HIGH PRODUCTION VOLUME (HPV) CHEMICAL CHALLENGE PROGRAM

LUBRICATING OIL BASESTOCKS

CATEGORY ASSESSMENT DOCUMENT

Submitted to the US EPA

by

The American Petroleum Institute (API) Petroleum HPV Testing Group

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EXECUTIVE SUMMARY

This document addresses the potential mammalian and environmental hazards of petroleum substances known as lubricating oil basestocks (LOBs), also referred to as basestocks or lubricating basestocks. LOBs are the primary hydrocarbon components of industrial lubricants including engine oils, transmission fluids, hydraulic fluids, gear oils, metalworking oils, greases, heat transfer oils, general-purpose oils, and machine oils. The more intensively refined basestocks (reduced levels of undesirable components/impurities) may also be used as food machinery lubricants, pharmaceutical white oils, laxatives, body lotions, cosmetics, direct food additives, and products used in a number of food-contact applications.

There are three sources of basestocks for substances in this HPV Category, namely 1) distillate basestocks derived from crude oil, 2) residual basestocks derived from crude oil, and 3) re-refined oil distillate basestocks. Basestocks derived from crude oil are produced by distillation under vacuum to yield a range of distillate fractions (raw distillate basestocks) and a vacuum residuum (only from crude oil). Removal of the asphalt components of the vacuum residuum results in raw residual basestocks. Re-refined basestocks are produced from used lubricating oils by similar distillation steps.

These crude oil and re-refined basestock fractions may then undergo a series of extractive or transforming processes that improve the basestocks' performance characteristics and reduce or eliminate undesirable components. The result is groups of lubricating oils based on the degree of processing. These groups are 1) raw or mildly refined LOBs, 2) other LOBs, and 3) white mineral oil.

Among these three groups, raw or mildly refined distillate basestocks are assumed to contain higher levels of undesirable components, have the largest variation of hydrocarbon molecules and have potential carcinogenic and mutagenic activity. Among undesirable components, polycyclic aromatic compounds (PACs) are considered to present the most significant toxicological hazard. Substances in this group are therefore assumed to be "mildly refined" from a toxicological perspective based on their potential mutagenicity and dermal carcinogenicity.

"Other LOBs" are produced by removal or transformation of undesirable components such as PACs. If this additional processing is adequate, the basestock is considered "highly refined" from a toxicological perspective and will not be mutagenic or carcinogenic. While most currently marketed LOBs are expected to be highly refined, verification by testing or review of the refining process is needed to ensure that they are not potentially hazardous. Only white oils are highly refined by definition.

Physical-Chemical Properties

The substances in this category are complex petroleum materials composed primarily of saturated hydrocarbons with carbon numbers ranging from C15 to C50. At ambient temperatures lubricating basestocks are liquids of varying viscosities, with negligible vapor pressures and solubility in water.

Environmental Fate

The environmental fate of lubricating oil basestocks is determined by the individual hydrocarbons present. Because of their physical and chemical properties, these substances will tend to agglomerate rather than disperse if released to the environment. Although they have very low vapor pressures, individual hydrocarbon compounds at the lower molecular weight range (e.g., C15 compounds) may volatilize during weathering. Individual aromatic components that evaporate would be expected to undergo rapid indirect photodegradation. LOBs are not expected to partition to water, because the water solubility of their constituent hydrocarbons is also very low and the components do not undergo hydrolysis reactions. Modeled partition coefficients of the low molecular weight hydrocarbons (e.g., C15 compounds) typically exceed 5, with higher molecular weight hydrocarbons having partition coefficients >20. Environmental distribution modeling predicts that components would generally partition to soil. Once released to the environment, LOBs are not likely to undergo rapid biodegradation.

Ecotoxicity

Existing ecotoxicity data on lubricating oil basestocks adequately describes their potential toxicity. LOBs are not acutely toxic to freshwater fish, invertebrates or algae at the water solubility limits of their constituent hydrocarbons. Data indicate that acute toxicity thresholds were >1000 mg/L when these substances were tested as water accommodated fractions (WAF). Reproduction and survival were unaffected in adult aquatic invertebrates (*Daphnia magna*) exposed for 21 days to >1000 mg/L WAF fractions of LOBs. Offspring produced during the test also appeared healthy with no adverse effects noted.

Human Health Effects

Multiple acute toxicity studies on a variety of LOBs have consistently shown these materials to have low acute toxicity by dermal, oral, and inhalation routes. Experimental data were not available for repeated-dose dermal studies with raw or mildly refined LOBs, but modeled predictions of the dose expected to cause a 10% difference in sensitive endpoints ranged from 38 to 2,000 mg/kg. Several repeated-dose dermal studies with highly refined LOBs having a range of viscosities consistently demonstrated NOAELs for systemic toxicity in the range of 1,000 to 2,000 mg/kg/day. Repeated inhalation of highly refined LOBs resulted primarily in local effects in the lung that were largely a response to the physical presence of particles with low toxicity. An overall NOAEC for local effects in the respiratory tract is 210 mg/m^3 based on these studies, while a NOAEC for systemic effects probably exceeds 1,000 mg/m^3. In subchronic oral studies on white mineral oils, observed increases in weights of liver, lymph nodes, and spleen at the highest doses were associated with deposition of the lipophilic oil, but minimal pathological changes have been observed. Extensive follow-up testing has demonstrated a unique sensitivity of a rodent strain (Fischer 344) to mineral oil after ingestion, resulting in significant oil uptake, deposition, and a characteristic histological response. Other rodent strains and species do not display this sensitivity to ingested mineral oil. Effects of highly refined LOBs, with little PAC and other contaminants, should be qualitatively similar to white oils; but raw or mildly refined LOBs may present a greater hazard.

Based on the large number of tests on various LOBs, the raw or mildly refined LOBs would be expected to be mutagenic *in vitro* and possibly *in vivo*. Highly refined LOBs and white oils would not be expected to be mutagenic.

Experimental data on the dermal developmental toxicity of raw or mildly refined LOBs were not available, but modeled predictions of the dose expected to cause a 10% difference in sensitive endpoints ranged from 28 to 2000 mg/kg/day In contrast, NOAELs in dermal studies with highly refined LOBs and a white mineral oil were 900 to 2,000 mg/kg (the highest dose tested in a given study). Similarly, an inhalation study with a highly refined distillate LOB showed a NOAEC of 1,000 mg/m^3 and an oral study with a white mineral oil showed a NOAEL of 5,000 mg/kg/day.

Highly refined LOBs are likely to have little, if any, effects on reproductive parameters. Although reproductive toxicity of raw or mildly refined LOBs has not been determined directly, the NOAEL for reproductive toxicity is not expected to be lower than the NOAEL for developmental toxicity of petroleum substances with similar PAC content.

Regarding cancer, there is a large body of toxicity data relating to raw or mildly refined LOBs that dates back over 50 years. These LOBs produce skin cancer in the mouse and can possibly cause cancer of the respiratory tract upon inhalation of aerosols of the material. Highly refined LOBs do not produce dermal tumors in mice and are not expected to be carcinogenic.

1. DESCRIPTION OF LUBRICATING OIL BASESTOCKS

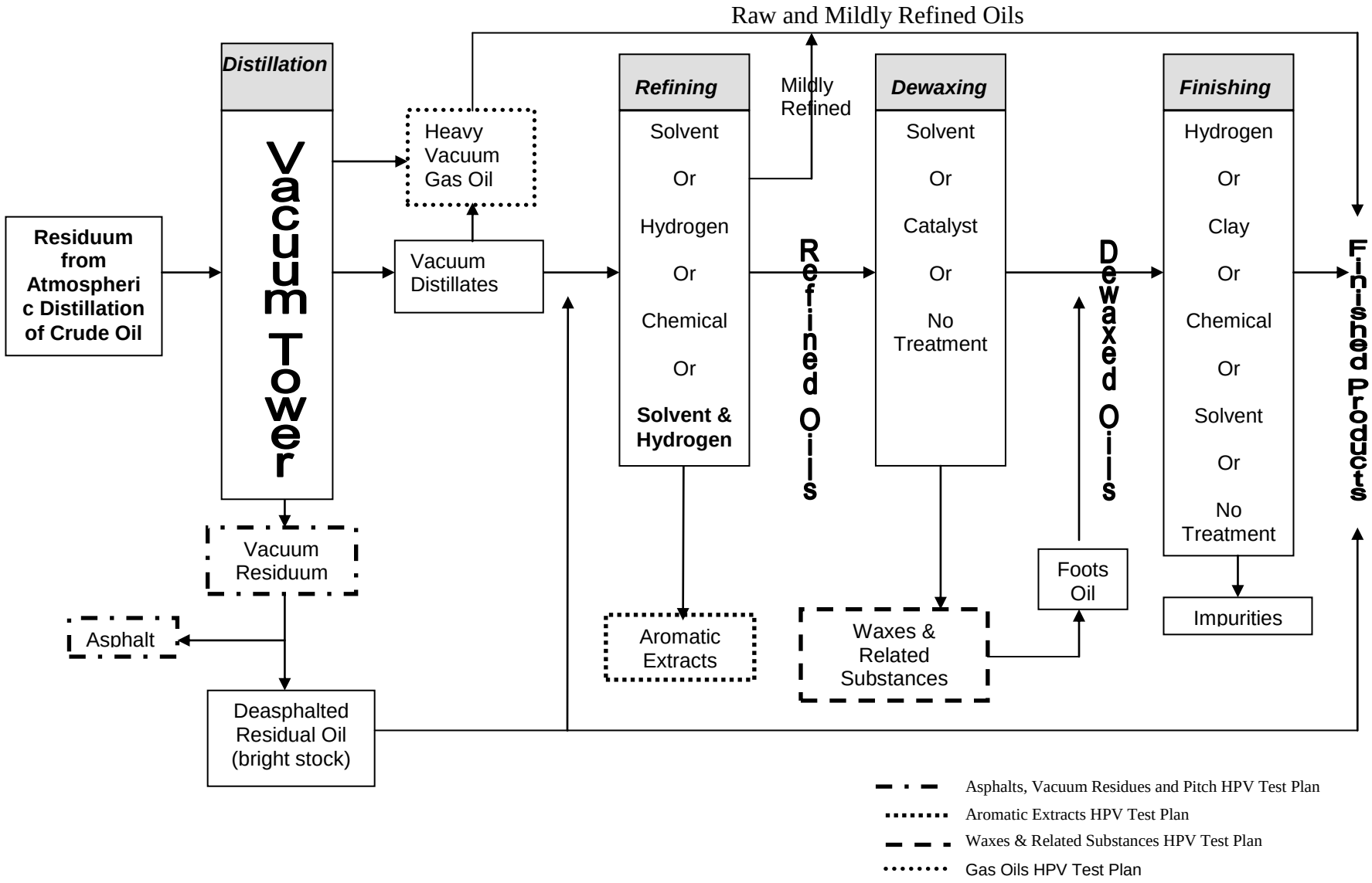
1.1. Definitions and Manufacture

Lubricating Oil Basestocks (LOBs) are substances derived from the refining of petroleum crude oil, primarily through the application of different processes such as solvent extraction or hydrogenation. LOBs are the basic starting liquid in the formulation of a variety of lubricants that provide lubrication, dissipation of heat, inhibition of corrosion, sealing, cleaning of moving parts, removal of debris or contaminants, and other functions in many applications.

The LOB category includes both refinery streams and finished products. The substances in this category are complex petroleum materials that typically boil between 570 to 1,110ºF (300 to 600°C) and are composed primarily of saturated hydrocarbons with carbon numbers ranging from C15 to C50. The molecular makeup of these oils consists of paraffinic, isoparaffinic, naphthenic, and aromatic hydrocarbon constituents that vary in complexity and carbon number. At ambient temperatures, all the materials in the category are liquids of varying viscosities with negligible vapor pressures and water solubility. Because they are complex substances, the lubricating oil basestocks are typically not defined by detailed compositional information but instead by process history, physical properties, and product use specifications. Whereas detailed compositional information may be limited, general compositional information can be inferred from the basestock's physical properties, e.g., the higher the boiling temperature range of a fraction, the higher the molecular weight of the oil's components.

As shown in the Figure 1, those LOBs derived from crude oil and included in the category are produced by the vacuum distillation of the residuum from atmospheric distillation of crude oil. This vacuum distillation produces a range of distillate fractions (raw distillate basestocks) and a vacuum residuum. Removal of the asphalt components (e.g., asphaltenes, resins) from the vacuum residuum results in raw residual basestocks. The raw distillate and residual basestocks can either be blended into other process streams or undergo additional refining in order to produce "finished" basestocks. The additional refining consists of a series of extractive or transforming processes that improve the basestocks' performance characteristics and remove, reduce, or transform undesirable components. An example of a transforming process is hydrocracking, a process in which aromatics are converted to naphthenics and paraffins by catalytically breaking carbon-carbon bonds under high pressure hydrogen.

Figure 1. Generalized examples of possible processes used in the production of LOBs.



The undesirable materials generally are either deleterious to product performance and/or are potentially carcinogenic. These undesirable components include aromatics, metals, waxes, and trace components such as sulfur. The aromatics include polycylic aromatic compounds (PACs), a group that encompasses polycyclic aromatic hydrocarbons (PAHs) and molecules previously called polynuclear aromatics (PNAs). Some PACs are heterocyclic aromatic ring molecules with inclusions of nitrogen, sulfur, and/or oxygen (N, S, and O). Aromatics have undesirable volatility and poor oxidative stability in most lubricant applications. Normal paraffins (waxes) have poor low temperature properties. Sulfur causes deposits, off color, and odor, while nitrogen causes deposits and promotes oxidation. The final premium lube basestocks have low levels of nitrogen and sulfur and are comprised predominantly of naphthenic and isoparaffinic hydrocarbons. Naphthenics have good low temperature viscosity and oxidative stability while isoparaffins possess excellent oxidation stability, good viscosity characteristics, and low volatility.

The more extensive the extractive and/or transforming processes that an oil undergoes, the more "severe" is its processing. Terms such as "mildly" and "highly" are also used to describe the degree of processing, although these terms are relative and need to be considered in the context of the overall process history. Within the basestock category, the raw or mildly refined basestocks contain the highest levels of undesirable components, have the largest variation of hydrocarbon molecules and in the case of distillate basestocks, have shown the highest potential carcinogenic and mutagenic activity. Because of the "subtractive" nature of basestock processing, streams that have been highly processed have much lower levels of undesirable components, a narrower range of hydrocarbon molecules, and very low toxicity.

This report uses the terms "highly refined" to describe those basestocks that have been refined such that they are not expected to present a significant toxicological hazard, primarily based on potential mutagenicity and dermal carcinogenicity. In contrast, "raw or mildly refined" basestocks have not been refined to that extent and could have a significant toxicological hazard. The distinction between "highly refined" and "raw or mildly refined" basestocks can be based on a number of considerations. Simple process criteria such as temperature and pressure during hydrotreatment (including hydrogenation and inactivation of PACs) do not provide adequate information to determine if sufficient refining has been performed to meet the toxicological criteria. More specific variables such as the design of equipment, selection of crude oil, hydroprocessing catalyst, temperature, residence time, and selection of solvents are among additional variables that contribute to the level of treatment of the final basestock. For that reason, various tests are used on the finished basestocks to determine whether their treatment has been sufficiently severe. Such tests include the optimized Ames assay (ASTM E 1687), IP346 assay (IP, 1980), and skin-painting tests in mice. Analysis of PAC content by GC (Roy et al., 1985; Roy et al., 1988) also provides useful supporting data.

There are three sources of basestocks for substances in this HPV Category, as listed here.

1) Distillate basestocks derived from crude oil
2) Residual basestocks derived from crude oil
3) Re-refined oil distillate basestocks from used lubricating oil

Unlike the distillate and residual basestocks derived from crude oil, re-refined oil distillate basestocks are made from a feedstock of used lubricating oils rather than virgin crude oils. The used oil is re-refined to remove impurities and contaminants such as PAC or solvents that have been introduced during use, collection, and/or storage of the used oil. Passenger vehicle engine oils (PVEOs), a major source of the used oil, accumulate materials from the wear on the engine as well as some compounds that form during combustion of fuels in the engine. Most notably, polycyclic aromatic compounds (PAC) are known to increase with time in mineral-oil based PVEOs (Hewstone, 1994; McKee and Plutnick, 1989). Some PACs are carcinogenic, and used PVEOs have been found to be mutagenic in bacteria (Pasquini and Monarca, 1983; Dutcher et al, 1986; Granella and Clonfero, 1991) and carcinogenic in chronic dermal studies in mice (Grimmer et al, 1982; McKee and Plutnick, 1989; Singer et al, 1986). An adequate re-refining process must be designed to remove or transform these contaminants to produce re-refined oils with acceptable performance characteristics and toxicological properties.

During their production, the distillate and residual LOBs derived from crude oil and the re-refined LOBs may undergo a series of extractive or transforming processes that both improve the basestocks' performance and reduce or eliminate undesirable components. This results in three groups based on the degree of processing.

1) Raw or mildly refined LOBs
2) Other LOBs
3) White mineral oils.

