg/m3, or 2200 mg/m3 (mice and female rats). The NTP concluded that there was some evidence of carcinogenic activity in male rats due to an increase in adrenal gland tumors and equivocal evidence of carcinogenic activity in female mice due to an increase in liver tumors. The judgment that the liver tumor incidence was equivocal was related to a determination by the NTP that these tumors were secondary to an increase in body weight in female mice. There was no evidence of carcinogenicity in female rats

or male mice.

Groups of 50 male and 50 female Wistar rats and B6C3F mice were exposed to Stoddard solvent IIC (CAS RN 64742-88-7) in two year studies. The test material was described as being composed primarily of C10-C13 aliphatic constituent with <1% aromatics. Male rats were exposed at concentrations of 0, 138, 550, or 1100 mg/m3; the female rats and mice were exposed at levels of 550, 110 or 2200 mg/m3 [the maximally attainable vapor concentration]. The exposure levels were based on 2 week and 3 month preliminary studies. Exposures were, 6 hours plus T90 (12 minutes) per day, 5 days per week for 105 weeks. Groups of 10 rats/sex/exposure level were exposed at the same levels in 14 week satellite studies to assess kidney effects. Clinical findings were recorded twice daily. The animals were weighed initially, weekly, and at the end of the studies. Necropsies were performed on all rats. The heart, right kidney, liver, lung, right testis, and thymus were weighed. Histopathologic examinations were performed on all rats and mice.

Results of the rat study

Neoplastic Effects

Kidney: In the standard evaluation of a single hematoxylin and eosin stained section of the left and right kidney, the incidences of mild to moderate renal tubule and transitional epithelial hyperplasia in 550 and 1,100 mg/m3 males were significantly increased. The incidences of renal tubule adenoma and renal tubule carcinoma in exposed groups of male rats were similar to those in the chamber controls at the standard evaluation. Renal tubule hyperplasia, adenoma, and carcinoma are thought to represent a continuum in the progression of proliferative lesions of the renal tubule epithelium. Because there were increased incidences of renal tubule hyperplasia (a preneoplastic lesion) in male rats, additional kidney sections were evaluated, and additional renal tubule hyperplasias and adenomas were identified. In the extended evaluation, the significantly increased incidences of renal tubule hyperplasia in 550 and 1,100 mg/m3 males were confirmed. In the extended evaluation, the incidence of renal tubule adenoma was greater in 1,100 mg/m3 males than in the chamber controls; however, the increase was not significant; the incidences of renal tubule carcinoma in exposed groups of males were similar to that in the chamber control group.

Adrenal Medulla: The incidences of benign and, benign or malignant pheochromocytoma (combined) occurred with positive trends in males, and the incidences in the 550 and 1,100 mg/m3 groups were significantly increased. The incidences of benign pheochromocytoma in 550 and 1,100 mg/m3 males and benign or malignant pheochromocytoma in 1,100 mg/m3 males exceeded the historical ranges in chamber controls. Benign pheochromocytomas were characterized by a proliferating mass of adrenal medullary cells that compressed adjacent tissue. Malignant pheochromocytomas were generally larger with invasion of or beyond the adrenal capsule. The incidence of hyperplasia of the adrenal medulla in 550 mg/m3 males was significantly increased. Medullary hyperplasia was characterized by an increase in basophilia of medullary cells that sometimes accompanied increased size and minimal compression of the adjacent tissue.

	Male F344/N Rats	Female F344/N Rats
Concentrations in air	Chamber control, 138, 550, or 1100 mg/m3	Chamber control, 550, 1100, or 2200 mg/m3
Survival rates	29/50, 19/50, 21/50, 16/50	36/50, 30/50, 32/50, 25/50
Body weights	Exposed groups similar to the chamber control group	Exposed groups similar to the chamber control group
Notable Nonneoplastic effects	In the 3 month studies there were significant increases in granular casts and cortical tubule regeneration at 550 and 1100 mg/m3. In 2 year studies there were significant increases in renal tubular hyperplasia at 550 and 1100 mg/m3 and mineralization at all exposure levels.	Non-neoplastic renal effects were observed in in 3 month and two year studies..
Neoplastic effects	Adrenal medulla:benign and malignant pheochromocytoma Control = 6/50, 138 mg/m3 = 9/50, 550 mg/m3 = 13/50 ($p < 0.05$), 1100 mg/m3 = 19/50 ($p < 0.01$) Kidney Renal Tubule Adenomas	The adrenal and kidney tumors in male rats were considered to have been treatment related

	Control = 3/50 138 mg/m3 = 2/50 550 mg/m3= 3/50 1100 mg/m3 = 7/50	

Results of the mice study

Neoplastic Findings

Liver: The incidences of hepatocellular adenoma occurred with a positive trend in female mice, and the incidences of multiple hepatocellular adenoma in male and female mice from the 2200 mg/m3 exposure group were significantly increased; however, the incidences of adenoma or carcinoma (combined) and carcinoma alone in exposed males and females were not significantly increased. The increased incidence of multiple hepatocellular adenoma in 2,200 mg/m3 males was not considered related to Stoddard solvent IIC exposure because the incidences of all adenomas (including multiple) were not significantly increased in the exposed groups. The incidences of hepatocellular adenoma in 550 and 2,200 mg/m3 males and 1,100 and 2,200 mg/m3 females and of hepatocellular adenoma or carcinoma (combined) in 550 mg/m3 males and 2,200 mg/m3 females exceeded the historical ranges in chamber controls; the incidences in chamber control males and 1,100 mg/m3 females were at the upper end of the historical ranges.

Lung: The incidences of alveolar/bronchiolar adenoma or carcinoma (combined) were decreased in exposed males, and the decrease in the 550 mg/m3 group was significant (chamber control, 13/50; 550 mg/m3, 4/49; 1,100 mg/m3, 6/50; 2,200 mg/m3, 6/50). The incidence in the chamber controls was at the lower end of the historical range in chamber controls, and the incidences in the exposed groups were less than the historical range [85/250 (34% ± 7%), range 26%-44%].

	Male B6C3F1 Mice	Female B6C3F1 Mice
Concentrations in air	Chamber control, 550, 1100, or 2200 mg/m3	Chamber control, 550, 1100, or 2200 mg/m3
Survival rates	34/50, 32/50, 27/50, 32/50	36/50, 34/50, 27/50, 34/50
Body weights	Exposed groups similar to the chamber control group	Exposed groups greater than the chamber control group
Nonneoplastic effects	none	none
Neoplastic effects	None considered treatment related	Hepatocellular adenoma Control = 9/50 550 mg/m3 = 12/50 1100 mg/m3 = 12/50 2200 mg/m3 = 18/50 (p = 0.032)

Conclusions

The NTP concluded that under the conditions of these 2-year inhalation studies, there was some evidence of carcinogenic activity of Stoddard solvent IIC in male F344/N rats based on increased incidences of adrenal medulla neoplasms (pheochromocytoma). There was no evidence of carcinogenic activity of Stoddard solvent IIC in female F344/N rats exposed to 550, 1100, or 2200 mg/m3.

The NTP further concluded there was no evidence of carcinogenic activity of Stoddard solvent IIC in male B6C3F1 mice exposed to 550, 1100, or 2200 mg/m3. There was equivocal evidence of carcinogenic activity of Stoddard solvent IIC in female B6C3F1 mice based on increased incidences of hepatocellular adenoma. Equivocal evidence of carcinogenic activity is demonstrated by studies that are interpreted as showing a marginal increase of neoplasms that may be chemical related. The NTP pointed out that liver tumors in B6C3F1 mice are sensitive to body weight changes and noted that statistical analysis was consistent with the view that the increased liver tumors in female mice in this study were the consequence of increased body weight. That was the basis for the overall determination by the NTP that the evidence of carcinogenic effects in mice was equivocal.

The NTP also pointed out that the exposure of male rats to Stoddard solvent IIC resulted in non-neoplastic lesions of the kidney characteristic of alpha 2u-globulin. [The pathology data are summarized in the table above. The NTP also documented an increase in alpha 2u globulin using immuno-staining techniques.

Toxicological Relevance of Carcinogenesis Findings

As summarized above, the NTP considered that the increased liver tumor incidence in female mice was equivocal based on a statistical analysis which indicated that this increase could be explained by the increased body weights of the mice in that group. The NTP also appeared to put little weight on the renal tumors in male rats as other data were obtained during this study to show that levels of α2u-globulin were increased providing support for the view that these tumors, although treatment-related, are not relevant to humans.

The toxicological significance of the pheochromocytomas is less clear. The appearance of elevated levels of pheochromocytomas seems to have first drawn attention in the context of an NTP carcinogenicity study of talc in which it was noted that this particular type of tumor appears spontaneously at relatively high incidence in the F344 rats. After further review of the historical information on tumors of this type, NTP scientists pointed out that hyperplasia and neoplasia of the adrenal medulla is relatively common in rats but rare in humans and other species. They suggested that there might be a link between the induction of chronic progressive nephropathy (CPN), an aging lesion particular prevalent in F344 rats which is exacerbated by certain chemical agents, and adrenal changes.

In a review on pheochromocytomas in rats, it was noted that the pheochromocytomas are a common spontaneous tumor in male Fischer 344 rats with average frequencies in control groups nearing 40% in the 1990s but between 12% and 16% since the rat diets were changed in 2000. In contrast, pheochromocytomas are rare in humans, occurring with an incidence of 1/100,000. A number of mechanisms have been proposed to account for the high incidence in humans; the authors of the review included Stoddard solvent IIC as among those for which the tumors may have been secondary to nephrotoxic effects. They also noted that "[T]here is to date no indication that the substances inducing pheochromocytomas also induce corresponding tumors in humans; however, the database for a final conclusion is inadequate. Ultimately as the underlying mechanism for pheochromocytoma development in rats is not known, they could not exclude the possibility that chemical exposure could be a risk factor in humans. But the authors did conclude that the pheochromocytomas in rats were a secondary effect, making it unlikely that it would be relevant to humans exposed at lower levels than those used in the experimental studies.

Reproductive and Developmental Toxicity

There were two developmental toxicity studies on category members (C_9-C_{11} mixed aliphatic solvent, C_{10}-C_{12} isoalkanes) in which exposure was by inhalation; two repeated dose/reproductive toxicity screening tests on category members (C_{10}, C_{11} normal paraffinic solvents) in which exposure was oral; a repeated dose/reproductive toxicity screening test on a C_9-C_{16} analogue substance in which exposure was dermal; a reproductive toxicity test on a C_9-C_{16} analogue substance in which the exposure was oral, and a classical developmental toxicity study on a C_9-C_{16} analogue substance. There were no effects on either fertility or development in any of these studies. Additionally, there have been 7 repeated exposure studies in which the reproductive organs were examined and found to have not been affected by test material administration.

These studies provide evidence that members of the C_9-C_{14} Aliphatic [$\leq$ 2% Aromatic] Hydrocarbon Solvents Category would not be expected to be reproductive or developmental toxicants.

There are several studies for reproductive and/or developmental effects that have been conducted with members of the C_9-C_{14} Aliphatic [$\leq$2% Aromatics] Hydrocarbon Solvents Category products. There is also data available for two analogue substances hydrodesulfurized kerosine (CAS RN 64742-81-0, analogue) and jet fuel (JP-8, analogue). Hydrodesulfurized kerosene was tested in a reproductive toxicity/repeated dose toxicity screening test in which test material was applied dermally. JP-8 was tested in separate studies of fertility and developmental effects. These two analogue substances are petroleum fuels, described as containing primarily C_9-C_{16} aliphatic constituents with aromatic contents limited to a maximum of 25% (although the samples used in these tests contained about 20% aromatics. The data provided by tests of category and analogue substances subsumed the carbon numbers and molecular types found in the C9-C14 aliphatic (<25 aromatic) category.