Among these groups, raw or mildly refined distillate basestocks are assumed to contain the higher levels of undesirable components, have the largest variation of hydrocarbon molecules and have potential carcinogenic and mutagenic activity. Among undesirable components, PACs are considered to present the most significant toxicological hazard. Raw or mildly refined distillate basestocks are assumed not to be "highly refined" from a toxicological perspective based on their potential mutagenicity and dermal carcinogenicity.

The chemical name of many basestocks does not provide sufficient information to determine if a given sample of the basestock will meet the criteria for being highly refined, even though basestocks with that chemical name generally meet the criteria. For that reason, several basestocks have been placed in the subgroup of "other LOBs". Basestocks in this subgroup are expected to be highly refined and to pass predictive tests such as those described above. However, this assumption should be verified by an evaluation for a given basestock before that basestock can be designated as "highly refined". As described previously, verification can be done through documentation of process history or with screening tests such as the optimized Ames test and/or the IP346 test.

Only white mineral oils are highly refined by definition. White mineral oil is manufactured by very severe refining processes such as deep solvent extraction, heavy hydrotreatment, and other finishing steps. PAC levels and the overall toxicity of these oils have been known for many years to be extremely low. Also, in the USA, white mineral oils must meet stringent government product specifications for indirect or direct food contact use or in pharmaceutical applications.

1.2. Assignment of CAS Numbers

The CAS numbers and definitions of refinery streams, including LOBs, were developed in response to Section 8(b) of the Toxic Substances Control Act. This section of TSCA required identification and registration with the Environmental Protection Agency before July 1979 of each "chemical substance" being manufactured, processed, imported or distributed in commerce. Due to analytical limitations and known variability in refinery stream composition, identification of every specific individual molecular compound in every refinery process stream under all processing conditions was impossible. Recognizing these problems, the American Petroleum Institute (API) recommended to the EPA a list of generic names for refinery streams consistent with industry operations and covering all known processes used by refiners. The list, including generic names, CAS numbers and definition of each stream, was published by the EPA as "Addendum I, Generic Terms Covering Petroleum Refinery Process Streams."

Because of the variability inherent in the processing of petroleum materials, the definitions API developed for the CAS numbers are qualitative in nature, written in broad, general terms. The definitions often contain ranges of values, with little if any quantitative analytical information or concern for possible compositional overlaps. Many of the definitions also include information on the material's process history. In fact, process history and not chemical composition was one of the primary criteria used by API to differentiate streams and assign CAS numbers.

In practice, process history was defined as the final process step a refinery stream had undergone. Information on intermediate processing steps was generally not included in the CAS definition. The result is that the CAS definitions for the LOBs often do not provide an accurate assessment of the refining history for a specific stream. For example, a light paraffinic stream that has been solvent-refined, then hydrotreated, and finally dewaxed will be given the same CAS number as a stream which has only been dewaxed:

> Distillates (petroleum), solvent-dewaxed light paraffinic (CASRN 64742-56-9): A complex combination of hydrocarbons obtained by removal of normal paraffins from a petroleum fraction by solvent crystallization. It consists predominantly of hydrocarbons having carbon numbers predominantly in the range of C15 through C30 and produces a finished oil with a viscosity of less than 100 SUS at 100°F (19cSt at 40°C).

The 36 CAS numbers covered by this document are listed in Appendix 1. The raw or mildly refined distillate LOBs are assumed not to be highly refined. White mineral oil is assumed to be highly refined because it meets government specifications for specific applications. For "other LOBs", it is not possible to determine the severity of refining from the CAS number alone due to the lack of details on process history in many of the CAS definitions.

1.3. Uses

LOBs are the primary hydrocarbon components of industrial lubricants including engine oils, transmission fluids, hydraulic fluids, gear oils, metalworking oils, greases, heat transfer oils, general-purpose oils, and machine oils. The more intensively refined basestocks (reduced levels of undesirable components/impurities) may also be used as food machinery lubricants, pharmaceutical white oils, laxatives, body lotions, cosmetics, direct food additives, and in a

number of food-contact applications.

1.4. Typical Physical and Chemical Properties

Table 1 contains physical and chemical properties for selected typical LOBs. As discussed previously, it is not possible to determine the degree of refining for many of the LOBs by the CAS number alone. Nonetheless, the LOBs in Table 1 are generally expected to be highly refined.

Table 1. Physical and Chemical Properties of Selected Lubricating Oil Basestocks

Basestock Description	Kinematic viscosity *		Flash Point (°C)	Pour Point (°C)	Density (kg/l)	Average Molecular Weight
	at 40°C (mm^2/s)	at 100°C (mm^2/s)				
Distillate Basestocks Derived From Crude Oil						
Solvent-dewaxed, light paraffinic (64742-56-9)	8.4	2.4	157	-18	0.85	280
Solvent-dewaxed, heavy paraffinic (64742-65-0)	25.1	4.8	204	-12	0.86	390
Hydrotreated, light paraffinic (64742-55-8)	17.0	3.7	190	-18	0.86	360
Hydrotreated, heavy paraffinic (64742-54-7)	73.9	9.1	232	-9	0.88	500
Hydrotreated, light naphthenic (64742-53-6)	8.5	2.2	145	-60	0.87	290
Hydrotreated, heavy naphthenic (64742-52-5)	145	10.5	220	-24	0.91	440
Residual Basestocks Derived From Crude Oil						
Solvent-dewaxed residual oil (64742-62-7)	1300	50	285	-6	0.95	700
Re-refined Oil Distillate Basestock						
Lubricating oils (petroleum), hydrotreated spent (64742-58-1)	11.8 – 46	2.9 – 7.0	180 - 240	-18 to -12	0.858 – 0.867	325 - 470

*Kinematic viscosity is often expressed in Centistokes (cSt). 1 mm^2/second (mm^2/s) = 1cSt.

Data on distillate and residual basestocks derived from crude oil are derived from CONCAWE (1997).

1.4.1 Physical/Chemical Properties - Distillate Basestocks Derived from Crude Oil

Distillate basestocks derived from crude oil are found in the majority of the lubricating products sold to the public and contain components with boiling points typically ranging from 570 to 1,110°F (300 to 600°C) (CONCAWE, 1997). Distillate basestocks are often described as either "naphthenic" (saturated ring hydrocarbons) or "paraffinic" (straight or branched chain hydrocarbons) depending on their crude source and/or the dominant hydrocarbons present. The difference between naphthenic and paraffinic basestocks is one of relative percentage since naphthenes and paraffins are present in both types of oils. Thus, a highly purified medicinal white oil might be called a paraffinic oil if it is 60% paraffins and 30% naphthenes or a naphthenic oil if it is 60% naphthenes and 30% paraffins. Basestocks are also often described as either "light" (viscosity less than 19 cSt @ 40°C) or "heavy" (viscosity greater than 19 cSt @ 40°C). The distinctions between naphthenic and paraffinic or between light and heavy LOBs are

primarily used to distinguish parameters for product applications and lubricant quality rather than health or safety characteristics, since a significant amount of toxicology data exists that shows little differentiation among these four classifications (see robust summary).

Among the distillate basestocks derived from crude oil, the raw or mildly refined basestocks receive no or minimal treatment beyond the initial vacuum distillation. Consequently, they contain the highest levels of undesirable components, have the largest variation of hydrocarbon molecules and have shown the highest carcinogenic and mutagenic activity. Raw or mildly refined distillate basestocks are used in only a small number of applications such as certain general-purpose lubricants that are consumed in use (once-through lubricants) and heat treatment oils. Because human exposures to raw distillate basestocks are limited to occupational settings, human exposures are restricted to droplet aerosols, liquid on the skin, and occasional accidental ingestion. However, these oils are clearly identified by the manufacturers as potential carcinogens and hazardous to health.

Almost all commercial basestocks used in the United States are highly refined. For the purposes of the HPV program, a critical feature of the distillate basestocks is the severity of the refining or processing that any particular oil has undergone. The focus on the degree of processing is supported by the physical and chemical characteristics of the materials, the subtractive nature of the processing the basestocks undergo, and the existing toxicology database. Numerous tests have shown that a lubricating basestock's mutagenic and carcinogenic potential correlates with its content of 3-7 ring PAC and the level of DMSO-extractables, both characteristics that are inversely related to the degree of processing (Doak, et al., 1983; Halder, et al., 1984; IARC, 1984; Kane, et al., 1984; Singer, 1986; Chasey, et al., 1993; Roy, et al. 1988, 1996; Blackburn, et al., 1984; 1986; 1996; CONCAWE, 1994; European Union 1994). The same inverse relationship exists for non-carcinogenic endpoints in subchronic studies and for developmental toxicity as shown both by data compiled for this program and by the development of empirical models which predict systemic and developmental effects based on PAC content (Simpson, et al.; 2008; API, 2008; TERA, 2008).

Highly refined distillate basestocks are produced from raw basestock fractions by additional processing designed to reduce or transform the undesirable components (see Figure 1). In general, each additional step of processing (increasingly severe processing) results in

1) lower levels of unwanted components, such as aromatics (including PACs), heterocyclics, waxes and trace components such as sulfur,
2) a narrower range of hydrocarbon molecules (increasing concentration of paraffins and naphthenes), and
3) reduced or non-detectable carcinogenic and mutagenic activity.

Very highly refined basestocks (white oils) undergo numerous processing steps that essentially eliminate or transform all undesired components, including aromatics. These very highly refined white oils are used for medical purposes and to lubricate machinery and other equipment when there is potential for contact with food. When used in food, food contact, cosmetic, pharmaceutical and related applications, white oils have to meet stringent purity requirements as described in the respective national Pharmacopoeia and international legislation. These regulations generally specify melting ranges, color, polycyclic aromatic hydrocarbon content and

other impurity limits (US FDA, 2002; USP, 2002; CONCAWE, 1984, JECFA 2002). Refined lubricants destined for non-medicinal/food/cosmetic applications are not processed to the same level of severity as the white oils.

As examples, Table 2 contains detailed compositional and physicochemical properties for two samples that represent the boundaries of the distillate basestocks in terms of possible health effects. The raw oil (API Sample 84-01) was carcinogenic in a skin-painting assay in mice and would be expected to have appreciable amounts of PACs. In contrast, the medicinal grade white oil has essentially no PACs and could be used as a food additive or laxative, or for other medicinal purposes.

Table 2. Physical and Chemical Properties of Representative Distillate Basestock Samples

	Raw[1]	Highly refined[2]
Name	Light paraffinic distillate	White mineral oil
CAS Number	64741-50-0	8042-47-5
Avg Molecular Weight (gm/mol)	300	320
Density @15°C	0.8651	0.857
Viscosity @40°C (centistokes)	14.07	13.3
Viscosity @100°C (centistokes)	2.79	3.08
Pour Point (°F)	+ 60	-32.8
Distillation °F @ 760mm		
5% (vol)	658	509
50%	711	689
95%	790	833
Refractive Index RI units @20°C	1.4815	1.4688
Total Sulfur (wt *%)*	0.38	<.0001
Heavy Metals Total mg/kg	<1	<1
Hydrocarbon Type		
Nonaromatics (wt %)	79.1	
Aromatics (wt %)	20.9	

1) API sample 84-01 (API, 1987b)
2) CONCAWE Report 93/56 (1993), Page 3, Table 2, Sample N10

1.4.2 Physical/Chemical Properties - Residual Basestocks Derived from Crude Oil

Residual basestocks are derived from the residuum of the vacuum distillation tower and may contain components boiling as high as 800°C (CONCAWE, 1997). As can be seen from Table 1, the residual oils have molecular weights that are much higher than the distillate basestocks. Residual basestocks are primarily used in situations requiring oils with high viscosity, e.g. gear oils.

Although residual oils tend to have relatively higher PAC levels when assayed by traditional methods (e.g., IP346), no adverse effects have been seen in either i*n vitro* mutagenicity or dermal carcinogenicity testing of residual basestocks, regardless of the degree of processing they have

undergone. Ultraviolet, HPLC/UV, GC/MS, and infrared analyses of these oils indicate that the aromatics they contain are predominantly 1-3 rings that are highly alkylated (paraffinic and naphthenic). Because these alkylated 1-3 ring aromatics are found in such a high boiling material (> 1070°F), it is estimated that their alkyl side-chains would be approximately 13 to 25 carbons in length. These highly alkylated aromatic ring materials are either devoid of the biological activity necessary to cause mutagenesis and carcinogenesis or are largely not bioavailable to target cells within the organism (Roy, et al., 1988). Nonetheless, most of the CAS numbers in this group require screening by IP346 or other suitable methods to verify that refining has been sufficient to produce oils which are "highly refined" in a toxicological sense.

1.4.3 Physical/Chemical Properties - Re-Refined Oil Distillate Basestocks

Examples of information on physical and chemical properties of re-refined oil distillate basestocks from one supplier are in Table 3. Samples of re-refined oils should meet the criteria in ASTM D6074 (Standard Guide for Characterizing Hydrocarbon Lubricant Base Oils).

Table 3. Examples of Physical and Chemical Properties of Re-Refined Oil Distillate Basestock Samples

	Low Viscosity Re-Refined Oil	Higher Viscosity Re-Refined Oil
CAS Number	64742-58-1	64742-58-1
Avg Molecular Weight (gm/mol)	325	470
Specific Gravity @15°C	0.8580	0.8670
Viscosity @40°C (centistokes)	11.8	46.0
Viscosity @100°C (centistokes)	2.9	7.0
Pour Point (°F)	-0.4	10.4
Noack Distillation (wt %)		8
Refractive Index RI units @20°C	1.4746	1.4771
Total Sulfur (ppm)	250	340
Hydrocarbon Type		
Saturates (wt %)	85.0	89.0
Aromatics (wt %)	14.7	10.7
Polar Compounds	0.3	0.3

1.5 Analytical Characterization

Depending on the crude oil and refining conditions, some refinery substances contain PACs. Although similar to PAHs that contain two or more fused-aromatic rings consisting only of carbon and hydrogen, PACs are a broader group of compounds that also includes heteroatomic compounds in which one or more of the carbon atoms in the PAH ring system are replaced by nitrogen, oxygen, or sulfur atoms. Hundreds to thousands of individual PACs are produced during the formation of crude oil as organic matter is converted into petroleum under elevated pressure and moderate temperatures (130 – 150 °C). The resulting PACs include a complex variety of parent (i.e., unsubstituted) and alkylated structures. The alkyl-substitutions are usually one to four carbons long and can include non-carbon compounds such as sulfur. Multiple alkyl and cycloparaffin substitutions of the parent structure are also common, especially in higher

boiling fractions of petroleum. The relative abundance of the alkylated polycyclic aromatics (C1-C4) in petroleum far exceeds the abundance of the parent compounds (C0) (Speight, 2007). The fact that the concentration of alkylated polycyclic aromatics is much greater than the parent polycyclic aromatics is the main feature of the PACs found in petroleum (Altgelt and Boduszynski, 1994).

The PAC content (expressed as a "PAC profile", the weight percent in the sample of each ring-class of PACs, such as 1-ring, 2-ring, etc.) of some petroleum substances has been shown to be highly correlated with biological and toxicological effects in repeated-dose and developmental toxicity studies (Simpson, et al 2008). For that reason, available data on the percent of each ring-class of PACs in individual samples are shown in Appendix 2 for the raw or mildly refined LOBs.

2. CATEGORY DEFINITION AND JUSTIFICATION

The following assumptions based on observations were made during the analysis of existing data and evaluation of the adequacy of those data.

1) The materials included in the Lubricating Oil Basestocks category are related in both process and physical/chemical perspectives.
2) The potential human health effects of a specific distillate basestock derived from crude oil or used oil is inversely related to the severity and/or extent of processing the oil has undergone, because
    a) the potential for adverse effects of these materials are associated with undesirable components (PACs) and
    b) the levels of the undesirable components and impurities are inversely related to the degree of processing.
3) Lubricating oil basestocks (derived from crude oil or used oil) that receive the same extent of processing will have similar toxicities.

CAS numbers and descriptions within the HPV Lubricating Oil Basestocks are in Appendix 1. The rationale behind combining these refinery streams into a category was based upon the similarity of production processes within the refinery. More specifically, all are produced from vacuum distillates via additional processing, yielding substances having relatively low PAC and relatively low biological activity. The physical/chemical properties of these substances are directly related to their carbon ranges and to a much lesser extent to the paraffinic or naphthenic character of the feedstocks from which they were derived. The carbon ranges of paraffinic and naphthenic oils as well as the absence or reduced levels of aromatic or PAC species influence the volatility, water solubility, and viscosity of these substances, which in turn determines their environmental fate, ecotoxicity, and potential bioavailability of toxic components.

3. TEST MATERIALS

3.1 Previous Studies

LOBs have been adequately tested in a variety of toxicity tests. Those tests are summarized in the following pages. Additional data are available from human experience. It is worth noting that the steps were taken by the industry several decades ago to increase refining severity to reduce the level of PACs in LOBs intended for finished lubricants. This shift occurred because of evidence of skin cancer in humans occupationally exposed to unrefined LBOs and confirmation in animal studies that PACs were the causative agents. The present document and supporting data focus on LOBs as they are currently manufactured and not on data from those older LOBs that were not highly refined.