Reproductive toxicity

The study of hydrodesulfurized kerosene (CAS RN 64742-82-1), followed the guidelines of OECD TG 421. The test material, described as a C_9-C_{16} petroleum fuel containing approximately 80% aliphatic and 20% aromatic (primarily alkylated single ring compounds) constituents. The hydrodesulfurized kerosene was administered dermally at doses equivalent to 0, 165, 330, or 494 mg/kg/day to male and female Sprague-Dawley rats in groups of 10/sex. Dosing was initiated 14 days prior to mating and continued through 2 weeks of mating and 20 days of gestation. Females and their litters were sacrificed on post-natal day 4; all males were sacrificed 7 days after termination of the last female. The doses were chosen based on a preliminary study in which it was shown that approximately 500 mg/kg/day was the highest dose that could be repeatedly applied without producing unacceptable levels of skin irritation. Among the males there were no effects on survival or weight gain during the study, and at terminal sacrifice the only statistically

significant effect was an increase in kidney weight in animals from the high dose group. Among the females there were no effects on mating, litter size, offspring body weights or offspring survival. An overall conclusion from the study was that the No Observed Adverse Effect Level for all reproductive and developmental parameters assessed was 494 mg/kg/day, the highest dose tested.

The jet fuel reproductive toxicity studies were by oral gavage. To assess the potential for reproductive effects in males, male Sprague-Dawley rats were given 0, 750, 1500 or 3000 mg/kg JP-8 ; an aliphatic carbon range of C_9-C_{16}, aromatics <25%) daily by gavage for 70 days prior to mating with naive females to assess fertility and sperm parameters (similar to OECD TG 415). Males continued to be treated during the mating period to termination after a total of 90 days of treatment. There was a statistically significant reduction in body weight gain in male rats from the 3000 mg/kg bw/day group. But there were no effects on fertility, no changes in sperm parameters, and no gross or histological effects on reproductive organs. The reproductive NOAEL = 3000 mg/kg bw/day for male rats.

To assess the potential for reproductive effects in females, female Sprague-Dawley rats were dosed (0, 325, 750, 1500 mg/kg) with JP-8 an aliphatic carbon range of C_9-C_{16}, aromatics <25%) daily by gavage for a total of 21 weeks (90s-day plus mating with naive males, gestation and lactation) in an effort to assess general toxicity, fertility and reproductive endpoints (similar to OECD TG 415). All surviving dams were sacrificed on post-natal day 21. Body weight gain was significantly reduced in females in the 1500 mg/kg/day group. But there were no significant differences in rates of fertility, length of gestation, litter size or live birth index. There was an effect of treatment on body weight gain of offspring, but the differences between groups were reduced with increasing time without treatment. The NOAEL was 1500 mg/kg bw/day for female fertility, the highest dose tested. The NOAEL for the pups was 750 mg/kg bw/day based on a decrease in body weight which correlated with a decrease in maternal body weight at 1500 mg/kg bw/day.

A reproduction/developmental Toxicity Screening Test in Sprague-Dawley rats, similar to OECD TG 422, was conducted using Undecane (CAS RN: 1120-21-4). The administration of the test substance was carried out by oral gavage. The volume administered was 5 mL per kg of body weight in doses of 0, 100, 300 or 1000 mg/kg/day. The test material was suspended in olive oil. The dose administration period was 46 days, which including 14 days before mating and during the mating period for males. The dose administration period for the female rats began 14 days before mating and continued until after the first 3 days of nursing. The administration was started when the animals were 10 weeks old. The results of the repeated dose part of this study are summarized in the repeated dose toxicity section. In the reproductive and developmental toxicity portion of this study, There were no significant differences in body weight gain. Liver and adrenal weights were elevated in the high dose group, but there were no unusual histological findings. There were also no differences in mating frequency. No effects of undecane administration were observed on the sex cycle of females and copulation and conception of males and females. In addition, no effects of undecane administration were observed on the weights of reproductive organs (testis, epididymis and ovary) and there were no abnormalities noted in the dissection and histopathological examination. There were no histopathological findings in cases where animals failed to successfully mate; abnormal deliveries (2 in the 300 mg/kg/day group and 1 in the 1000 mg/kg/day group) were confirmed to be spontaneous and at frequencies similar to historical controls. Those cases observed in the present study were considered to be unrelated to undecane. There were no differences in the number of live pups born in the control, 100 mg/kg, or the 1000 mg/kg treated animals; there was a decrease in the 300 mg/kg group, but as no difference was noted in the 1000 mg/kg treated animals, this finding was determined by the authors to not be test material related. There was no difference in the number of pups alive on post-natal day 4. The body weights at post-natal day 4 of both males and females in the 1000 mg/kg group were slightly reduced (-5.6% and -4.1%), but were not significantly different from the weights of offspring in the control group, and there were no notable clinical or pathological effects. The NOAEL for reproductive performance and developmental effects is considered to be 1000 mg/kg/day.

A Combined Repeated Dose Toxicity Study with the Reproduction / Developmental Toxicity Screening Test similar to OECD TG 422 was conducted using decane, CAS RN: 124-18-5. Animals were dosed with 0, 25, 150, or 1000 mg/kg/day (10 ml/kg dosing volume), once a day, 7 days a week via oral gavage. No deaths or clinical signs of toxicity or behavioral changes were noted. The results of the repeated dose assessment are reported in the section on repeated dose toxicity. In the assessment of developmental and reproductive effects there were no treatment-related effects at any dose level on any of the reproductive parameters evaluated in this study. These included measures of reproductive performance (mating, conception, gestation length, and liter size), offspring survival (gestation and postnatal survival indices, percent pre- and post-implantation loss). There were no treatment-related effects at any dose level on any of the developmental parameters evaluated in this study including external abnormalities of pups, number of live and still births, mortality, sex determination, and weights of pups. Based on these data, the no-observable-adverse-effect level (NOAEL) for developmental toxicity was 1000 mg/kg/day and the NOAEL for reproductive dose and reproductive toxicity was 1000 mg/kg/day.