3.2 New Studies

Since the original submission of the Test Plan (March 2, 2004), the API has obtained additional compositional information on representative samples of LOB supplied by US refineries sponsoring this category. These data have helped to clarify and characterize compositional variability among category members. As explained in subsequent sections, the data from PAC-2 analyses have been used to predict outcomes for some endpoints for some substances.

4. PHYSICAL-CHEMICAL PROPERTIES

4.1 Physical-Chemical Screening Information Data Set (SIDS)

The physical-chemical endpoints in the HPV chemicals program include the following:

- Melting Point
- Boiling Point
- Vapor Pressure
- Octanol/Water Partition Coefficient
- Water Solubility

Because the substances in this HPV category are complex and have variable composition, it is not possible to measure or calculate a single numerical value for most of the physicochemical properties. The range of individual hydrocarbon components in LOBs defines these properties. For example, a LOB does not have a defined boiling point, but rather a boiling point range.

Although some data for products in this category exist, not all of these endpoints are defined and a consensus database for chemicals that represent products in this category does not exist. Therefore, calculated and measured representative data has been identified and a technical discussion provided, where appropriate. The EPI-Suite™ computer model, as discussed in the US EPA document entitled "The Use of Structure-Activity Relationships (SAR) in the High Production Volume Chemicals Challenge Program" has been used to calculate physical/chemical properties of representative constituents of lubricating basestocks (US EPA, 2000).

Because of the diversity of compounds encompassing lubricating basestocks, it is not feasible to model the physicochemical endpoints for each potential compound. Rather, modeling efforts were directed towards those hydrocarbon components of the basestocks that would most likely enter various environmental media. Since molecular weight and structural conformation determine in large part the solubility and vapor pressure characteristics of the hydrocarbons,

modeling focused on representative lower molecular weight hydrocarbons (paraffinic, naphthenic and aromatic). The C15 hydrocarbons were selected since they are the shortest carbon chain length compounds in the basestocks, which consist primarily of C15 to C50 compounds (CONCAWE, 1997). C20 and C50 hydrocarbons were also modeled to provide a broader representation of the component hydrocarbons.

4.1.1. Melting Point

For complex substances such as petroleum products, melting point may be characterized by a range of temperatures reflecting the melting points of the individual components. To better describe the physical phase or flow characteristics of petroleum products, the pour point is routinely used. The pour point is the lowest temperature at which movement of the test specimen is observed under prescribed conditions of the test (ASTM, 2002a). The pour point increases as an oil's viscosity increases. Pour point values for a number of lubricating basestocks have been reported in the literature (Doak, et al., 1983; CONCAWE, 1984; 1993; 1997; Baker, 1984; Singh and Gulati, 1987; Sequeira, 1992; Montanari, et al., 1999). For example, the pour points measured for eight various raw and highly refined basestocks ranged from –60 °C to –6 °C (CONCAWE, 1997). The American Petroleum Institute (1987b) measured the pour points of three LOBs by ASTM D97, a method standardized for petroleum products. The pour point values for a hydrotreated light naphthenic oil (CAS 64742-53-6), a hydrotreated heavy naphthenic oil (CAS 64742-52-5), and a light paraffinic oil (CAS 64741-50-0) were -29°C, +4.4°C, and +15.5°C, respectively.

Conclusions: Pour points vary among different basestocks. Measured pour points for raw and highly refined basestocks have ranged from –60°C to +15.5°C.

4.1.2. Boiling Point:

Because they are complex substances, lubricating basestocks do not have a single numerical value for boiling point, but rather a boiling range that reflects the individual components. Constituent hydrocarbons of oils produced from vacuum distillation have boiling points ranging from about 300 to 600°C for the distillate fraction and up to 800°C for the residual fraction (CONCAWE, 1997). Boiling ranges for a variety of lubricating basestocks have been reported (CONCAWE, 1984; McKee, et al., 1989b; Skisak, et al., 1994; Kramer, et al., 1999). For example, distillation ranges have been reported for three lubricating basestock refinery streams; 313 to 432 °C (raw, light paraffinic distillate: CAS No. 64741-50-0), 232 to 418 °C (hydrotreated light naphthenic; CAS No. 64742-53-6), and 338 to 604 °C (hydrotreated heavy naphthenic; CAS No. 64742-52-5) (API, 1987b).

Conclusions: Distillation ranges vary among different basestocks. Cited ranges span 232 to 604°C. Residual basestocks can contain constituents that boil up to 800°C.

4.1.3. Vapor Pressure

Vapor pressures of lubricating basestocks are reported to be negligible (CONCAWE, 1997). In one study, the measured vapor pressure of a solvent de-waxed residual basestock was 1.7×10^{-4}

Pa by the vapor pressure balance method (Hazelton UK, 1991). However, this result is outside the sensitivity range for the method. OECD (1995) cites a sensitivity range of 10^{-3} to 1 Pa for the vapor pressure balance method. While it may not be possible to accurately measure the vapor pressures of basestocks due to limitations of the methods, the Epi-Suite™ (US EPA, 2000) computer program can provide estimated vapor pressure values for individual constituents. Since basestocks are composed of C15 to C50 paraffinic, naphthenic, and aromatic hydrocarbon isomers, representative components were selected to calculate a range of vapor pressures. For substances such as petroleum products, vapor pressure is dependent on the vapor pressure of each constituent and the mole fraction of the constituent in solution (Raoult's Law). The estimated vapor pressure values for these selected components of basestocks ranged from 1×10^{-16} Pa to 0.46 Pa. Based on Raoult's Law the expected total vapor pressure for basestocks would be exceedingly low and likely below standard measurement techniques. According to CONCAWE (1997), at ambient temperatures, almost all lubricating oil basestocks have negligible vapor pressure.

Conclusions: Lubricating oil basestocks have negligible vapor pressure at ambient temperatures.

4.1.4. Partition Coefficient

For substances such as the LOBs, the percent distribution of the hydrocarbon groups (i.e., paraffins, naphthenes, and aromatics) and the carbon chain lengths determine in-part the partitioning characteristics. Generally, hydrocarbon chains with fewer carbon atoms tend to have lower partition coefficients than those with higher carbon numbers (CONCAWE, 2001). However, due to their complex composition, unequivocal determination of the log K_{ow} of these hydrocarbon substances cannot be made. Standard tests for partition coefficient are intended for single substances and are not appropriate for complex substances such as lubricating oil basestocks. However, it is possible to determine a distribution of partition coefficients by analytical techniques, and Shell (1998) attempted this for a residual oil (CAS 64742-62-7) using reverse phase thin layer chromatography. This is not a standardized method, but the description is similar to the reverse phase HPLC technique (OECD method 117) in that the test substance is compared to a mixture of reference substances having log Kow values from 1.1 to 6.3. The authors found no movement from the origin, and since the spot position was outside the calibration range, concluded the log Kow was >6 (Shell, 1998).

A perspective of the distribution of partition coefficients for hydrocarbons in lubricating oil basestocks also was provided by estimating the log Kow for representative structures using the WSKOW routine of the Epi-Suite™ models (US EPA, 2000). As described in the robust summary, selected C15, C20 and C50 hydrocarbons were evaluated. Results showed typical log K_{ow} values from 5.7 and higher for constituents having 15 carbon atoms. Those with longer carbon chains had substantially higher log K_{ow} values. The modeled values were consistent with log K_{ow} values of >4 for lubricating oil basestocks reported by CONCAWE (1997) as well as with the Shell (1998) data.

Conclusions: Estimated log K_{ow} values for constituent compounds in LOBs typically are >4.

4.1.5. Water Solubility

When released to water, basestocks will float and spread at a rate that is viscosity dependent. While water solubility of basestocks is typically very low, individual hydrocarbons exhibit a wide range of solubility depending on molecular weight and degree of unsaturation (CONCAWE, 2001). Decreasing molecular weight (i.e., carbon number) and increasing levels of unsaturation increases the water solubility of these materials. As noted for partition coefficient, unique values for water solubility of lubricating basestocks cannot be provided due to their complex characteristics, and standard tests for water solubility are intended for single substances and are not appropriate for complex substances such as lubricating oil basestocks. Therefore, the water solubilities of individual C15, C20, and C50 hydrocarbons representing the different groups making up basestocks (i.e., paraffins, naphthenes, and aromatics) were modeled using the WSKOW V1.40 subroutine of Epi-Suite™ (US EPA, 2000). Based on water solubility modeling of those structures, aqueous solubilities are typically much less than 1 ppm.

Conclusions: The estimated water solubility values for individual hydrocarbons representing the different groups that make up basestocks is typically much less than 1 ppm.

4.2 Assessment Summary for Physical-Chemical Endpoints

Lubricating oil basestocks have typical pour points between –60°C and +15.5°C. Boiling points of constituent hydrocarbons vary with the type of basestock, but may range between 232°C and 600°C for distillate basestocks and up to 800°C for residual basestocks. These substances have negligible vapor pressure and partition coefficients of >4 for constituent hydrocarbons. Water solubility is < 1 ppm.

5. ENVIRONMENTAL FATE

5.1 Environmental Fate Endpoints

To assess the environmental fate properties for the HPV program, the U.S. EPA has selected important fate endpoints by which these substances may be characterized. The environmental fate endpoints include the following:

- Photodegradation
- Stability in water [Hydrolysis]
- Transport Between Environmental Compartments [Fugacity/Distribution]
- Biodegradation

Because the materials included in this category are complex substances of differing compositions, it is not possible to measure or calculate a single numerical value for several of the properties related to environmental fate. Rather, these properties are defined by the range of individual hydrocarbon compounds in the LOBs. The typical battery of tests used to measure the environmental fate of a material is not easily performed on the materials of this category because of their physical and chemical properties. Therefore, components of the LOBs will be modeled where necessary using Epi-Suite™ (U.S. EPA, 2000).

5.1.1. Photodegradation

5.1.1.1. Direct Photodegradation

The direct photolysis of an organic molecule occurs when it absorbs sufficient light energy to result in a structural transformation. Only light energy at wavelengths between 290 and 750 nm can potentially result in photochemical transformations, although absorption is not always sufficient for a chemical to undergo photochemical degradation (Harris, 1982a). The degrees and rates at which these compounds might engage in direct photolytic reactions depend upon penetration of light with sufficient energy to affect a chemical change.

Saturated and one-ring aromatic hydrocarbons do not show absorbance in the 290 to 800 nm range and would not be expected to photodegrade. Polycyclic hydrocarbons have shown absorbance in this range of light energy and could potentially undergo photolysis reactions. The degrees and rates at which these compounds photodegrade depend on whether conditions allow penetration of light with sufficient energy to affect a change. For example, polycyclic compounds bound to sediments may persist due to limited energy absorption as a consequence of limited penetration of light.

5.1.1.2. Indirect Photodegradation

Components in LOBs that do not directly photodegrade (e.g., paraffins, naphthenes, and one-ring aromatic compounds) may be subject to indirect photodegradation. Indirect photodegradation is the reaction with photosensitized oxygen in the atmosphere in the form of hydroxyl radicals (OH^-). In general, lubricating basestocks have negligible vapor pressures and volatilization is not expected to be a significant removal mechanism for the majority of constituent hydrocarbons. However, some components (e.g., C15 branched paraffins and naphthenes) appear to have the potential to volatilize. The potential to undergo indirect photodegradation can be estimated using the atmospheric oxidation potential (AOP) model subroutine (AOPWIN V1.90) in the Epi-Suite™ computer models (US EPA, 2000). This program calculates a chemical half-life and an overall OH^- reaction rate constant based on a 12-hour day and a given OH^- concentration. Atmospheric oxidation rates and half-lives were calculated for the lowest molecular weight constituents of various components of lubricating oil basestocks (e.g., C_{15} hydrocarbon structures), since these would have the most potential to volatilize to the atmosphere. AOP half-life estimates for these compounds ranged from 0.053 to 0.66 days and show a lack of persistence in the atmosphere.

Conclusions:
While LOBs have negligible vapor pressure and would not be expected to partition to the atmosphere, any release to the air is expected to result in rapid decomposition by indirect photodegradation.

5.1.2. Stability in Water

Chemicals that have a potential to hydrolyze include alkyl halides, amides, carbamates, carboxylic acid esters and lactones, epoxides, phosphate esters, and sulfonic acid esters (Harris,

1982b). Because LOBs do not contain significant levels of these functional groups, these substances are not subject to hydrolysis.

Conclusions:
LOBs are stable to hydrolysis.

5.1.3. Transport between Environment Compartments (Fugacity/Distribution)

Fugacity-based multimedia modeling can provide basic information on the relative distribution of chemicals between selected environmental compartments (e.g., air, water, soil, sediment, suspended sediment and biota). The US EPA has agreed that computer modeling techniques are an appropriate approach to estimating chemical partitioning (fugacity is a calculated endpoint and is not measured). A widely used fugacity model is the EQC (Equilibrium Criterion) model (Mackay et al, 1996; Mackay et al, 1997). The EQC model is a Level 1 (i.e., steady state, equilibrium, closed system and no degradation) model that utilizes the input of basic chemical properties including molecular weight, vapor pressure, and water solubility to calculate distribution within a standardized regional environment. EPA cites the use of this model in its document "Determining the Adequacy of Existing Data" that was prepared as guidance for the HPV chemicals program (U.S. EPA, 1999).

Results of Level 1 models are basic partitioning data that allow for comparisons between chemicals and indicate the compartment(s) to which a chemical is likely to partition in the environment. One drawback of these and higher level models is their inability to predict the distribution of the entire set of constituents comprising complex petroleum streams. To gain an understanding of the potential environmental distribution for these complex substances, modeling was performed for different C_{15} and C_{50} compounds representing common isomeric structures in LOBs (e.g., isoparaffins, naphthenes, and aromatics). Therefore, the partitioning data represent the low and high ends of the molecular weight spectrum for representative hydrocarbon compounds making up these substances. Other compounds having molecular weights between the low and high ends of the molecular weight spectrum are expected to have partitioning behaviors that fall within the ranges.

Upon a release of these substances, the individual constituents will begin to partition in accordance with their own intrinsic physical-chemical characteristics. EQC modeling results show that constituent compounds in lubricating oil basestocks will partition principally to soil, although some of the lowest molecular weight constituents may enter the atmosphere (Table 4).

Table 4. Environmental Distribution of Representative Hydrocarbon Compounds in Lubricating Oil Basestocks Determine by the EQC Level 1 Fugacity Model.

	Percent Distribution in Environmental Compartment					
	Air	Water	Soil	Sediment	Susp Sed	Biota
C15 compounds	0.7 – 68	<0.1 - 1	31 - 97	0.7 - 2	<0.1	<0.1
C20 compounds	<0.1 – 9.0	<0.1	89 - 98	2	<0.1	<0.1
C50 compounds	<0.1	<0.1	98	2	<0.1	<0.1

Conclusions:
LOBs are complex substances comprised of hydrocarbon compounds having high molecular weights and low water solubilities. When released to the environment, individual hydrocarbons will partition in accordance with their specific physical-chemical attributes. Fugacity modeling of individual constituents in these substances shows that individual hydrocarbons will partition mostly to soil, with only the lowest molecular weight components distributing to the air. However, the physical state of these substances will limit the extent to which this occurs.

5.1.4. Biodegradation

Twenty-eight biodegradability studies have been reported for a variety of LOBs. Based on the results of ultimate biodegradability tests using modified Sturm and manometric respirometry testing the basestocks are expected to be, for the most part, inherently biodegradable. Biogradation rates found using the modified Sturm procedure ranged from 1.5 to 29%. Results from the manometric respirometry tests on similar materials showed biodegradation rates from 31 to 50%. Biodegradation rates measured in 21-day CEC tests for similar materials ranged from 13 to 79% (BP International Ltd., 1990a-j; 1991a-k; EMBSI, 1995a-d; Shell Research Ltd., 1986; 1987).

The biodegradation rates given above are supported by the conclusions of a CONCAWE review of the biodegradation data for lubricating basestocks (CONCAWE, 1997). The review concluded that the extent of biodegradation measured for a particular LOB is dependent not only on the procedure used but also on how the sample is presented in the biodegradation test. In spite of the presentation method, LOBs typically are not readily biodegradable in standard 28-day tests. However, since the oils consist primarily of hydrocarbons that are ultimately assimilated by microorganisms, these substances were considered to be inherently biodegradable.

Conclusions:
LOBs are not readily biodegradable. However, hydrocarbons in general are known to be inherently biodegradable.

5.2 Assessment Summary for Environmental Fate

Upon a release, the individual constituents in LOBs partition to different environmental compartments and degrade in accordance with their own physical-chemical properties. Most constituents will partition to the soil, although some of the lowest molecular weight compounds may enter the atmosphere. Those constituents that partition to the air are predicted to undergo rapid photodegradation via indirect pathways. Components in these substances are highly insoluble in water and do not undergo hydrolysis reaction; however, any dissolved fractions become available for biodegradation. The rate of mineralization may be slow and insufficient for a classification of readily biodegradable. However, all hydrocarbons are considered to be capable of being utilized by microbial communities, and LOBs are considered inherently biodegradable.

6. ENVIRONMENTAL EFFECTS

6.1. Aquatic Endpoints - Acute Toxicity

The HPV Chemical Test Program includes acute toxicity to a freshwater fish, an invertebrate (*Daphnia magna*), and an alga. The substances in the LOB category are expected to have a similar degree of toxicity for all of these aquatic species when studies using similar solution preparation and exposure techniques are compared. This is because the hydrocarbon constituents in these substances elicit acute aquatic toxicity through non-polar narcosis, for which the mechanism of action is disruption of biological membrane function (van Wezel and Opperhuizen, 1995). For this reason, LOBs share a common mode of action, and their acute toxicities would be expected to fall within a relatively narrow range. Any differences between toxicities (i.e., LC/LL50, EC/EL50) can be explained by the differences between the target tissue-partitioning behaviors of the individual chemicals (Verbruggen et al., 2000).

Multiple acute studies covering fish, invertebrates, and algae have been conducted to assess the ecotoxicity of various LOBs. None of these studies has shown evidence of acute toxicity to aquatic organisms. The ecotoxicity data on these substances are supported by studies on a homologous series of alkanes and alkylbenzenes (Adema and van den Bos Bakker, 1986; Adema, 1991). These studies demonstrated that acute toxicity for individual alkanes was no longer evident when the molecular size was ≥C10 (e.g., decane). At that point, the bioavailable fraction was limited by the low water solubility of these compounds, and no toxicity was produced. The same was shown for alkylbenzenes when total carbon numbers were ≥C15 (e.g., nonylbenzene). Since basestocks consist of carbon compounds from C15 to C50, component hydrocarbons that are of acute toxicological concern are, for the most part, absent in these materials or exist at such low concentrations that acutely toxic concentrations would not exist in aqueous fractions.

The endpoint values cited in the robust summaries and described below for the three trophic levels reflect the loading rates of the test substance added to exposure solutions. Termed water accommodated fractions (WAF), the WAF preparation is recommended as the appropriate procedure for testing complex substances comprised of constituents with low water solubility (OECD, 2000). Dispersion studies are also included below.

6.1.1 Acute Toxicity to Aquatic Vertebrates

Table 5 presents the results of acute toxicity tests to freshwater fish.

Table 5. Acute Toxicity of Selected Lubricating Oil Basestocks to Freshwater Fish in Standard Four-Day Exposures.

Test Substance	Test Species and Type (WAF or dispersion)	Toxicity Endpoint	Endpoint Value, mg/L (loading rate)	Reference
CAS No. 64742-54-7, distillates (petroleum), hydrotreated heavy paraffinic	fathead minnow; limit test; WAF	96-h LL50 NOELR	>100 100	EMBSI, 1995e
CAS No. 64742-62-7, distillates (petroleum), solvent de-waxed residual oil	fathead minnow; limit test; WAF	96-h LL50 NOELR	>100 100	EMBSI, 1995f
CAS No. 64742-65-0, distillates (petroleum), solvent de-waxed heavy paraffinic	fathead minnow; limit test; WAF	96-h LL50 NOELR	>100 100	EMBSI, 1995g
CAS No. 64741-89-5, distillates (petroleum), solvent-refined light paraffinic	trout; limit test; dispersion	96-h LL50 NOELR	>1000 1000	BP International Ltd., 1990k
CAS No. 64741-95-3, distillates (petroleum), solvent deasphalted bright stock	trout; limit test; dispersion	96-h LL50 NOELR	>1000 1000	BP International Ltd., 1990l
CAS No. 64742-01-4, distillates (petroleum), solvent refined residual oil	trout; limit test; dispersion	96-h LL50 NOELR	>1000 1000	BP International Ltd., 1990m

Results of three limit tests conducted using WAF exposure solutions failed to demonstrate toxicity to fathead minnows at the maximum loading rate of 100 mg/L. Results were similar when lubricating base oils were tested as dispersion. Three limit tests showed no toxicity to rainbow trout when tested at a maximum concentration of 1000 mg/L.

In addition to the standard 4-day exposures, a number of extended acute studies were carried out to 7-days of exposure. These studies were conducted as limit tests using the dispersion technique of exposure. One LOB, a solvent-refined heavy paraffinic oil (CAS No. 64741-88-4) was repeatedly tested in six trials. Results of the 7-day studies are shown in Table 6.

Table 6. Acute Toxicity of Selected Lubricating Oil Basestocks to Freshwater Fish in Extended Acute Exposures.

Test Substance	Test Species and Type (WAF or dispersion)	Toxicity Endpoint	Endpoint Value, mg/L (loading rate)	Reference
CAS No. 64741-89-5, distillates (petroleum), solvent-refined light paraffinic	trout; limit test; dispersion	7-d LL50 NOELR	>1000 1000	BP International Ltd., 1990n
CAS No. 64742-01-4, distillates (petroleum), solvent refined residual oil	trout; limit test; dispersion	7-d LL50 NOELR	>1000 1000	BP International Ltd., 1990o
CAS No. 64741-88-4, distillates (petroleum), solvent refined residual oil [1]	trout; limit test; dispersion	7-d LL50 NOELR	>1000 1000	BP International Ltd., 1990p-u

[1] CAS No. 64741-88-4 was tested in six experiments; all results were identical.

Conclusions:
LOBs are not acutely toxic to freshwater fish.

6.1.2 Acute Toxicity to Aquatic Invertebrates

Two species of aquatic invertebrates (*Daphnia magna* and *Gammarus sp*.) were exposed to WAF solutions up to 10,000 mg/L for 48 and 96-hours, respectively (Shell Research Ltd., 1988). Table 7 presents the results of those tests.

Table 7. Acute Toxicity of Selected Lubricating Oil Basestocks to Freshwater Invertebrates.

Test Substance	Test Species and Type (WAF or dispersion)	Toxicity Endpoint	Endpoint Value, mg/L (loading rate)	Reference
CAS No. 64742-53-6 or 64741-97-5, distillates (petroleum), hydrotreated or solvent-refined light naphthenic	*Daphnia magna*; 4-concentration levels; WAF	48-h EL50 NOELR	>10,000 10,000	Shell Research Ltd (1988)
CAS No. 64742-53-6 or 64741-97-5, distillates (petroleum), hydrotreated or solvent-refined light naphthenic	*Gammarus* sp.; 4-concentration levels; WAF	96-h EL50 NOELR	>10,000 10,000	Shell Research Ltd (1988)

The data show that the test substances used in testing aquatic invertebrates did not produce any acute toxicity at a maximum WAF loading rate of 10,000 mg/L.

Conclusions:
LOBs are not acutely toxic to freshwater invertebrates.

6.1.3 Toxicity to Aquatic Plants (Algae)

Four tests were conducted on three different LOB samples. One sample was tested twice. Table 8 presents the results of those studies.

Table 8. Toxicity of Selected Lubricating Oil Basestocks to a Freshwater Alga.

Test Substance	Test Species and Type (WAF or dispersion)	Toxicity Endpoint	Endpoint Value, % of WAF	Reference
CAS No. 64741-88-4, distillates (petroleum), solvent-refined heavy paraffinic [1]	*Scenedesmus subspicatus*; limit test; diluted WAF	E_bL50 NOELR	>50% 50%	BP International Ltd., 1990v,w
CAS No. 64741-89-5, distillates (petroleum), solvent-refined light paraffinic	*Scenedesmus subspicatus*; limit test; diluted WAF	E_bL50 NOELR	>50% 50%	BP International Ltd., 1990x
CAS No. 64742-01-4, distillates (petroleum), solvent-refined residual oil	*Scenedesmus subspicatus*; limit test; diluted WAF	E_bL50 NOELR	>50% 50%	BP International Ltd., 1990y

[1] CAS No. 64741-88-4 was tested two times with identical results.

The tests presented in Table 8 were conducted on a 50% dilution of a WAF prepared at a loading rate of 1000 mg/L. While this manner of testing did not follow the conventional procedures for creating exposure solutions, the data provide a basis for concluding that LOBs are not likely to produce adverse effects on freshwater algae.

Conclusions: LOBs are not likely to produce adverse effects on the growth of algae.

6.2 Aquatic Endpoints - Chronic Toxicity

6.2.1 Chronic Toxicity to Aquatic Invertebrates

Multiple chronic ecotoxicity studies have shown no adverse effects to daphnid survival or reproduction. Table 9 shows the results of those studies.

Table 9. Chronic Toxicity of Selected Lubricating Oil Basestocks to *Daphnia magna*.

Test Substance	Test Species and Type (WAF or dispersion)	Toxicity Endpoint	Endpoint Value, mg/L (loading rate)	Reference
CAS No. 64741-88-4, distillates (petroleum), solvent-refined heavy paraffinic [1]	D. magna WAF	21-d EL50 NOELR	>1000 1000	BP Oil Europe, 1995a-c
CAS No. 64741-89-5, distillates (petroleum), solvent-refined light paraffinic [2]	D. magna WAF	21-d EL50 NOELR	>1000 1000	BP Oil Europe, 1995d,e
CAS No. 64741-95-3, distillates (petroleum), solvent deasphalted bright stock	D. magna WAF	21-d EL50 NOELR	>1000 1000	BP Oil Europe, 1995f
CAS No. 64742-01-4, distillates (petroleum), solvent-refined residual oil	D. magna WAF	21-d EL50 NOELR	>1000 1000	BP Oil Europe, 1995g
CAS No. 64742-53-6, Distillates (petroleum), hydrotreated light naphthenic	D. magna WAF	21-d EL50 NOELR	--[3] 10	Shell Research Ltd., 1995
CAS No. 64742-55-8, Distillates (petroleum), hydrotreated light paraffinic	D. magna WAF	21-d EL50 NOELR	>1000 1000	Shell Research Ltd., 1994
CAS No. 64742-65-0, distillates (petroleum), solvent de-waxed heavy paraffinic	D. magna WAF	21-d EL50 NOELR	>1000 1000	Shell Research Ltd., 1994

[1] CAS No. 64741-88-4 was tested four times with identical results.

[2] CAS No. 64741-89-5 was tested two times with identical results.

[3] The test of CAS 64742-53-6 had a mid-level exposure (100 mg/L) in which all daphnids died. The cause was attributed to a non-treatment related effect of unknown cause. The 1000 mg/L treatment had 60% survival.

In 10 of 11 chronic studies, daphnids were exposed for 21 days to WAF preparations of LOBs with no ill effects on survival or reproduction at the maximum concentration of 1000 mg/L. The one test in which toxicity was measured in the mid-level exposure also showed a reduced reproduction at the 1000 mg/L WAF level. However, this was an exception, and the weight of experimental evidence leads to the conclusion that lubricant base oils do not cause chronic toxicity in *Daphnia magna*. CONCAWE (1997) concluded that these substances are not expected to show chronic toxicity to aquatic invertebrates and fish.

Conclusions:
LOBs are not expected to cause chronic toxicity in aquatic invertebrates.

6.3. Assessment Summary for Environmental Effects

The available acute toxicity test data for aquatic organisms shows that no acute effects would be expected from exposure to substances in the lubricating oil basestock category. With the principal hydrocarbons in these substances falling within the range of C15 to C50, no acute toxicity effects would be anticipated. This is because acute toxicity reported for alkanes and alkylbenzenes is not expressed for molecular weight compounds representative of ≥C10 and ≥C15, respectively. In chronic exposures to freshwater invertebrates, toxicity is typically not observed, and the weight of the scientific evidence leads to the conclusion that these substances do not cause chronic toxicity in aquatic organisms.

7. HUMAN HEALTH ENDPOINTS

Many toxicology studies have been reported for both highly refined LOBs and LOBs that are not highly refined. Reports of animal studies ranging from acute toxicity tests to long-term carcinogenicity studies appear in published literature. Additional reviews by various individual authors and expert panels have also been published (Bingham et al., 1980; WHO, 1982; IARC, 1984; API, 1992; SCF, 1995; JECFA, 1996; CONCAWE, 1997). The toxicity testing has consistently shown that highly refined LOBs have overall low toxicity. Raw or mildly refined LOBs have limited acute toxic potential but been shown to be both mutagenic and carcinogenic. The raw or mildly refined oils also can affect various organ systems during repeated-dose studies and developmental toxicity studies.

The greater toxicity of raw or mildly refined LOBs with dermal exposure is associated with the presence of relatively higher amounts of PACs. It has been known that biologically significant effects of several types of refinery streams in both developmental and repeated-dose studies appeared to be related to the total amount of 3-7 ring PACs (Feuston et al, 1994). Samples with high PAC content would be expected to have high mutagenicity indices in the optimized Ames test, produce tumors in skin-painting assays, and have significant systemic effects in repeated-dose and developmental toxicity studies. Samples with low PAC content would not produce such effects. This relation between PACs and toxicity was qualitative and was not quantitatively predictive for individual samples.

More recently, empirically based models have become available to predict quantitatively the effect of individual samples of several petroleum substances on sensitive endpoints in developmental toxicity and subchronic toxicity studies performed via the dermal route. These statistical models, developed by the Petroleum High Production Volume Testing Group (HPVTG), quantitatively predict effects by individual samples on selected sensitive endpoints based on the profile of 1-7 ring PACs in each sample (Simpson, et al, 2008; API, 2008; TERA, 2008). The models are based on a number of toxicity studies on petroleum substances for which there are also analyses of PAC content using a “PAC-2” method. The PAC-2 analyses provided the weight percent of each ring class that served as a basis for the models (the ARC in Appendix 2). The endpoints used in the models were selected by an extensive analysis to determine the most sensitive endpoints among studies of both developmental toxicity and repeated-dose toxicity.

These models are applicable to LOBs and have been used to predict the possible toxicity of untested samples described later in this document. Additional details are provided in subsequent sections. Appendix 3 contains a summary describing the association between toxicity and PAC content and also a brief description of the statistical models. More complete descriptions of the models are in other referenced documents (API, 2008; TERA, 2008).

As a result of modeling and statistical evaluation, the following three types of quantitative values are used in this document.
1) Data on tested samples from appropriate studies, such as NOAELs and LOAELs
2) Predicted dose-responses (PDR_{10}s), dose predicted to cause a change of 10% from control value based on models using the PAC profile of untested samples
3) Read-across from tested or modeled samples to untested samples

7.1. Acute Toxicity

Data from acute oral and dermal toxicity tests were available for a raw light paraffinic distillate (CAS No. 64741-50-0). No animals died in either study and abnormal clinical signs were minimal. As this sample was a raw distillate, it would be "worst case" with respect to highly refined oils.

In general, all the acute oral and dermal studies of the various "other LOBs" demonstrated very low toxicity. Data from several acute tests on highly refined distillate LOBs are summarized in Table 10. One of the samples in the table (API 83-12) was not highly refined, but it also had low oral (LD50 >5000mg/kg) and dermal (LD50 >2000 mg/kg) acute toxicity.

Acute inhalation studies on "other LOBs" have consistently shown minimal effects. As an example, rats were exposed for 4 hours to 0, 0.11, 0.52, or 2.46 mg/L of Stock 141 (CAS No. 64742-65-0). Half of the animals in each group were sacrificed on the following day; remaining animals were observed for 2 weeks. No effects were observed on clinical signs, body weights, organ weights (liver, kidney, and wet and dry lung), or histopathology of lung, nose, liver, kidney, and mediastinal lymph nodes (Mobil, 1984a). See Table 10 for other acute inhalation studies.

In general, both highly refined basestocks and raw or mildly refined basestocks have low acute oral and dermal acute toxicity. The inhalation toxicity for "other LOBs" was low and it is likely that acute effects from inhaled raw or mildly refined distillate LOBs would be similar. No data on acute toxicity were available for either residual LOBs or re-refined LOBs; but these substances are not expected to be acutely toxic, provided that the samples meet the criteria in ASTM D6074 (Standard Guide for Characterizing Hydrocarbon Lubricant Base Oils).

Table 10. Summary of Data on Acute Toxicity of LOBs in Mammals.

	Oral LD50		Dermal LD50		LC50	
CAS Number	**mg/kg**	**Sample and Reference**	**mg/kg**	**Sample and Reference**	**mg/L**	**Sample and Reference**
Raw and Mildly Refined LOBs						
64741-50-0	>5,000	API 84-01 (API, 1986d)	>2,000	API 84-01 (API, 1986d)		
64742-53-6[1]	>5,000	API 83-12 (API, 1986c)	>2,000	API 83-12 (API, 1986c)	2.18[1]	API 83-12 (API, 1987a)
Other LOBs						
64741-88-4					>5.53	MRD-87-102 (Exxon, 1988c)
64741-96-4	>5,000	API 79-1 (API, 1982c)	>5,000	API 79-1 (API, 1982c)		
64741-97-5	>5,000	API 78-5 (API, 1982a)	>5,000	API 78-5 (API, 1982a)		
64742-52-5	>5,000	API 83-15 (API, 1986f)	>2,000	API 83-15 (API, 1986f)		
64742-54-7	>15,000	Ssangyong 150N (Mobil, 1983a)	>5,000	Ssangyong 150N (Mobil, 1983b)		
64742-56-9	>5,000	API 78-9 (API, 1982b)	>5,000	API 78-9 (API, 1982b)	>5.4	MRD-87-099 (Exxon, 1988a)
64742-65-0	>5,000	API 79-3, 79-4, and 79-5 (API, 1982d, e, f)	>5,000	API 79-3, 79-4, and 79-5 (API, 1982d, e, f)	>4.03	MRD-87-101 (Exxon, 1988b)
	>15,000	Stock 141 (Mobil, 1982a)	>5,000	Stock 141 (Mobil, 1982b)	>2.46	Stock 141 (Mobil, 1984a)
64742-70-7	>15,000	Stock 142 (Mobil, 1983c)	>5,000	Stock 142 (Mobil, 1983d)	>2.40	Stock 142 (Mobil, 1984b)
White Mineral Oil						
8042-47-5					>2.46	Stock 461 (Mobil, 1985a)

1) Although this CAS number typically is in the "other LOB" group, sample API 83-12 was not highly refined and caused tumors in a skin-painting assay in mice. It also has a low viscosity (53 SUS at 100°F, or about 8.3 cSt at 100°F), which very likely was the basis for the low LC50 (Dalbey et al, 2008).