Developmental toxicity studies

A Prenatal Developmental Toxicity Study equivalent or similar to OECD TG 414 with Hydrocarbons, C_9-C_{11}, isoalkanes, cyclics, < 2% aromatics (CAS RN 64742-48-9). The test material was administered to pregnant female Sprague-Dawley rats by inhalation exposure to vapor concentrations of 0, 300 or 900 ppm (5220 mg/m3), 6 hours/day during gestation days 6 to 15 to assess developmental toxicity. Included in this study was a negative control (chamber exposed) group and a positive control group that was treated via gastric intubation on gestational days 6-15 with 400mg/kg/day of acetylsalicylic acid. All surviving females were sacrificed on Day 21 of gestation and fetuses were examined for external, soft tissue and skeletal malformations.

Maternal Effects. Animals treated with 900 ppm exhibited a slight increase in excessive lacrimation during the treatment and post-treatment periods. This same group also exhibited an increased incidence of brown flakes in the fur covering the head area during the treatment period. Premature delivery of the litter on Day 21 of gestation prior to maternal sacrifice was observed in one negative control female, and two test material treated females. There were no remarkable gross postmortem changes in the treated adult females. All other physical observations occurred with similar frequencies in all groups and were considered to represent common observations noted in rats in the laboratory environment. Positive control animals demonstrated maternal toxicity.

Embryotoxic / Teratogenic effects. All fetal survival, size and sex data for groups treated with test material were comparable to negative control data. Slight delays or variation in the normal ossification process were observed in treated animals. However, such variations are common as the time of normal ossification can vary and were comparable to the variation observed in the control animals. The incidence of fetuses with external malformations and incidences of litters containing malformed fetuses in the groups treated with test material were considered comparable to the control data. No significant differences in the incidence of visceral malformations was observed in the treated groups. The incidence of fetuses with soft tissue malformation in groups treated with test material was comparable to the negative control. Positive control animals demonstrated developmental toxicity.

Pregnancy rate, mortality, body weight gain and gross postmortem observations were unaffected by treatment. Hydrocarbons, C_9-C_{11}, normal paraffins, isoalkanes, cyclics, < 2% aromatics treatment at either dose level had no effect on reproductive endpoints, fetal size, sex distribution, ossification variation, or fetal examination endpoints. Thus, there was no evidence of maternal or fetal toxicity at either exposure level of Hydrocarbons, C_9-C_{11}, normal, isoalkanes, cyclics, < 2% aromatics tested. Based on these results, both the maternal and developmental NOAELs were greater than or equal to 900 ppm (5220 mg/m3).

Hydrocarbons, C_{10}-C_{12}, isoalkanes, < 2% aromatics (CAS RN 90622-57-4) was administered to pregnant female Sprague-Dawley rats by inhalation exposure to vapor concentrations of 0, 300 or 900 ppm, 6 hours/day during gestation days 6 to 15 to assess developmental toxicity. Included in this study was a negative control (chamber exposed) group and a positive control group that was treated via gastric intubation on gestational days 6-15 with 400mg/kg/day of acetylsalicylic acid.

Maternal toxic effects. Animals treated with 900 ppm exhibited a slight increase in excessive lacrimation during the treatment and post-treatment periods. This same group also exhibited an increased incidence of brown flakes in the fur covering the head area during the treatment period. Premature delivery of the litter on Day 21 of gestation prior to maternal sacrifice was observed in one negative control female, and two test material treated females. There were no remarkable gross postmortem changes in the treated adult females. All other physical observations occurred with similar frequencies in all groups and were considered to represent common observations noted in rats in the laboratory environment. Positive control animals demonstrated maternal toxicity.

Embryotoxic / teratogenic effects. All fetal survival, size and sex data for groups treated with test material were comparable to negative control data. Slight delays or variation in the normal ossification process were observed in a few treated animals. However such variations are common as the time of normal ossification can vary and were comparable to the variation observed in the control animals. The incidence of fetuses with external malformations and incidences of litters containing malformed fetuses in the groups treated with test material were considered comparable to the control data (<5% and no dose response). No significant difference in the incidence of visceral malformations was observed in the treated groups. The incidence of fetuses with soft tissue malformation in groups treated with test material was comparable to the negative control. Positive control animals demonstrated developmental toxicity.

Hydrocarbons, C_{10}-C_{12}, isoalkanes, < 2% aromatics treatment at either dose level had no effect on reproductive endpoints, fetal size, sex distribution, ossification variation, or fetal examination endpoints. Pregnancy rate, mortality, body weight gain and gross postmortem observations were unaffected by treatment. Thus, there was no evidence of maternal or fetal toxicity at either exposure level of the chemical tested. Based on these results, both the maternal and developmental NOAELs were greater than or equal to 900 ppm (5220 mg/m3).

In addition to the above, there were no apparent effects on in utero development or post-natal survival of offspring in the reproductive toxicity/developmental toxicity screening tests of the category substances decane or undecane or the analogue substances JP-8 or hydrodesulfurized kerosene. There was also a more classical developmental toxicity study of JP-8 in which test material was given by gavage to time-pregnant Sprague-Dawley rats on days 6-15 of gestation in doses of 0, 500, 1000, 1500 or 2000 mg/kg/day. There was significant maternal mortality (9/30) in the 2000 mg/kg/day group, but among the survivors, there were no significant differences in pregnancy rates, litter sizes or frequency of live fetuses/litter. The uterine examinations did not identify any malformations. There were effects on maternal weight in all of the dose groups, and significantly reduced fetal weights were noted in the1500 and 2000 mg/kg/day groups. The authors considered that 500 mg/kg/day was a NOAEL for maternal effects and 1000 mg/kg/day was a NOAEL for fetal effects.