An eye irritation study in rabbits of CAS#64742-53-6 was considered to elicit only 'slight' irritation while numerous studies of various "other LOBs" were judged to be 'non-irritating' in the rabbit eye. Based on data from a primary dermal irritation study, CAS# 64742-53-6, a mildly refined distillate, was considered somewhat irritating to rabbit skin. Based on a number of in vivo skin irritation studies in both animals and humans for the highly refined distillate oils, the dermal irritation potential is non-irritating to weakly or slightly irritating to the skin. Ocular and dermal irritation with other LOBs would be expected to be similar. Tests for dermal sensitization for both mildly refined and highly refined distillate LOBs were consistently negative (non-sensitizing). (Data are not shown.)

Conclusions (Acute Toxicity):
Multiple acute toxicity studies on a variety of LOBs have consistently shown these materials to have low acute toxicity by dermal, oral, and inhalation routes. None of the basestocks were

considered sensitizing, and most were slight to non-irritating to the skin with acute exposures. Highly refined basestocks are non-irritating to the eye with acute exposure.

7.2. Repeated-Dose Toxicity

7.2.1 Repeated-Dose Toxicity with Dosing via Dermal Route: Observed NOAELs

As is apparent in section 1.3 on uses of LOBs, the dermal route is expected to be the primary route of exposure to LOBs under most conditions. It was therefore considered to be the most relevant route of exposure.

In a series of studies summarized in Table 11, rats were treated dermally for 13 weeks, 5 days per week with highly refined LOBs. Although the CAS numbers for these LOBs are in the "other LOBs" group, the particular samples in Table 11 were considered to be highly refined based on process history or appropriate testing (e.g., optimized Ames or skin-painting tests). Therefore the results from these tests can be used for read-across only to other LOBs that also are highly refined. Endpoints included clinical signs, body weight, and, at necropsy following the in-life phase, hematology, clinical chemistry, urinalysis, selected organ weights, and histopathology.

These highly refined LOBs showed limited evidence of systemic effects. More specifically, across eight repeated-dose dermal studies in rats, there were some changes in organ weights in some studies (e.g., with Ssangyong 150N), but no toxicologically relevant histological effects were reported. The body weights of treated males were significantly lower than sham-treated controls in four of the eight 13-week studies on highly refined LOBs, ranging from 87.3% to 90.2% of control weights in these four studies. In contrast, body weights of females were affected in only one of the eight studies. Although these lower body weights were treatment-related, their toxicological significance is uncertain. Because the lower body weights were not associated with pathological changes or, in most cases, differences in organ weights, the lower body weights appear to be related to the mode of dosing rather than to inherent toxicity of the test substances.

The reason for the lower body weights is not known, but could be related to the application of large volumes of mineral oil and the resulting stress or disturbances in normal biological functions, such as thermal equilibrium. Another possible factor is slight dermal irritation. The fact that lower body weights were not observed during subchronic exposures of rats to highly refined LOBs administered orally or by inhalation (described in subsequent sections) also supports the premise that the differences seen with dermal administration were related to the mode of dosing rather than to inherent toxicity of the LOBs.

Since the lower body weights might be linked to the experimental model and did not appear to be associated with significant systemic effects, these differences in body weights are not considered adverse in this document. In other words, the lower body weights could be used to set a NOEL or LOEL for treatment-related differences, but not a NOAEL for adverse systemic effects related to the test substance. The NOAELs in Table 11 reflect systemic toxicity and do not include lower body weights or local effects on the skin.

In addition to the studies on LOBs, a study was also conducted with a sample of heavy vacuum gas oil (HVGO, identified with tracking number CRU 85244) that is used here as an example of a PAC-containing material similar to raw LOBs. HVGO caused mortalities at 2000 mg/kg/day and systemic effects at 500 and 1000 mg/kg/day. The overall NOAEL in this study was 125 mg/kg/day.

Table 11. Summary of Data on Toxicity in the Rat with Repeated Dermal Administration of LOBs.

CAS Number	Substance Name	Summary of Study[1]	Systemic NOAEL[2], LOEL, or NOEL (mg/kg/day)
Raw / Mildly Refined LOBs			
64741-57-7 (from Heavy Fuel Oils Category)	Heavy vacuum gas oil (CRU No. 85244, an example of a similar PAC-containing substance)	30, 125, 500, or 2000 mg/kg was given 5 days/wk for 13 wk to rats. Unscheduled deaths of 2 of 10 males at 2000 mg/kg were considered treatment-related. Growth rates of both sexes at 2000 mg/kg were reduced compared to controls. Other differences included reduced erythrocytes and platelets at 500 (females) and at 2000 mg/kg (both sexes). Relative thymus weights were reduced while relative liver weights were increased at 500 and 2000 mg/kg (both sexes). Histologically, decreased erythropoiesis and fibrosis of the bone marrow occurred in 2000 mg/kg males and thymic lymphocytes were reduced in both sexes at 2000 mg/kg. The study director concluded that the LOAEL was 500 mg/kg and the NOAEL for both males and females was 125 mg/kg (Mobil. 1988c).	125 (NOAEL) 500 (LOAEL)
Other LOBs			
64742-54-7	Distillates (petroleum), hydrotreated heavy paraffinic (Highly refined based on testing of this sample)	800 and 2000 mg/kg of Ssangyong 150N were given non-occluded 5 days/wk for 13 weeks to Sprague-Dawley rats. Slight dermal irritation was visible. Body weights were significantly lower in treated males at both doses. No dose-response was apparent and the lower body weight was judged not to be toxicologically significant. Liver weights were higher than controls by 14% in females at 2000 mg/kg and liver weight relative to body weight was increased in both sexes. However, histological changes were minimal and the higher weights were considered an adaptive response. Thymus weight was decreased in males at 2000 mg/kg and adrenal weight was increased in females at 2000 mg/kg. No histological changes were observed in either organ and the differences in weight were not judged to represent an adverse effect. The study director concluded that the NOAEL for systemic effects was 2000 mg/kg/day (Mobil, 1988a). The Petroleum HPV Testing Group assigned a LOEL of 800 mg/kg based on lower body weights in treated males.	2,000 (NOAEL) 800 (LOEL)

Table 11 Continued:

64742-65-0	Distillates (petroleum), solvent-dewaxed heavy paraffinic (Highly refined based on testing of other samples from same refining process)	2000 mg/kg of Stock 141 was given non-occluded 5 days/wk for 13 weeks to Sprague-Dawley rats. No dermal irritation was visible and histological changes were minimal. Liver weights were increased in males, but no histological changes were observed (Mobil, 1983e). Relative liver weight was higher in both sexes of treated animals. The study director did not assign a NOAEL, but did state that "Stock 141 elicited no toxic responses in the treated animals". Therefore the Petroleum HPV Testing Group assigned a NOAEL of 2000 mg/kg/day and a LOEL of 2,000 mg/kg based on higher liver weight in males and higher relative liver weight in both sexes.	2,000 (NOAEL and LOEL
	Distillates (petroleum), solvent-dewaxed heavy paraffinic (Highly refined based on testing of other samples from same refining process)	2000 mg/kg of Stock 300 was given non-occluded 5 days/wk for 13 weeks to Sprague-Dawley rats. No dermal irritation was visible, but was apparent histologically. Relative liver weights were higher in females, but no histological changes were observed. This difference was not judged by the authors to be adverse (Mobil, 1983f). The study director did not assign a NOAEL, but did state that "Stock 300 elicited no toxic responses in the treated animals". Therefore the Petroleum HPV Testing Group assigned a NOAEL of 2000 mg/kg/day and a LOEL based on higher relative liver weight in females.	2,000 (NOAEL and (LOEL)
	Distillates (petroleum), solvent-dewaxed heavy paraffinic (Highly refined based on testing of other samples from same refining process)	2000 mg/kg of Stock 335 was given non-occluded 5 days/wk for 13 weeks to Sprague-Dawley rats. No dermal irritation was visible, but was apparent histologically. Relative liver weights increased in females, but no histological changes were observed. (Mobil, 1983g). The study director did not assign a NOAEL, but did state that "Stock 335 elicited no toxic responses in the treated animals". Therefore the Petroleum HPV Testing Group assigned a NOAEL of 2000 mg/kg/day and a LOEL of 2,000 mg/kg based on higher relative liver weight in females.	2,000 (NOAEL and LOEL)
	Distillates (petroleum), solvent-dewaxed heavy paraffinic (Highly refined based on testing of this sample)	1000 mg/kg of solvent dewaxed heavy paraffinic distillate was given non-occluded 5 days/wk for 13 weeks to Sprague-Dawley rats (10/sex). Body weights in males were 12.8% lower than sham-treated controls. Liver weights increased in females, but were within the range of historical controls and no microscopic correlates were observed. The lower body weight in males was not considered by the study director to be adverse and no systemic toxicity was observed (API, 2010a). The Petroleum HPV Testing Group assigned a NOAEL of 1,000 mg/kg and, due to lower body weight in males, a LOEL of 1,000 mg/kg.	1,000 (NOAEL and LOEL)

Table 11 Continued:

64742-70-7	Paraffin oils (petroleum), catalytic dewaxed heavy (Highly refined based on testing of other samples from same refining process)	1720 mg/kg of Stock 142 was given non-occluded 5 days/wk for 13 weeks to Sprague-Dawley rats. Slight dermal irritation was visible. Body weights were significantly lower in treated males, but the difference was thought to result from unusually high body weights in the control group. Weights of the liver and adrenals were higher in treated females, but no significant histological changes were observed except for occasional small aggregates of cells with foamy appearing cytoplasm (vacuolar degeneration) in only a very small portion of the liver of treated females. The increase in liver weight might have been an adaptive response. Hematocrit and hemoglobin were significantly lower in treated males, but the difference was not judged to be toxicologically significant sine the values were within the normal range (Mobil, 1986). The study director did not assign a NOAEL. Based on the lack of apparent adverse effects in final report, the Petroleum HPV Testing Group assigned a NOAEL of 1,720 mg/kg/day. This dose was also the LOEL due to increased liver weight in females.	1,720 (NOAEL and LOEL)
72623-83-7	Lubricating oils (petroleum)C_{25}, hydrotreated bright stock-based (Highly refined based on testing of other samples from same refining process)	2000 mg/kg of Stock 345 was given non-occluded 5 days/wk for 13 weeks to Sprague-Dawley rats. No dermal irritation was visible, but slight changes were observed histologically. Relative liver weights increased significantly in females, but no histological changes were observed. Relative kidney weight was higher in treated males, primarily reflected a decrease in body weight (Mobil, 1983h). The study director did not assign a NOAEL, but did state that "Stock 345 elicited no toxic responses in the treated animals". Therefore the Petroleum HPV Testing Group assigned a NOAEL of 2,000 mg/kg and a LOEL of 2,000 mg/kg based mainly in increased liver weight in females.	2,000 (NOAEL and LOEL)
White Mineral Oil			
8042-47-5	White mineral oil (petroleum) (Highly refined white oil)	125, 500, and 2000 mg/kg of Stock 461 was given non-occluded 5 days/wk for 13 weeks to Sprague-Dawley rats. Erythema, scabs, and flaking of skin were visible. Body weights decreased at higher doses (~10% lower at 2000 mg/kg than controls). Organ weights were unaffected. Histopathological data are not available. The study director assigned a NOAEL of 125 mg/kg on the basis of lower body weight (unfasted) during the biophase and marginally lower serum albumin in males (Mobil, 1988b). In this document, that difference in body weight is not considered to reflect adverse systemic effects related to the LOB and a marginal change in serum albumin is not sufficient to establish a NOAEL. Therefore a NOAEL could not be established due to the lack of histopathology.	Not Established

1) Only potentially significant changes are presented in the table.
2) NOAELs and LOAELs are for systemic effects and not for local changes such as changes in the skin following dermal application.

Similar results were obtained in studies of shorter duration using rabbits as the test species. One set of 5 studies was performed in rabbits with dosing 5 days/week for 4 weeks with 1,000 mg/kg/day. Dermal irritation was noted in most cases and sporadic changes occurred that were not judged to be adverse changes (Exxon, 1991a and b). NOAELs were 1,000 mg/kg/day, as shown in Table 12.

Table 12. Summary of Data on Toxicity in the Rabbits with Repeated Dermal Administration of LOBs.

CAS Number	Substance Name	Summary of Study[1]	Systemic NOAEL[2] (mg/kg/day)
Other LOBs			
64741-88-4	Distillates (petroleum), solvent-refined heavy paraffinic	1000 mg/kg of MRD-87-102 was given 5 days/wk for 4 weeks to New Zealand white rabbits. Skin irritation was slight in most animals and no systemic effects were reported (Exxon, 1991b) A NOAEL was not provided in the study report, but the Petroleum HPV Testing Group assigned a NOAEL of 1,000 mg/kg based on the lack of observed effects.	1,000
64742-56-9	Distillates (petroleum), solvent-dewaxed light paraffinic	1000 mg/kg of MRD-87-099 was given 5 days/wk for 4 weeks to New Zealand white rabbits. Significant skin irritation occurred. Relative liver weight marginally greater (9%) in males relative to controls (Exxon, 1991a). A NOAEL was not provided in the study report, but the Petroleum HPV Testing Group did not consider the difference in relative liver weight to be an adverse effect. Therefore the NOAEL would be 1,000 mg/kg.	1,000
64742-65-0	Distillates (petroleum), solvent-dewaxed heavy paraffinic	1000 mg/kg of MRD-87-100 was given 5 days/wk for 4 weeks to New Zealand white rabbits. Significant skin irritation occurred. Relative liver weight marginally (14%) in males relative to controls. A NOAEL was not provided in the study report, but the Petroleum HPV Testing Group did not consider the difference in relative liver weight to be an adverse effect. (Exxon, 1991a)	1,000
		1000 mg/kg of MRD-87-101 was given 5 days/wk for 4 weeks to New Zealand white rabbits. Slight skin irritation occurred and no systemic effects were reported (Exxon, 1991a). A NOAEL was not provided in the study report, but the Petroleum HPV Testing Group assigned a NOAEL of 1,000 mg/kg based on the lack of observed effects.	1,000
64742-62-7	Residual oils, petroleum, solvent-dewaxed	1000 mg/kg of MRD-87-103 was given 5 days/wk for 4 weeks to New Zealand white rabbits. Significant skin irritation occurred. A marginal increase in SDH was not considered to be biologically significant by the study director. A marginal decrease (12%) in relative kidney weight in males occurred (Exxon, 1991b). A NOAEL was not provided in the study report, but the Petroleum HPV Testing Group did not consider this difference in relative kidney weight to reflect an adverse effect, particularly given the lack of histological changes. Therefore the NOAEL would be 1,000 mg/kg.	1,000

1) Only potentially significant changes are presented in the table.
2) NOAELs are for systemic effects and not for local changes such as changes in the skin following dermal application.

Other subacute dermal studies were performed in rabbits with a series of LOBs provided by manufacturers to the American Petroleum Institute (API, 1986a and b; API, 1987c; CONCAWE, 1997). Doses were given three times weekly for 21 or 28 days and ranged from 200 to 5000 mg/kg/day. The only consistent effect was skin irritation with many of the tested samples, ranging from "none detected" to "moderate" on the Draize scale. Systemic effects were observed in one study with API 83-15 and consisted of decreased body weight, increased relative liver weight in females, elevated SGOT and SGPT, and subacute hepatitis (API, 1987c). Reduced testicular weight was seen in rabbits with 2000 mg/kg of API 83-12 (API, 1986a), but this sample had a relatively low viscosity (8.4 cSt at 40°F) and a high primary dermal irritation index (5.4). "Moderate" dermal irritation was seen in the 28-day dermal study and may have contributed to an effect on the testes. (This assessment on API 83-12 was made by the Petroleum HPV Testing Group and was based in part on McKee et al (1985).) No systemic effects were reported in the studies with 7 other LOBs. Overall, these studies indicated few effects other than reduced body weight and reduced testicular weight, both of which may have been secondary to dermal irritation.

7.2.2 Repeated-Dose Toxicity with Dosing via Dermal Route: Modeled Predictions

Since experimental data were not available for repeated-dose dermal studies with raw or mildly refined LOBs, the potential toxicity of the untested samples listed in Appendix 2 was predicted using the models based on PAC content. That is, PDR_{10}s were calculated for each sample based on the PAC profile of that sample. (See Appendix 3 for further background and details.) The PDR_{10} is a dose predicted to cause a change of 10% from control value. The calculated PDR_{10}s for each sensitive endpoint with samples of raw and mildly refined LOBs are shown in Table 13; the lowest PDR_{10} was identified for each sample as the "sample PDR_{10}".

Blank cells in Table 13 indicate that useable data were not available; for example, the LOB sample had a PAC profile outside those used to develop the models. Note that a PDR_{10} is not necessarily an indicator of an adverse effect. PDR_{10}s for the tested sample of HVGO are included for comparison.

The sample PDR_{10} for the raw and mildly refined LOBs in Table 13 ranged from 38 to 2,000 mg/kg. The sample PDR_{10} was based on each of the four sensitive endpoints for at least one sample, as seen in the table. The sample of tested HVGO from Table 11 had a sample PDR_{10} of 118 mg/kg, which was comparable to its experimental NOAEL of 125 mg/kg.

Table 13. Repeat-dose PDR_{10} (mg/kg) predicted for dermal dosing with one sample of HVGO and with raw/mildly refined LOBs[1]

Sample No.	CAS No.	Relative Liver Weight PDR_{10}		Absolute Thymus Weight PDR_{10}		Platelet Count PDR_{10}		Hemoglobin Concentration PDR_{10}		Sample PDR_{10} (lowest value)	Basis for Sample PDR_{10}
		Male	Female	Male	Female	Male	Female	Male	Female		
HVGO (CRU 85244)	64741-57-7	380	377	133	118	360	365	935	934	118	Thymus, F
Site# 23, Sample# 11	64741-50-0	2000	2000	>2000	>2000	>2000	>2000	2000	2000	2000	Hemoglobin, M & F
Site# 12, Sample# 22	64741-51-1										
Site# 12, Sample# 26	64741-51-1	353	351	80	71	62	63	323	323	62	Platelets, M & F
Site# 23, Sample# 9	64741-51-1	>2000	>2000	>2000	>2000	>2000	>2000	>2000	>2000	>2000	All endpoints
Site# 37, Sample# 3	64741-51-1	290	288	208	184	545	553	683	683	184	Thymus, F
Site# 37, Sample# 4	64741-51-1	163	162	80	71	246	250	362	362	71	Thymus, F
Site# 33, Sample# 3	64741-52-2	483	480	2000	2000	2000	2000	2000	2000	480	Relative liver weight, M & F
Site# 7, Sample# 4	64741-52-2										
Site# 33, Sample# 2	64741-53-3	114	113	43	38	72	73	222	222	38	Thymus, F

1) Blank cells indicate that useable data were not available.

7.2.3. Conclusions (Toxicity with Repeated Dosing via Dermal Route)

Experimental data were not available for raw or mildly refined LOBs, but modeled values for PDR_{10}s were used to predict toxicity. The lowest modeled PDR_{10} for each sample of raw and mildly refined LOBs ranged from 38 to 2,000 mg/kg. A tested HVGO had a NOAEL of 125 mg/kg and a sample PDR_{10} of 118 mg/kg. The variable PAC content of substances such as raw and mildly refined LOBs determines the range of hazard.

For highly refined LOBs, several repeated-dose dermal studies in both rats (13-week exposures) and rabbits (3-4 week exposures) with LOBs of various CAS numbers and ranges of viscosities consistently demonstrated NOAELs for systemic toxicity in the range of 1,000 to 2,000 mg/kg/day, typically the highest doses tested. There were no consistent pathological changes. There were some differences in hematological parameters but these were judged to be not toxicologically significant as they were not consistently observed. Liver weights tended to be slightly increased in several studies, most often seen in only one gender of the treated animals. However, as no histopathological changes were seen in the livers, the effects on liver weight were considered to be evidence of systemic exposure but not toxicity.

For the "other LOBs", the potential toxicity with repeated dermal dosing would be expected to vary with the PAC content of the individual samples, which in turn would depend on the extent of refining. If an individual sample with a CAS number in the "other LOBs" can be demonstrated to be highly refined, then read-across from the samples in Table 11 can be applied to it. If the sample has not been demonstrated to be highly refined, then its toxicity can be estimated with the PAC models or read-across from the raw/mildly refined LOBs can be used.

7.2.4. Repeated-Dose Toxicity with Dosing via Respiratory Route

Although the dermal route is expected to be the primary route of exposure to LOBs, certain end uses of LOBs, particularly in metal removal fluids, can result in formation of aerosols, creating the potential for exposure by inhalation. For that reason, data from inhalation tests conducted with aerosolized LOBs are included here.

In three four-week inhalation studies (Dalbey, et al., 1991), repeated exposures to aerosols of highly refined LOBs did not results in treatment-related clinical signs (apart from occasional loose stools) or effects on body weights, hematological or clinical chemical parameters, or sperm morphology. Wet and dry lung weights were increased in a dose-related manner. For both males and females, the ratios of wet to dry lung weights were significantly increased at the highest concentrations of all three basestocks. Treatment-related changes observed microscopically in the lungs and tracheobronchial lymph nodes of many treated animals consisted of foamy macrophages with numerous vacuoles of varying size in the alveolar spaces. These results are summarized in Table 14.

Although 1000 mg/m^3 could justifiably be considered the NOAEL for these three studies due to the non-adverse nature of accumulation of alveolar macrophages in the lungs without other accompanying effects, a NOAEL of 210 mg/m^3 was chosen because of increased lung weight

only at the highest dose. Further rationale for this choice and a discussion of earlier published inhalation studies is in Dalbey and Biles (2003).

Table 14. Summary of data on toxicity in mammals with repeated inhalation exposures to LOBs.

CAS Number	Substance Name	Summary of Study[1]	NOAEL[2] (mg/m^3)
Raw / Mildly Refined LOBs			
Other LOBs			
64742-54-7	Distillates (petroleum), hydrotreated heavy paraffinic	Rats were exposed to approximately 0, 50, 210, or 1000 mg/m^3 of aerosolized LOB 6 hr/day, 5 days/wk for 4 wk. Treatment-related changes included increased lung weight and microscopic accumulation of foamy alveolar macrophages in lungs. (Dalbey et al, 1991)	210
64742-70-7	Paraffin oils (petroleum), catalytic dewaxed heavy	Rats were exposed to approximately 0, 50, 210, or 1000 mg/m^3 of aerosolized LOB 6 hr/day, 5 days/wk for 4 wk. Treatment-related changes included increased lung weight and microscopic accumulation of foamy alveolar macrophages in lungs. (Dalbey et al, 1991)	210
White Mineral Oil			
8042-47-5	White mineral oil (petroleum)	Rats were exposed to approximately 0, 50, 210, or 1000 mg/m^3 of aerosolized LOB 6 hr/day, 5 days/wk for 4 wk. Treatment-related changes included increased lung weight and microscopic accumulation of foamy alveolar macrophages in lungs. (Dalbey et al, 1991)	210

1) Only potentially significant changes are presented in the table.
2) Since no significant effects were seen beyond the lungs, the portal of entry, these NOAELs are for pulmonary effects and not for systemic changes beyond the respiratory tract. NOAELs are taken from Dalbey and Biles (2003).

Supporting evidence comes from a poster presentation on 14-day inhalation studies with two highly refined base oils (summarized in Whitman et al, 1989). Rat (both sexes) were exposed to aerosol concentrations of approximately 50, 500, and 1500 mg/m^3 for 6 hr/day. Increased lung weight was seen at the highest concentration and, to a lesser extent, at the mid-dose. Inflammatory cells were seen in terminal bronchioles and alveolar ducts. Perivascular and peribronchial lymphoid proliferations were also observed in the lungs, and evidence of mild irritation was noted in the anterior nasal mucosa. The NOELs were >50 mg/m^3.

Conclusions (Toxicity with Dosing via Respiratory Route)

Repeated inhalation of highly refined distillates resulted primarily in local effects in the lung that were largely a response to the physical presence of oil particles with low toxicity. An overall NOAEL of 210 mg/m^3 for 90-day exposures is reasonable based on the cited studies and previously published work. An estimated NOAEL for systemic toxicity beyond the lungs would most likely exceed 1000 mg/m^3 for the tested oils.

7.2.5. Repeated-Dose Toxicity with Dosing via Oral Route

Oral administration of raw or mildly refined LOBs has not been considered to be a relevant route of exposure. No data are available for oral studies on these LOBs, and no models are available to predict effects from oral dosing with the raw or mildly refined LOBs.

Significant oral exposures are not expected with highly refined LOBs with the exception of white oils, which are used in medicinal or other applications. For that reason, data from repeated-dose toxicity tests on white oils conducted with oral dosing are included here.

No subchronic ingestion studies with LOBs have been done because LOBs generally are not ingested by people. However food/medicinal grade white mineral oils are used in both direct and indirect food applications, medical applications such as laxative and excipients in pills, and in cosmetic applications (i.e., lip care) with some limited oral ingestion. Because of these intended uses, ingestion studies of white oils have been performed. Little difference is expected between the effects of white oils and highly refined LOBs due to low PAC content. More significant levels of PACs in the raw or mildly refined LOBs would be expected to contribute to repeated dose/chronic toxicity, and read-across from the generally low toxicity from white oils may not be appropriate for these substances.

Examples of repeated-dose ingestion studies on white oils are summarized in Table 15. The main findings were accumulation of oil and microgranulomas in livers of one strain of rat (Fisher 344) together with histiocytosis in the mesenteric lymph nodes (MLN). The F-344 rat appears to be uniquely sensitive to this effect (Miller et al, 1996). Additional information from pharmacokinetic and toxicokinetic studies in rats is available (Albro and Fishbein, 1970; Halladay et al, 2002; JECFA, 2002; Scotter et al, 2003). These effects are due to saturated hydrocarbons in the range of C20-C30 and not related to PACs, so they are not predicted by the PAC models.

An independent workshop of international human/veterinary pathology experts was held at the Fraunhofer Institute in May 2001 to evaluate significance of the liver and MLN findings in the F344 rat. The panel concluded that the lesions observed in the rat were qualitatively similar for all oils and waxes that have been tested, differing only in severity. They also concluded that the lesions in the F344 rat were unlike those tissue changes found in humans associated with ingestion of mineral hydrocarbons (white oil) over time. Also, the available data suggest that the granulomatous lesions experimentally induced by white oil-feeding, particularly in the liver of F344 rats, are exaggerated toxicological responses peculiar to this strain of rats (Carlton et al, 2001).

Table 15. Examples of studies with repeated oral doses of white oils in mammals.	
Summary of Study	**Systemic NOAEL**
White oil was used as vehicle control in a combined 90 –day repeat dose and reproductive toxicity study in Sprague-Dawley rats. The dose, given by gavage, was 5 ml/kg, 5 times/wk for 13 weeks. Endpoints included hematology, clinical chemistry, organ weights, and histopathology. No comment was made that the control (white oil) values were outside of the normal range for control animals and no adverse histological observations were made (McKee *et al.*, 1987b). Sample: CASRN 8012-95-1, mineral oil [USP], a white mineral oil	5 ml/kg/day by gavage
Four white mineral oils (one low-viscosity oleum-treated oil, one low viscosity hydrotreated oil, and two higher viscosity hydrotreated oils) were fed to Long Evans rats and beagle dogs at dietary concentrations of 0, 300, and 1500 ppm for 90 days. Endpoints included mortality, clinical signs, food consumption, organ weights, hematology, clinical chemistry, urinalysis, gross pathology and histopathology. No evidence of significant toxicological effects was seen in either species (abstract by Bird, et al, 1990). The studies were also cited with more details in API (1992). Sample: CASRN 8042-47-5, white mineral oil (petroleum)	1,500 ppm in diet
Ninety-day dietary studies were performed in Fisher 344 rats with two food-grade white oils, one processed by oleum (acid) treatment and the other processed by hydrotreatment. In the first study, rats (both sexes) were fed dietary concentrations of either oil at 5,000, 10,000 or 20,000 ppm. In the second study, only female rats were fed diets containing 10, 100, 500, 5,000, 10,000 or 20,000 ppm of either oil (approximately equivalent to daily doses of 0.65, 6.5, 32.5, 325, 650, and 1250 mg/kg bw, respectively). Endpoints included body weight, food consumption, hematology, clinical chemistry, necropsy, organ weights, and histopathology. Clinical signs and body weights were unaffected in both studies. Slight leukocytosis and granulocytosis was seen in both sexes with either oil at 20,000 ppm. Slight hypochromic microcytic anemia was observed in the females given 20,000 ppm oleum-treated oil. Changes in clinical chemical parameters were indicative of slight hepatic effects and were more severe and numerous in females. Effects were more marked with oleum-treated oil than with hydrotreated oil, although the difference may have been due to specification rather than processing. Dose-related histological changes were observed in mesenteric lymph node, liver and spleen after 90 days and were more marked in females than in males and in both sexes rats fed oleum-treated oil compared to fed hydrotreated oil. The severity of response in livers of rats fed diets containing oleum-treated white oil was very slight to moderate at 10,000 and 20,000 ppm and absent in the 5,000 ppm males. The response was very slight to moderate in the 100 and 500 ppm females and absent in 10 ppm females. The NOELs, based on histiocytosis in the mesenteric lymph nodes, were 10 and 100 ppm for the oleum-treated and hydrotreated white oils, respectively (Baldwin et al., 1992). Sample: CASRN not provided, identified as food grade white oils	10 – 100 ppm in diet for F-344 rats

Table 15 Continued:

Ninety-day oral studies were performed with six different food grade white oils of varying viscosity, feedstock (naphthenic versus paraffinic) and refining conditions (acid treatment versus hydrotreatment). The oils were identified as N10A, N15H, N15A, P15H, P70H and P100H; the higher viscosity numbers represented the oils with higher molecular weight (MW). Fischer 344 rats (both sexes) received dietary concentrations of 20, 200, 2,000, and 20,000 ppm (approximately equivalent to daily doses of 2, 20, 200, and 2,000 mg/kg bw, respectively). Endpoints included body weight, food consumption, clinical signs, hematology, serum chemistry, organ weights, necropsy, and histopathology. Effects were inversely related to MW. For example, the oil with the highest MW produced no effects other than increases (~10%) in food consumption and ASAT in males at 20,000 ppm. Histological examination revealed a small amount of mineral hydrocarbon in the livers of these males. In contrast, the oil with the lowest MW caused a similar increase in food consumption among males at 20,000 ppm, plus increased organ weights (liver, mesenteric lymph nodes, spleen, kidney), evidence for the presence of nonpolar hydrocarbons, and other observations suggestive of an inflammatory response (e.g., granulomas/microgranulomas in liver and hystiocytosis in mesenteric lymph nodes). The NOELs and LOELs, based on the occurrence of histiocytosis in the mesenteric lymph nodes, were a LOEL of 20 ppm for N15H (MLN histiocytosis at all doses), a NOEL of 20 ppm for N10A, P15H, N70A, and P70H (MLN histiocytosis at 20 ppm and greater), and a NOEL of 20,000 ppm for P100H (no effects at all doses) (Smith et al, 1996). Sample: CASRN not provided, identified as food grade white oils	Values in F-344 rats ranged from LOEL of 20 ppm in diet for low viscosity oil to NOEL of 20,000 ppm in diet for high viscosity oil.
Effects of 90-day dietary administration of a food-grade white oil were compared in F-344 and Sprague-Dawley rats. Groups of 15 females of each strain were fed diets containing 0, 2,000 or 20,000 ppm (~160 and 1600 mg/kg bw) P15H white oil. Ten rats per group were sacrificed after 90 days for toxicological evaluation and 5 rats were sacrificed after 91 days for analysis of mineral hydrocarbons in tissues. An additional 20 F-344 females/group were fed 0 or 20,000 ppm; half were sacrificed at 30 days and the remaining half at 61 days to follow the time-course of the development of any lesions. Endpoints included clinical signs, body weight, food consumption, hematology, serum chemistry, necropsy, organ weights, and histopathology. Clinical signs, body weight, and food consumption were unaffected in both strains of rats. In F-344 rats, white cell count increased in both treated groups in a dose-related manner. The absolute and relative liver weights of F-344 rats given 20,000 ppm were 20% and 30% higher than controls, respectively, and at 2,000 ppm both absolute and relative liver weights were 10% higher. Weights of mesenteric lymph nodes were higher only with 20,000 ppm. Histopathological changes in the livers of the treated F-344 rats consisted of an increased incidence of microgranuloma after 61 days in more than 80% of the animals given 20,000 ppm. By 90 days microgranuloma were also observed at 2,000 ppm. Central necrosis and Langhan's type cells were occasionally seen in microgranuloma. The incidence and severity were both dose- and temporally-related as the	20,000 ppm in Sprague-Dawley rats and <2,000 ppm in F-344 rats

appearance of granuloma occurred at 61 days in the high dose group and was present in both dose groups at 92 days. Histiocytosis occurred in the mesenteric lymph nodes of the F-344 rats in the 20,000 ppm dose group after 30 days. Microgranulomas were observed at 61 and 92 days in the 20,000 ppm and also in the 2000 ppm groups at 92 days. The incidence and severity of the microgranulomas were increased in a dose related manner. In contrast, no significant differences in hematology, serum chemistry, or organ weights were noted in Sprague-Dawley rats. Histopathologically, no microgranulomas were seen in Sprague-Dawley rats, but there was a slightly increased incidence of minimal multifocal chronic inflammation at 20,000 ppm. No histological changes were observed in the mesenteric lymph nodes of the Sprague-Dawley rats. A NOEL was not established experimentally in the F-344 rat; the NOEL in Sprague-Dawley rats was 20,000 ppm. Firriolo *et al.* (1995) Sample: CASRN not provided, identified as low-viscosity white mineral oil	

In humans, lipogranulomas in the liver, lymph nodes and spleen appear to result from ingestion of mineral oil. (Fleming et al., 1998; Carlton et al., 2001) These lipogranulomas occur in a high percentage of people but they do not progress and are not associated with clinical abnormalities (Fleming et al., 1998). In contrast to the inflammatory character of the microgranulomas observed in F344 rats, human lipogranulomas have been described as small histiocytic collections with minimal signs of inflammation and the human lipogranulomas have not been observed to progress to clinically significant lesions (Fleming et al., 1998 and Carlton, 2001).