Neurobehavioral toxicity

Members of the C9-C14 aliphatics (<2% aromatics) category as well as a number of constituents of these solvents have been tested for acute central nervous system effects. As summarized below, aliphatic hydrocarbons with carbon numbers up to approximately C10 can produce acute, reversible effects on the central nervous system. Hydrocarbon solvents with carbon numbers greater than C10 do not produce acute CNS effects at the maximally attainable vapor concentrations. In one repeated dose study, rats were exposed to isoparaffinic hydrocarbons for 13 weeks at levels of 668, 2220, or 6646 ppm (24,300 mg/m3). There were no persistent effects in assessments of motor activity or functional observations and no pathologic changes in the central or peripheral nervous systems. A summary article reported that a low (<0.4%) aromatic aliphatic solvent (CAS RN 64742-48-9) did not cause gross or pathological changes to the central or peripheral nervous system or produce neurochemical changes. In neurobehavioral assessments no effects were found in the majority of the assessed parameters but there was a decrease in dark field motor activity. One study reported effects in an electrophysiological study.

Animal Studies

An article reports the results of neurobehavioral tests of n-octane (CAS RN 111-65-9) and n-decane (CAS RN 124-18-5) normal paraffinic constituents (n-paraffins). Clinical effects, motor activity, functional observations, and visual discrimination performance were evaluated shortly after exposure.

n-Octane. Rats were exposed for 8-hours for 3 consecutive days to 0, 1405, 4248, or 14002 mg/m3 of n-octane. There were no treatment related effects in the FOB measurements. Foot-splay was significantly increased in the 1405 mg/m3 exposure group, and hind-limb grip strength was significantly increased in the 4248 mg/m3 exposure group. As an exposure-response relationship was not demonstrated, these effects were judged to be unrelated to treatment. There were no statistically significant effects on motor activity. Visual discrimination performance testing did not reveal any treatment-related effects. There were no group differences in number of trials completed or discrimination accuracy. There were no differences in frequency of repetitive errors or in lever response latency. There was a statistically non-significant reduction in frequency of very short latency responses (<1 second), but this difference was also observed in the pretest examination, and the frequency did not change during the study. Thus, it seems unlikely that it was a treatment-related effect. Similarly, there were no treatment-related differences in short (<2 seconds) or long (>6 seconds) latency responses. The overall assessment was that n-octane did not affect visual discrimination performance at exposure levels up to 14000 mg/m3.

n-Decane. Rats were exposed for 8-hours for 3 consecutive days to 501, 1510, and 5005 mg/m3 of n-decane. The only significant difference in any of the FOB measurements was a statistically significant reduction in grip strength in the 5005 mg/m3 exposure group after the third 8-hour exposure. There were no effects on motor activity. Visual discrimination performance testing did not reveal any treatment-related differences in number of trials completed or discrimination ratios. Frequency of response during the ITI was not significantly different between groups during the 3-day exposure period. There were differences in frequency of repetitive errors and responses during the ITIs, but as the most highly exposed animals performed better than the controls, this was judged to have not been a toxicologically relevant finding. There were differences in lever response latency, but these were not statistically significant. There was a statistically significant increase in the frequency of long (i.e., >6 seconds) latency responses. The overall assessment was that n-decane had some minimal, reversible effects on visual discrimination performance at an exposure level of 5000 mg/m3. The NOAEL = 1500 mg/m3.

Rats were exposed to n-alkanes ranging from C_9-C_{13} for 8 hour periods. In the study of nonane, Sprague-Dawley rats were exposed to concentrations ranging from 2414 to 5280 ppm. The authors reported mortality among the rats and calculated that the LC_{50} value for nonane was 4467 ppm (23,775 mg/m3). The authors also reported that there was evidence of acute CNS effects and that both the time to onset and severity of effects was related to the vapor concentrations to which the rats were exposed. In studies of n-decane, n-undecane, n-dodecane and n-tridecane the rats were exposed for 8 hours to the maximally attainable vapor concentrations. There were no deaths and no evidence of

CNS effects. The authors also measured blood/air and brain/air ratios for these substances and reported that these ratios declined with increasing carbon number above C_{10}.

Rats were exposed to Hydrocarbons, C_9-C_{11}, cyclics, <2% aromatics (CAS RN 64742-48-9) test atmosphere for 8 hours/day for 3 consecutive days at 0 (air), 1000 mg/m3 (170ppm), 2500 mg/m3 (430ppm), 5000 mg/m3 (860ppm). All rats were checked for health and viability at least once daily. Body weight was recorded during randomization on days of testing. Results of the behavioral tests indicated only minimal effects of exposure to a C10 cycloparaffinic solvent on neurobehavioral measures at the highest dose tested (5000 mg/m3) including gait abnormalities and psychomotor slowing. Short-term high level exposure to Hydrocarbons, C_9-C_{11}, cyclics, <2% aromatics induced mild and non-persistent neurobehavioral effects on functional observations and measures of learned performance. Minimal effects were observed during or after 3 consecutive 8 hour exposures to Hydrocarbons, C_9-C_{11}, cyclics, <2% aromatics at an exposure level of 5000 mg/m3. Exposure to 1000 or 2500 mg/m3 on a group basis did not induce exposure-related neurobehavioral effects. The effects are consistent with narcosis and the NOAEC = 2500 mg/m3.