A collective review of mineral hydrocarbon-related histological changes by several human and veterinary pathologists concluded that the changes induced by waxes and white oils in the F344 rat are different from those seen in human tissues and the latter human changes are considered incidental and inconsequential (Carlton et al., 2001).

As stated earlier, the use of oral repeated-dose studies on white oils to predict the outcome of oral repeated-dose studies with other LOBs must be done with some interpretative caution. API believes that highly refined LOBs, with little PAC and other contaminants, should be qualitatively similar to white oils after repeated dose by the ingestion route. This conclusion is primarily due to the poor absorption (particularly with longer carbon chains) of the oil through the GI tract as well as the general lack of toxic constituents. However, these conclusions should not be applied to raw or mildly refined LOBs.

Conclusions (Toxicity with Dosing via Oral Route)

Oral administration of raw or mildly refined LOBs has not been considered to be a relevant route of exposure. No data are available for oral studies on these LOBs and no models are available to predict effects from oral dosing with the raw or mildly refined LOBs.

Significant oral exposures are not expected with highly refined LOBs with the exception of white oils. In subchronic oral studies on white mineral oils, observed increases in weights of liver, lymph nodes, and spleen at the highest doses were associated with deposition of the lipophilic oil and minimal pathological changes. These effects were limited to the Fischer 344 rat and are not

relevant to humans. Effects of highly refined LOBs, with little PAC and other contaminants, should be qualitatively similar to white oils.

7.2.6. Conclusions (Repeated-Dose Toxicity)

Modeled PDR_{10}s for repeated-dose dermal exposures to raw and mildly refined LOBs ranged from 38 to 2,000 mg/kg. A tested HVGO had a NOAEL of 125 mg/kg and a sample PDR_{10} of 118 mg/kg. The variable PAC content of substances such as raw and mildly refined LOBs determines the range of hazard.

For highly refined LOBs, several repeated-dose dermal studies in both rats (13-week exposures) and rabbits (3-4 week exposures) with LOBs of various CAS numbers and ranges of viscosities consistently demonstrated NOAELs for systemic toxicity in the range of 1,000 to 2,000 mg/kg/day, typically the highest doses tested. Repeated inhalation of highly refined LOBs resulted primarily in local effects in the lung that were largely a response to the physical presence of oil particles with low toxicity. An estimated overall NOAEL of 210 mg/m^3 for 90-day exposures is a reasonable choice for effects in the lungs. An estimated NOAEL for systemic toxicity beyond the lungs would most likely exceed 1000 mg/m^3 for the tested oils. In subchronic oral studies on white mineral oils, observed increases in weights of liver, lymph nodes, and spleen at the highest doses were associated with deposition of the lipophilic oil and minimal pathological changes. These effects were limited to the Fischer 344 rat and are not relevant to humans.

7.3. Genetic Toxicity *In Vitro* and *In Vivo*

7.3.1. *In Vitro* (Mutagenicity)

In assays of mutagenicity *in vitro*, the optimized Ames assay was designed for use with petroleum-derived substances due to their limited solubility in water. The mutagenicity index (MI) was determined from the slope of the dose-response curve in Salmonella strain TA 98. An MI greater than 1.0 was indicative of mutagenicity and possible carcinogenicity. A number of raw or mildly refined distillate basestocks derived from crude oil have been shown to be mutagenic in this assay, with a strong correlation between mutagenicity and 3-7 ring PAC content (Blackburn, et al., 1986, Roy, et al., 1988; Mackerer et al, 2003). In contrast, highly refined distillate basestocks derived from crude oil have no measurable PACs or low concentrations of 3-7 ring PACs and also have low mutagenicity indices (Blackburn, et al., 1984, 1986; Roy, et al., 1988). Regarding residual LOBs, samples of a vacuum residuum and four residual basestocks were negative in an optimized Ames assay (EMBSI, undated a and b; Petrolabs, 1998; 2000).

Numerous tests have shown that a LOB's mutagenic and carcinogenic potential correlates with its 3-7 ring PAC content and with the level of DMSO extractables (e.g. IP346 assay), both characteristics that are directly related to the degree and conditions of processing (Halder, et al., 1984; IARC, 1984; Kane, et al., 1984; Chasey, et al., 1993; Roy, et al. 1988, 1996; Blackburn, et al., 1984, 1986; 1996; CONCAWE, 1994; European Union 1994). Those LOBs that are highly

refined are not expected to have significant genetic toxicity while those LOBs that are raw or mildly refined might and often do have significant genetic toxicity *in vitro*.

In addition to measured MIs, modeled predictions can be made of the outcome of optimized Ames assays based on the PAC content of petroleum substances. Data on the relation between PAC content and mutagenicity index for several LOBs were included in the empirical derivation of the predictive model. Although the model was not needed for this category assessment, it is available for use as a predictive tool on samples of LOBs for which PAC data are available (Nicolich et al, 2010).

With respect to *in vitro* gene mutations in mammalian cells, the mouse lymphoma assay was conducted on API 83-12, a raw or mildly refined LOB (CAS#64742-53-6) that produced tumors in a mouse skin-painting assay. Increased mutation frequency was seen, but primarily at high doses that were also cytotoxic, rendering the assay's results questionable (API, 1986e). The mouse lymphoma assay was also conducted on 5 paraffinic and 2 naphthenic highly refined LOB's and the results were negative or equivocal. These results were questionable because there was no dose-response and the samples were poorly soluble. (See page 60 of the 2004 Robust Summary on Lubricating Oil Basestocks for additional details.)

7.3.2. *In Vivo* (Chromosomal Aberrations)

No *in vivo* genotoxicity data are available for the raw basestocks. However, solvent extracted paraffinic oils were inactive in the micronucleus assay (McKee et al, 1990) and micronucleus tests with petroleum streams that contain higher amounts of PACs have also been negative, leading to the conclusion that PAC-containing petroleum substances do not produce chromosomal effects when tested in SIDS-level assays under *in vivo* conditions (McKee et al, 2010).

Seven highly refined LOBs were tested in male and female Sprague-Dawley rats using a bone marrow cytogenetics assay (Conaway, et al., 1984). The test materials were administered via gavage at doses ranging from 500 to 5000 mg/kg. Dosing occurred for either a single day or for five consecutive days. None of the LOBs produced a significant increase in aberrant cells. This information is consistent with the results of *in vitro* mutagenicity tests on similar basestocks and is of sufficient quality to allow it to be used to fulfill the data needs for the *in vivo* genotoxicity endpoint on the "highly refined" basestocks.

7.3.3. Conclusions (Genetic Toxicity *In Vitro* and *In Vivo*)

In vitro mutagenicity studies have shown a consistent relationship among the degree and conditions of processing that a LOB undergoes, the associated 1-7 ring PAC content, and mutagenic potency of the LOB. Raw or mildly refined LOB's appear to be mutagenic in bacterial assays and equivocal to positive in mammalian cell point mutation assays, but negative in cytogenetic assays. Highly refined distillate and residual LOB's are negative in all *in vitro* mutagenicity assays.

Extensive *in vitro* studies of the distillate basestocks have shown a consistent relationship

between the degree/conditions of processing distillate basestocks undergo (and associated 1-7 ring PAC content) and the oil's lack of mutagenic potency. Both highly refined LOBs and raw and mildly refined LOBs, like other PAC-containing petroleum substances, are not expected to produce chromosomal effects when tested in SIDS-level assays under *in vivo* conditions.

7.4. Developmental Toxicity

7.4.1. Developmental Toxicity with Dosing via Dermal Route: Observed NOAELs

As is apparent in section 1.3 on uses of LOBs, the dermal route is expected to be the primary route of exposure to LOBs under most conditions. It was therefore considered to be the most relevant route of exposure for developmental endpoints. Available information from developmental studies using the dermal route is summarized in the following text and in Table 16.

No developmental toxicity studies have been reported for raw or mildly refined distillate basestocks. However, a developmental toxicity screening study has been reported for heavy vacuum gas oil (HVGO), a material similar to the raw distillate basestocks (Mobil, 1987d). As a raw material, HVGO contains the broadest spectrum of chemical components and highest concentration of bioavailable/biologically active components of all the materials addressed in the LOB category. Therefore data for this sample of HVGO is included here as an example of a PAC-containing material similar to raw LOBs. Because of their low level of processing in comparison to other category members, the raw LOBs will also have higher concentrations of biologically active components. In the Mobil study, HVGO was applied daily to the skin of pregnant rats on days 0-19 of gestation. Dose levels administered included: 30, 125, 500 and 1000 mg/kg (bw)/day. All animals were euthanized on day 20. The only dose-related finding at gross necropsy was pale colored lungs in four animals in the highest dose group and in one animal in the 500 mg/kg (bw)/day group. Mean thymus weights of animals in the highest dose group were approximately half those of the control groups. Although absolute liver weights were unaffected by exposure to the gas oil, mean relative liver weights were increased (approximately 15%) in groups exposed to doses greater than 125 mg/kg (bw)/day. Maternal and fetal body weights were reduced at 500 and 1000 mg/kg (bw)/day. Significant increases in resorptions were also seen in these two dose groups. Soft tissue variations and malformations, and skeletal malformations were also increased at 500 and 1000 mg/kg (bw)/day. The NOAEL for fetal and maternal effects was 125 mg/kg/day.

Several developmental toxicity studies of highly refined oils have been conducted following OECD 414 guidelines. In one, a highly refined LOB (CAS No.64742-65-0) with no measurable PACs was tested. This substance was administered neat by non-occluded dermal application to 25 pregnant female Crl:CD(SD) rats once daily from gestation days 0 through 19 at 1000 mg/kg/day. Test article-related effects in the dams were limited to a statistically significant increase in the mean weight of adrenal glands and a non-statistically significant decrease in mean thymus weight in the treated group compared to control; these were considered non-adverse. No test substance-related clinical findings were noted at the daily examinations, and maternal body weight body weight gain, net body weight, net body weight gain, gravid uterine weight, and food consumption were unaffected. Intrauterine growth and survival in the treated group were also

unaffected. No treatment-related adverse effects on fetal morphology, as measured by external, visceral, and skeletal malformations/developmental variations, were observed. Based on the lack of observed maternal or developmental toxicity, the study director considered a dose of 1,000 mg/kg/day to be the NOAEL for maternal and developmental toxicity (Goyak, et al, 2010; API, 2010b).

In a second study, a white mineral oil (CAS No. 8042-47-5) with a nominal viscosity of 80 SUS was tested in a study with a design similar to OECD Test Guideline 414 (Prenatal Developmental Toxicity Study), but with higher than typical limit doses and three routes of exposure. The oil was administered to different groups of female rats dermally, orally, or by inhalation. Groups of 20 pregnant females were treated on gestation days 6 to 19 with 2,000 mg/kg/day by dermal administration, 5,000 mg/kg/day by oral gavage, or 1,000 mg/m^3 for 6 hours per day by inhalation. Respective sham-treated control groups were included. Clinical signs, body weights, and food consumption were recorded for each dam. Dams were sacrificed on GD 20 and necropsied. Endpoints included serum chemistry, gross examination of thoracic and abdominal organs, weights of ovaries and uterus, number of corpora lutea per ovary, and weight of the gravid uterus. In the uterus, the number and location of implantations, early and late resorptions, and live and dead fetuses were recorded. Fetuses were measured, weighed, grossly examined, and evaluated for skeletal or visceral abnormalities. Erythema and flaking of the treated skin was seen in all but one female dosed dermally. Perianal staining was observed in all females treated orally and appeared to result from a clear oily anal discharge within a few hours of dosing. Otherwise no treatment-related changes were reported for each route in maternal or fetal endpoints, including maternal reproductive performance and survival or development of fetuses (Mobil. 1987b). The study director did not assign a NOEL, but the Petroleum HPV Testing Group determined that the dermal NOAEL was 2,000 mg/kg/day based on the study report.

Finally, a highly refined distillate LOB was tested in a study with a design similar to OECD Test Guideline 414. The main differences were that fewer females were used and that the high dose was twice that for the OECD limit dose. The test substance was a catalytic dewaxed heavy paraffinic oil (Stock 141, CAS No. 64742-70-7) with a viscosity of ~102 SUS at 100°F. Pregnant females were dosed dermally with 0, 125, 500, or 2,000 mg/kg/day on gestation days 0 to 19. Maternal endpoints included clinical signs, body weights, food consumption, serum chemistry, selected organ weights, and macroscopic appearance of organs. Additional endpoints included number of corpora lutea per ovary, weight of the gravid uterus, number and location of implantations, early and late resorptions, and live and dead fetuses. Fetuses were measured, weighed, grossly examined, and evaluated for soft tissue and skeletal abnormalities or variations. Aside from minor irritation on the skin of the dams, no treatment-related changes were observed (Mobil, 1987a). The study director concluded that the test substance did not adversely affect maternal reproductive performance, the survival or development of offspring, or teratogenicity. The study director did not assign a NOAEL, but the Petroleum HPV Testing Group determined that the maternal and fetal NOAELs were both 2,000 mg/kg/day based on the study report.

There are also data which can be used to assess the effects of highly refined LOBs on perinatal effects. Schreiner et al (1997) reported on a study based on OECD Test Guideline 421 with some additions to the design. The study was intended to evaluate the effects of dermally applied

kerosine at three dilutions in a USP white mineral oil (340 SUS, CAS No. 8042-47-5). A vehicle control was included in which animals were dosed only with the white oil at 1 ml/kg/day (~900 mg/kg/day). A separate control group received sham exposure including stroking of the skin with the tip of a syringe to mimic dosing and Elizabethan collars used on treated groups. Doses were applied daily to the shaved backs of females for 7 weeks (2 weeks premating, up to 2 weeks mating, and through gestation day 20. Dams and litters were sacrificed on postpartum day 4. Dosing of males began at the same time and continued through gestation until 1 week after the final sacrifice of females (8 week total). No significant differences were seen between males in the sham-exposed controls and the group receiving only mineral oil for body weights, weight gain, organ weights, macroscopic appearance of organs, or microscopic evaluation of testes and epididymides. No significant differences were seen between females in the sham-exposed controls and the group receiving only mineral oil for body weights, weight gain, organ weights, macroscopic appearance of organs, or microscopic evaluation of ovaries. Fertility index, live birth index, viability index, pup weight, number of corpora lutea, and other related parameters were not significantly different in the group treated with 1 ml/kg/day of mineral oil. In short, treatment with 1 ml/kg/day (~900 mg/kg/day) of mineral oil did not significantly affect any of the measured endpoints.

Table 16. Summary of NOAELs on developmental toxicity in mammals with dermal dosing.

CAS Number	Substance Name	Summary of Study	NOAEL (mg/kg/day)	Reference
Raw / Mildly Refined LOBs				
64741-57-7	Heavy vacuum gas oil (Not a LOB, but an example of a similar PAC-containing substance)	Similar to OECD Guideline 414	125	Mobil (1987d)
Other LOBs				
64742-65-0	Distillates (petroleum), solvent-dewaxed heavy paraffinic	OECD Guideline 414	1,000	Goyak, et al, 2010; API, 2010b
64742-70-7	Paraffin oils (petroleum), catalytic dewaxed heavy	Similar to OECD Guideline 414	2,000	Mobil, 1987a
White Mineral Oils				
8042-47-5	White mineral oil (petroleum)	OECD Guideline 421	~900 (1 ml/kg/day)	Schreiner, et al, 1997
		Similar to OECD Guideline 414	2,000	Mobil. 1987b

7.4.2. Developmental Toxicity, Dermal Route: Modeled Predictions

As with repeated-dose endpoints, modeled predictions of developmental toxicity have been developed for petroleum substances that contain measurable amounts of PACs (Simpson et al, 2008). The models are empirically based on the observation that the presence of PACs was related to the degree of effects in the most sensitive endpoints in dermal studies on

developmental toxicity in rats. The sensitive endpoints (those biological parameters most likely to be affected) are fetal body weight, number of live fetuses per litter, and percent resorptions. Although LOBs were not included in the development of the models for prenatal developmental toxicity, the PAC content of highly refined LOBs is generally quite low and the expected developmental effects following dermal application would be correspondingly low.