Rats were exposed to Hydrocarbons, C_{10}-C_{12}, isoalkanes, <2% aromatics (CAS RN 90622-57-4) test atmosphere for 8 hours/day for 3 consecutive days at 0 (air), 500 mg/m3 (85ppm), 1500 mg/m3 (260ppm), 5000 mg/m3 (860ppm). All rats were checked for health and viability at least once daily. Body weight was recorded during randomization on days of testing. Results of the behavioral tests showed some mild effects of exposure to Hydrocarbons, C_{10}-C_{12}, isoalkanes, <2% aromatics on learned performance measurements in the highest exposed test group (5000 mg/m3). Measures of performance speed were sensitive to the effects of Hydrocarbons, C_{10}-C_{12}, isoalkanes, <2% aromatics, while measures of discrimination accuracy and stimulus control were not affected. Correct choice latencies were slightly increased and only significant in the 5000 mg/m3 exposure group. Drink response latency was not significantly changed. No significant effects were observed in functional observational measurements and in measurements of motor activity. Short-term, high-level exposure to Hydrocarbons, C_{10}-C_{12}, isoalkanes, <2% aromatics induced mild, non-persistent neurobehavioral effects on measures of learned performance. Effects were observed during or after 3 consecutive 8 hour exposures at the highest tested concentration of 5000 mg/m3. Exposure to 500 mg/m3 or 1500 mg/m3 of Hydrocarbons, C_{10}-C_{12}, isoalkanes, <2% aromatics did not induce exposure-related neurobehavioral effects. The effects are consistent with narcosis and the NOAEC = 1500 mg/m3.

The potential for isoparaffinic hydrocarbons to produce acute central nervous system effects in CFW mice was evaluated. The animals were exposed for approximately 30 minutes in operant conditioning chambers modified for vapor exposure. The parameters measured were locomotor activity and ability to respond in tests of schedule-controlled operant behavior. There were two solvents with relevance to this category, once containing C_9-C_{11} constituents and the other C_{10}-C_{12}. The mice exposed to the C_9-C_{11} isoparaffinic solvent exhibited increased locomotor activity at levels that were significantly elevated above control values at 4000 and 6000 ppm (34,846 mg/m3), but no significant differences were found in the test for schedule-controlled operant behavior. Exposure to the C_{10}-C_{12} isoparaffinic solvent did not result in significant effects in either study. The authors of this study noted that because of its low vapor pressure, it was difficult to produce high vapor concentrations of the C_{10}-C_{12} isoparaffinic solvent.

Rats were exposed to wholly vaporized light alkylate naphtha distillate (LAND-2) (CAS RN 64741-66-8) generated in nitrogen, by inhalation in whole-body exposure cages 6 h/d, 5 d/wk for 13 wk at analytical concentrations of 668, 2220, and 6646 ppm (2.4, 8.1, and 24.3 g/m3). Neurobehavioral evaluations of motor activity (MA) and functional operational battery (FOB) were performed pretest and during wk 5, 9, 14, and 1 8 (recovery groups). Animals were not exposed to LAND-2 on the days of neurobehavioral testing. Exposure days were added to ensure that each animal received at least 65 exposures. Following 13 wk of exposure, 12 animals/sex/group were necropsied and microscopic examination was performed on selected tissues. Nervous tissue from 6 rats/sex/group was also examined microscopically. At the end of the 4-wk recovery period, 12 animals/sex from the high and control groups were necropsied and selected tissues examined microscopically. All animals survived the treatment period and were sacrificed according to study design at the end of 13 wk or at 18 wk (recovery groups). No test-related observations were noted in the exposure chambers during any exposure period for any treatment groups or during non-exposure periods There were small but statistically significant changes in hematological and clinical chemistry parameters, but the authors judged these effects to not be toxicologically relevant. These results are not considered LAND-2 related.

In the assessment of motor activity, the authors concluded that the effects observed are not neurotoxic effects but are indicative of acute central nervous system depression. In the functional observational battery, there was no test-material-related effect on any endpoint evaluated within the functional observational battery of tests. Pathology - At the wk 13 terminal sacrifice there were no microscopic findings in the brain, spinal cord, or peripheral nerves that could be attributable to exposure to LAND-2. The NOAEC of LAND-2 for subchronic toxicity is 6646 ppm and 6646 ppm (24300 mg/m3) for neurotoxicity.

In an article summarizing neurotoxicity studies of C9-C14 aliphatic solvents, it was reported that these substances do not produce gross or pathological changes in the central or peripheral nervous system. In neurobehavioral studies there

were no effects in most of the parameters assessed, but the authors did report decreased motor activity in the dark period. There were no effects on neurochemical parameters. In neurophysiological tests, it was reported that there were statistically significant effects in flash-evoked potential, somatosensory; evoked potential and auditory brain stem responses at exposure levels of 400 (2339 mg/m3) and 800 (4679 mg/m3) ppm. The authors of the review suggested that the neurophysiological methods may be more sensitive than histopathological, neurobehavioral and neurochemical methods.

Human effects

There are a number of reports dealing with the potential for hydrocarbon solvent exposure to cause chronic neurological effects in humans. A review of the epidemiological literature regarding exposure to hydrocarbon solvents, focusing on white spirit, a C9-C11 aliphatic hydrocarbon solvent containing approximately 15-20% aromatics and described by the CAS RN of 8052-41-3, 64742-82-1, and 64742-88-7 has been conducted. Similar reviews have been conducted by the International Programme on Chemical Safety (IPCS) and Scientific Committee on Occupational Exposure Limit (SCOEL). The IPCS and SCOEL evaluations were also re-evaluated by the ECHA Committee for Risk Assessment (RAC). These evaluations include retrospective epidemiological studies involving painters with long-term exposure to white spirit. Confounding factors in these studies include co-exposure to other solvents and a lack of measured exposure data. Epidemiological studies reported an increased incidence of complaints of memory impairment, fatigue, impaired concentration, irritability, dizziness, headache, anxiety and apathy. Several studies that included neuropsychological tests demonstrated impairment in some of these tests; primarily in the short-term visual memory test and in the symbol-digit test. In some studies, life-time exposure to high concentrations of white spirit was correlated with an increase incidence of effect. Using a weight of evidence approach, the RAC concluded that chronic exposure to these white spirits cause adverse central nervous system (CNS) effects that can progress in severity. These CNS effects can include deficits in psychomotor, perception, memory parameters, and disturbances in mood. With respect to the C9-C14 aliphatic hydrocarbon (<2% aromatics) category, it is not known whether the effects attributed to white spirit were due to the aliphatic or aromatic constituents or a combination thereof.

Chemicals in the category C9-C14 aliphatic (≤ 2%) hydrocarbon solvents posses properties indicating a hazard for human health (chemical pneumonitis if taken in to the lungs as liquids, severe irritant dermatitis due to defatting with prolonged or repeated exposure, liver enlargement and kidney changes in male rats in repeated dose toxicity studies [oral and inhalation; these changes may be secondary findings], increase in the frequency of kidney and adrenal gland tumors in male rats and liver tumors in female mice, potential for central nervous system effects). Adequate screening-level data are available to characterize the human health hazards of substances in the C9-C14 aliphatic (≤ 2%) hydrocarbon solvent category for the purposes of the OECD Cooperative Chemicals Assessment Programme.

Environment

Members of the C_9-C_{14} Aliphatic [≤2% aromatics] Hydrocarbon Solvents Category have the potential to volatilize from surface waters, based on Henry's Law constants (HLC) representing volatility for category members that range from 4.76×10^4 to 1.67×10^6 Pa-m^3/mole (at 25°C). In the air, category members have the potential to rapidly degrade through indirect photolytic processes mediated primarily by hydroxyl radicals ($^{\bullet}OH$) with calculated degradation half-lives ranging from 0.42 to 1.10 days or 10.8 to 26.4 hours based on a 12-hr day and an $^{\bullet}OH$ concentration of 1.5×10^6 $^{\bullet}OH/cm^3$. Aqueous photolysis and hydrolysis will not contribute to the transformation of category chemical constituents in aquatic environments because they are either poorly or not susceptible to these reactions. These chemicals are unlikely to degrade by hydrolysis as they lack a functional group that is hydrolytically reactive.

Mackay Level III modeling indicates that category member constituents partition mostly to the sediment and soil compartments rather than air compartment when an equal emission rate (1000 kg/hr) to the air, water, and soil compartment is assumed. When release occurs only to either the air, or soil compartment, constituents are indicated in the modeling to partition largely to the compartment to which they are released. When released to the water compartment, constituents are indicated by the model to partition to either water or sediment.

When released primarily to the air compartment, the primary mode of removal would be via indirect photodegradation. Although the substances and their chemical constituents demonstrate a range of water solubility with most constituents having relatively low solubility, wet deposition of category chemical constituents is not likely to play a significant role in their atmospheric fate because of their rapid photodegradation. Volatilization to the air can contribute to the loss of category chemical constituents from aqueous and terrestrial habitats.

Determining the biodegradation potential of UVCBs can be challenging. The result for each multi-constituent substance (UVCB) characterizes the biodegradability of that substance as a whole, but it does not suggest that each constituent of the UVCB is equally biodegradable. As with all ready biodegradation test guidelines, the test system and study design used with these substances (OECD TG 301F) is not capable of distinguishing the relative contribution of the

substances' constituents to the total biodegradation measured (constituents with higher branching/cyclic structures may degrade to a lesser extent than linear and less branched structures). The n-paraffin constituents have the potential to biodegrade rapidly based on results that support their characterization as readily biodegradable (80 to 100% in 28 days). In comparison, iso-paraffinic and cyclo-paraffinic constituents are expected to demonstrate a slower rate of biodegradation based on results for several isoparaffinic substances and one cyclo-paraffinic substance. Data for the cyclic substance covers the lower carbon range (C_9 to C_{11}) and does not meet the readily biodegradable criteria. Therefore, constituents in the higher carbon range (C_{12} to C_{14}) are also not expected to meet this criteria. Multi-constituent members of the category biodegraded to a varied extent, based on studies that followed the OECD TG 301F. Biodegradation was dependent on their composition. The overall conclusion for C_9-C_{14} Aliphatic [≤2% aromatics] Hydrocarbon Solvents Category members: some components of the category members (i.e. n-paraffins) are readily biodegradable, but some (i.e. cyclic, tertiary and quaternary branched components) may be less biodegradable, and not meet the readily biodegradable criteria.

Category members have a potential to bioaccumulate, based on calculated log BCF values for constituents that range from 2.78 to 4.06, and calculated BCF values of 598 to 11,430 L/kg wet-weight, based on the Arnot and Gobas model, that take into account biotransformation of the chemicals in fish tissue. Results of BCF studies for several constituent chemicals of category members are also available. Reported BCF ranges for n-dodecane range from 400 (aqueous) to tentative 4408 (dietary) l/kg wet weight, using fathead minnow and rainbow trout (although there are no internationally agreed methods for calculating BCF values from dietary studies). Also reported are a BCF value for iso-nonanes of 1468 l/kg wet weight with carp. Additional studies for other constituent chemicals were reported, on a wet-weight basis, for decahydronaphthalene, with values of 1290 to 2500 l/kg (carp) and 3313 l/kg (trout); and trimethyl-cyclohexane and tetramethyl-cyclohexane of 2168 l/kg and 4734 l/kg for trout, respectively. Determining the bioaccumulation potential of UVCBs can be challenging. BCF values for n-paraffins, iso-paraffins, and cycloparaffins can be different due to differences in metabolism. Constituents with higher branching/cyclic structures may therefore bioaccumulate to a greater extent than linear and less branched structures. It should be noted that for highly lipophilic constituents uptake through the diet may exceed the direct uptake through water. Estimated BAF values of 723 to 390,400 1/kg wet as derived by the BCFBAF model (Arnot and Gobas, upper trophic level including biotransformation rate estimates) of EPISuite were disregarded in this analysis because metabolism in the gut (which effectively reduces the dietary assimilation efficiency assumed in the food chain model calculation) is not specifically considered in isolation in the current model and may over-estimate bioaccumulation potential.

Acute aquatic toxicity data are available for fish, invertebrates, and freshwater algae. It may be shown that paraffinic hydrocarbons with a carbon number of 11 or greater (log Pow>5.5) do not exhibit acute aquatic toxicity due to water solubility limitations and slow uptake kinetics. Paraffinic hydrocarbons with a carbon number of 10 and below, are expected to exhibit acute aquatic toxicity in the range of 1 to 10 mg/L (based on nominal loadings), although measured LC_{50} and EC_{50} values of 0.01 to 0.2 mg/L have been reported. Cyclic paraffins in the C_9 to C_{10} range have also been shown to exhibit acute aquatic toxicity in the range of 1 to 10 mg/L (based on nominal loadings). Chronic *Daphnia magna* reproduction studies with n-nonane (CAS RN 11-84-2), n-undecane (CAS RN 1120-21-4), and n-dodecane (CAS RN 112-40-3), reported NOEC values of 0.005 and 0.0057 to 0.010 mg/L for nonane and undecane, respectively, and greater than water solubility (0.004 mg/L) for dodecane. Chronic studies using *Daphnia magna* with a substance in the C_{10}-C_{12} isoparaffinic range (CAS RN 90622-57-4) indicated an effect (NOEC = 0.025mg/L, based on measured concentration), but isoparaffins in the C_{11}-C_{13} range showed no observed effects up to 1 mg/L (highest nominal loading tested) for CAS RN: 90622-58-5.

Chemicals in this category with a carbon length of C_{10} and below possess properties indicating a hazard for the environment (acute toxicity for fish, invertebrates, and algae) in the range of 0.1 to 10 mg/L) based on measured concentrations. Those category members with a carbon length of C_{11} and above are not expected to exhibit acute aquatic toxicity due to water solubility limitations and slow uptake kinetics; available chronic toxicity data for invertebrates, fish, and algae are in the range of 0.005 – 1.0 mg/L, based on measured concentrations. Category members have a potential to bioaccumulate. Some components of the category members (e.g. n-paraffins) are readily biodegradable, but some components (cyclic, tertiary and quaternary branched components) may be less biodegradable, and not meet the readily biodegradable criteria. Adequate screening-level data are available to characterize the environmental hazard for the purposes of the OECD Cooperative Chemicals Assessment Programme.

Production/Use/Exposure

Production

As reported to the U.S. Environmental Protection Agency for the year 2006, companies produced or imported the following volumes of C9-C14 Aliphatic [≤2% aromatic] hydrocarbon solvents. Note that the Volume Survey is overall volume for the entire individual CAS RN and includes fuels, solvents and all other uses. It is expected that the solvent

portion of the volume for the C_9-C_{14} Aliphatic [<2% aromatic] Hydrocarbon Solvents Category would be significantly lower than the aggregate production volume:

C_9-C_{14} Aliphatic Hydrocarbon Solvents (≤2% aromatic) Production Volumes

Normal Paraffins	**111-84-2**	Nonane	227-454 metric tons (500□000 to < 1□million lbs)
	124-18-5	n-Decane	4,500-22,500 metric tons (10 to < 50 million lbs)
	1120-21-4	n-Undecane	22,680- 45,359 metric□tons (50 to < 100 million lbs)
	112-40-3	Dodecane	22,680- 45,359 metric tons (50 to < 100 million lbs)
	629-50-5	Tridecane	22,680- 45,359 metric tons (50 to < 100 million lbs)
	64771-72-8	Paraffins, (petroleum), normal C5-20	45,359- 226,796 metric tons (100 to < 500 million lbs)
	129813-67-8	Alkanes, C12-14	No data
	93924-07-3	Alkanes, C10-14	No data
Isoparaffins	**68551-16-6**	Alkanes, C9-11-iso-	4,500-22,500 metric tons (10 to < 50 million lbs)
	68551-17-7	Alkanes, C10-13-iso-	4,500-22,500 metric tons (10 to < 50 million lbs)
	90622-57-4	Alkanes, C9-13	No data
	68551-19-9	Alkanes, C12-14-iso-	450-4500 metric tons (1 million to < 10 million pounds)
	90622-58-5	Alkanes, C11-15, iso-	No data
Multi-constituent Solvents	**64741-65-7**	Naphtha, (petroleum), heavy alkylate	226,796-450,000 metric tons (500 million to < 1 billion lbs)
	64742-47-8	Distillates, (petroleum), hydrotreated light	450,000 or greater metric tons (1 billion pounds or greater)
	64742-48-9	Naphtha, (petroleum), hydrotreated heavy	450,000 or greater metric tons (1 billion pounds or greater)
	64742-88-7	Solvent naphtha, (petroleum), medium aliph.	450,000 or greater metric tons (1 billion pounds or greater)

Production of these C_9-C_{14} aliphatic [≤2% aromatics] hydrocarbon solvents is differentiated from other refinery substances such as gasoline and diesel fuel by including additional processing steps leading to finished substances with narrow distillation ranges, removal of sulfur- and nitrogen-containing compounds, and low color. The aromatic content in these substances is controlled to meet specific performance characteristics. These additional refining steps provide these hydrocarbon solvents with qualities suitable for applications in consumer goods.

Use

Hydrocarbon solvents in the C_9-C_{14} range with aromatic content less than 2% are considered to have a medium rate of evaporation and have a number of applications, including automotive products, paints and coatings, degreasers, wood/floor wax, diluent in asphalt applications, and as a pesticide carrier base. The predominant commercial uses of C_9-C_{14} Aliphatic [≤2% aromatics] hydrocarbon solvent substances are in paints and coatings, industrial solvents.

Exposure

Occupational workers are predominately exposed to C_9-C_{14} aliphatic hydrocarbons, ≤ 2% aromatics, through the inhalation of vapour due to the volatility of the constituents but exposure via dermal contact can also occur.

The general population is exposed to C_9-C_{14} aliphatic hydrocarbons, ≤ 2% aromatics, primarily through vapour inhalation or through dermal contact during the domestic use of paints and lacquers containing these substances. Due to the use pattern of all members in the category consumer exposure is expected.