Since experimental data were not available for dermal developmental toxicity studies with raw or mildly refined LOBs, potential toxicity of the untested samples listed in Appendix 2 was predicted using the models based on PAC content. As with the repeated-dose endpoints, PDR_{10}s were calculated for each sample based on the PAC profile of that sample (See Appendix 3). The PDR_{10} is a dose predicted to cause a change of 10% from control value. The calculated PDR_{10}s for each sensitive endpoint are shown in Table 17; the lowest of these values was identified for each sample as the "sample PDR_{10}". Blank cells indicate that useable data were not available; for example, the LOB sample had a PAC profile outside those used to develop the models. Note that a PDR_{10} is not necessarily an indicator of an adverse effect.

Table 17. Maternal and developmental PDR_{10}s (mg/kg/day) predicted for dermal dosing with raw/mildly refined LOBs and a sample of HVGO

Sample No.	CAS No.	Maternal Thymus Weight PDR_{10}		Fetal Body Weight PDR_{10}	Live Fetuses Per Litter PDR_{10}	Percent Resorptions PDR_{10}	Sample PDR_{10} (lowest value)	Basis for Sample PDR_{10}
HVGO, CRU 85244 **(Not a LOB)**	64741-57-7	261		530	157	262	157	Live fetuses
Site# 23, Sample# 11	64741-50-0	2000		>2000	2000	2000	2000	All endpoints
Site# 12, Sample# 22	64741-51-1						NA	
Site# 12, Sample# 26	64741-51-1			422			422	Fetal BW[1]
Site# 23, Sample# 9	64741-51-1	>2000		>2000	>2000	>2000	>2000	All endpoints
Site# 37, Sample# 3	64741-51-1	61		333	74	130	74	Live fetuses
Site# 37, Sample# 4	64741-51-1	23		182	59	100	59	Live fetuses
Site# 33, Sample# 3	64741-52-2			>2000	1842		1842	Live fetuses[1]
Site# 7, Sample# 4	64741-52-2						NA	
Site# 33, Sample# 2	64741-53-3	20		101	28	47	28	Live fetuses

NA = Not available
1) Sample PDR_{10} was derived from an incomplete set of PDR_{10}s.

Sample PDR_{10}s for the raw or mildly refined LOBs ranged from 28 to 2000 mg/kg/day. Such a wide range is not unexpected given the variation in PAC content among the samples. A similar range was observed with PDR_{10}s for repeated-dose toxicity.

PDR_{10}s are not shown for the "other LOBs" because sufficient data were available from toxicity tests on highly refined samples in this group.

7.4.3. Conclusions (Developmental Toxicity with Dosing via Dermal Route)

Although no developmental studies were available on raw or mildly refined distillate LOBs, sample PDR_{10}s ranged from 28 to 2000 mg/kg/day. The NOAEL of 125 mg/kg/day from a dermal study with HVGO, a similar PAC-containing material, was similar to its sample PDR_{10} of 157 mg/kg. In contrast, dermal studies with highly refined distillate LOBs and white mineral oil showed no effects; NOAELs were 900 to 2,000 mg/kg (the highest doses tested).

7.4.4. Developmental Toxicity with Dosing via Respiratory Route

Although the dermal route is expected to be the primary route of exposure to LOBs, significant inhalation exposures can occur, particularly through the use of LOBs in metal removal fluids. For that reason, data from inhalation tests conducted with aerosolized LOBs are included here.

A white mineral oil with lower viscosity was tested in a study with a design similar to OECD 414 (Prenatal Developmental Toxicity Study). The test substance was Stock 461 (80" white oil) with a nominal viscosity of 80 SUS and CAS number 8042-47-5. The oil was administered to female rats by inhalation at a single concentration of 1,000 mg/m^3 for 6 hours/day, higher than the typical limit concentrations. The inhalation NOAEC was 1,000 mg/m^3 (Mobil. 1987b). See the section on developmental toxicity with dosing via dermal route for additional details.

No developmental toxicity data are available for inhalation exposure to raw/mildly refined LOBs or "other LOBs".

Conclusions (Developmental Toxicity with Dosing via Respiratory Route)

An inhalation study with a highly refined distillate LOB showed a NOAEC of 1,000 mg/m^3. This NOAEC should also apply to those residual LOBs and re-refined LOBs that are highly refined and have low PAC content.

7.4.5. Developmental Toxicity with Dosing via Oral Route

Although the dermal route is expected to be the primary route of exposure to LOBs, significant oral exposures can occur with medicinal use of LOBs. For that reason, data from developmental toxicity tests conducted with oral dosing are included here.

As mentioned previously, oral exposure to general lubricant base oils is not expected. However white mineral oils can be ingested under certain circumstances. A white mineral oil with viscosity of 80 SUS was tested in a study with a design similar to OECD 414 (Prenatal Developmental Toxicity Study). The test substance was Stock 461 (80" white oil) with a nominal viscosity of 80 SUS and CAS number 8042-47-5. The oil was administered to female rats orally at a dose higher than the typical limit doses. The oral NOAEL was 5,000 mg/kg/day (Mobil. 1987b). See the section on developmental toxicity with dosing via dermal route for additional details.

A white mineral oil (food/drug grade highly refined, CAS No. 8012-95-1) was used as a vehicle

control in a reproductive/developmental toxicity study in Sprague Dawley rats reported by McKee, et al., (1987a). This oil was a hydrotreated white mineral oil that would now be classified by CAS number 8042-47-5 due to process history and specification. [CAS number 8012-95-1 is a non-specific identifier for "Paraffin Oil", with no other requirement. CAS number 8012-95-1 is not included in the LOB category.] In the present study, the white oil was used as a vehicle control for other tested groups and there were no untreated animals for comparison. Two separate groups of pregnant rats were administered 5 ml/kg/day of the basestock via gavage, on days 6 through 19 of gestation. In one of the two groups dosed with white oil, three malformed fetuses were found among three litters. One fetus had an extra lumbar vertebra, one had a discrete area of ossification in the area of the junction of the frontal and nasal bones, and the third had moderately dilated lateral ventricles of the brain. Three malformed fetuses were also found amongst three litters of the other group receiving white oil. Two of these three fetuses had a vertebral arterial canal of a cervical process fully ossified, while the third fetus had angulated ribs. The study authors considered these malformations to be minor and within the normal ranges for the strain of rat. Although there were no untreated animals for comparison to the white oil group, the results were considered to be within normal limits. Consequently, this study provides limited evidence of the lack of developmental effects of white oil.

Conclusions (Developmental Toxicity with Dosing via Oral Route)

An oral study with a white mineral oil showed a NOAEL of 5,000 mg/kg/day. This NOAEL was supported by a second, more limited, study. This NOAEL should also apply to those LOBs that are highly refined and have low PAC content.

7.4.6. Conclusions (Developmental Toxicity)

Although no developmental studies were available on raw or mildly refined distillate LOBs, sample PDR_{10}s ranged from 28 to 2000 mg/kg/day for samples of these LOBs. The NOAEL of 125 mg/kg/day from a dermal study with HVGO, a PAC-containing material similar to raw LOBs, was similar to its sample PDR_{10} of 157 mg/kg. In contrast, dermal studies with highly refined distillate LOBs and white mineral oil showed no effects, giving rise to much higher NOAELs. Similarly, an inhalation study with a highly refined distillate LOB showed a NOAEC of 1,000 mg/m^3 and an oral study with a white mineral oil showed a NOAEL of 5,000 mg/kg/day.

7.5. Reproductive Toxicity

No complete reproductive toxicity studies were identified for LOB. However, under the High Production Volume (HPV) Challenge Program, U.S. EPA has provided guidance on the requirements for evaluating reproductive toxicity. The EPA guidance indicates a reproductive toxicity study may not be required for certain petroleum substances if there is (1) a 90-day repeat-dose study in which the potential for effects on reproductive organs was assessed and (2) a developmental toxicity study (US EPA, 2010). Such data are available for highly refined LOBs. A study with a design similar to OECD Guideline 415 (One-Generation Reproduction Toxicity Study) was also available.

A reproductive study was conducted with a highly refined distillate LOB, Stock 461, which was a white mineral oil (CAS No. 8042-47-5) with a nominal viscosity of 80 SUS. Dermal doses applied to groups of Sprague-Dawley rats (20/sex) were 0 (untreated controls), 0 (sham-exposed controls), 125, 500, and 2,000 mg/kg/day. The test substance was applied to the shaved backs of both males and females and the sites were left uncovered. Elizabethan collars were used to minimize ingestion of the oil. Dosing (5 days/wk) began approximately 10 weeks before mating and continued during mating. Dosing of females was daily during gestation and then 5 days/wk during a 3-wk postpartum period. Dams were sacrificed on day 21 of lactation. Dosing of males was 5 days/wk throughout, but half of the males were sacrificed after mating while the remaining half was sacrificed within 2 weeks of the last sacrifice of pups (i.e., during postpartum weeks 5 and 6).

Maternal endpoints included body weight and food consumption, estrus cycle in a limited number of females, uterine and ovarian weights at necropsy, and number of implantations. During gestation, erythema, scabs, and flaking were observed on the skin of nearly all animals treated with Stock 461. Similar findings were reported during lactation. Body weight did not appear to be affected by treatment with Stock 461 and no effects of treatment with Stock 461 were noted at necropsies of dams. No effects were seen in dams on the percentage of pregnant females, duration of gestation, or number of implantation sites per dam.

All offspring were observed individually during the postpartum period until sacrifice for body weight, behavior, and appearance. All viable neonates were examined as early as possible for sex and external anomalies. Litters of sufficient size were culled to 8 pups on postpartum day 4 (4/sex if possible). The number of open eyelids for each pup was recorded on postpartum day 10 and continued until both eyelids were open. All pups were tested for surface righting reflex on postpartum day 14. Pups were weaned on postpartum days 21 and then sacrificed and necropsied with gross observations on postpartum day 28. No adverse effects were noted among the litters for Liveborn Index, Day 4 Survival Index, or Day 21 Survival Index. Mean pup weight was not affected by treatment during postpartum days 0 to 28. Eyelid dysjunction (opening) and surface righting reflex were not affected by treatment. Observations of offspring at birth and at necropsy were not affected by treatment. The study director concluded that dermal application of Stock 461 at doses up to 2,000 mg/kg/day beginning 10 weeks before mating did not have any adverse effects on reproductive performance of female rats or on the *in utero* and postnatal survival or development of offspring (Mobil, 1987c, API, 2010c).

The design of this study on Stock 461 was similar to OECD Guideline 415 (One-Generation Reproduction Toxicity Study). Differences included the use of 2,000 mg/kg rather than the limit dose of 1,000 mg/kg and administration of doses 5 times per week during much of the study rather than 7 times per week.

Organ weights and histopathology of sex organs were not directly available from this one-generation study. However, weights of reproductive organs were measured at necropsy in a companion 90-day dermal study with Stock 461 (Mobil, 1988b) and included ovaries, uterus, prostate and seminal vesicles (weighed together), testes, and epididymides. For reasons explained in Appendix 4, statistical analyses of these data were not available from the laboratory that performed the testing and were subsequently performed by an independent toxicologist and biostatistician for API. No treatment-related effects on organ weights were seen. Although

histopathology was not performed in either the reproduction study (Mobil 1987c) or the 90-day dermal toxicity study (Mobil, 1988b) with Stock 461, no treatment-related effects were seen during histological examination of testes in six 90-day dermal studies with highly refined LOBs or of ovaries in one of those studies, as shown in Appendix 4. Overall, available data did not indicate treatment-related effects in sex organs with dermal dosing of LOBs.

McKee, et al. (1987b) reported on a single generation study in which a white mineral oil (a food/drug grade highly refined basestock) was used as a vehicle control. This oil was a hydrotreated white mineral oil that would now be classified by CAS# 8042-47-5 due to process history and specification. [CAS# 8012-95-1 is a non-specific identifier for "Paraffin Oil", with no other requirement. CAS number 8012-95-1 is not included in the LOB category.] In the present study, the white oil was used as a vehicle control for other tested groups and there were no untreated animals for comparison. Each of the two separate vehicle control groups contained male and female Sprague-Dawley rats. The dosed animals were given a single daily dose of 5 ml/kg of the white oil (~4,500 mg/kg/day). Dosing was done via gavage, 5 days/week for 13 weeks. After 13 weeks of dosing, the animals were mated. The mated females were maintained without further dosing through gestation and lactation to post-partum day 21. Gross observations of pups and dams were generally unremarkable. In one basestock group, 3 malformed pups were found amongst 2 litters. Two of the malformed pups had syndactyly and renal agenesis, one of the pups also exhibited agnathia. The third pup had a small eye. In the other basestock group, four malformed pups were found amongst four litters. Two of the pups had tail abnormalities, one had a depression in the sternum and the fourth had a short snout. The study authors noted that a similar spectrum of malformations in Sprague-Dawley rats from the same supplier has been reported elsewhere. The authors also commented that this spectrum of malformations occurs spontaneously in the Sprague-Dawley rat. Although there were no untreated animals for comparison, the results with the white oil were considered to be within normal limits. Consequently, this study provides limited evidence of the lack of developmental effects of a highly refined LOB, namely white oil.

In a different study (WIL, 1995), a highly refined LOB (CAS No. 64742-54-7) was again used as the vehicle control in a screening test conducted according to the OECD Test Guideline 421 “Reproductive / Developmental Toxicity Screening Test”. A dose of 1.15 ml/kg (~1 g/kg) of the basestock was administered daily by oral gavage to male and female Sprague Dawley rats. Rats were dosed for a minimum of 14 days prior to mating. Dosing was continued after mating until a total dosing period of 30 days had elapsed for males and until day 4 of lactation for females (39 days). There were no clinical findings. Growth rates and food consumption values were normal. There was no effect on fertility and mating indices in either males or females. At necropsy, there were no consistent findings, and organ weights and histopathology were considered normal by the study’s authors. Although there were no untreated animals for comparison, the results with the highly refined LOBs were considered to be within normal limits. Fertility and mating indices were 100% and a NOAEL greater than 1.15 ml/kg/day (>~1,000 mg/kg/day) was determined. Consequently, these studies provide additional limited evidence of the lack of reproductive effects of highly refined LOBs.

In addition to these studies on LOBs, the potential for a variety of PAC-containing petroleum substances, including other LOBs, to affect reproductive organs was assessed via a series of 13-

week repeated-dose studies in which the testes, accessory sex organs, and epididymides were weighed in males and the potential for pathological changes was evaluated in microscopic examinations. There was little evidence of reproductive organ effects in the repeated-dose studies of LOBs or the other petroleum streams evaluated even at the highest non-lethal dose (Appendices 2 and 4 of API, 2008). The most sensitive endpoints of reproductive toxicity of PAC-containing petroleum substances are likely to be the sensitive endpoints observed in the developmental toxicity studies (i.e., decreased fetal survival and growth). Developmental toxicity was evaluated in a large number of developmental toxicity studies on high-boiling, PAC-containing petroleum substances, including LOBs, in which embryonal and fetal development were examined among the offspring of pregnant rats given the test material dermally. When developmental effects occurred, the most common and statistically significant effects at the lowest levels were decreases in fetal/pup survival and body weight (Feuston et al, 1994; API, 2008). There was little evidence of teratogenicity (i.e. malformations) in any of these developmental toxicity studies. As expected, increased incidences of skeletal variations (i.e., delayed ossification) were often observed at dose levels producing decreased fetal/pup body weight. Developmental toxicity was observed in these studies at dose levels that did not produce effects on weights or histology of reproductive organs or on semen quality in 13-week repeat-dose studies.

Lastly, screening-level fertility studies in males and females of a petroleum substance with high PAC content, i.e., syntower bottoms (CAS No. 64741-62-4, also termed clarified slurry oil or carbon black oil), by Hoberman et al (1995a) indicated that reproductive endpoints (e.g., sperm production and male and female fertility) were unaffected at 250 mg/kg/day applied dermally, a dose at which no litters survived in a dermal developmental toxicity study (Hoberman et al, 1995b). In the female screening reproductive toxicity study, females were exposed during the mating period and were not dosed during pregnancy. The lack of exposure during pregnancy may explain why there were no effects on litter size. Assuming that the reproductive toxicity of clarified slurry oil (a substance with high PAC content) is representative of other PAC-containing petroleum substances, it can be reasonably assumed that reproductive effects, such as fertility and sperm production, would not be sensitive effects of PAC-containing materials compared to developmental effects.

Based on the results of a large number of repeat-dose studies and developmental toxicity studies of LOBs and other PAC-containing petroleum substances (Appendices 2 and 4 of API, 2008), as well as the two reproductive toxicity screening studies of carbon black oil, the most sensitive endpoints related to reproductive and developmental toxicity appear to be those associated with the survival and growth of fetuses and offspring. Effects on fertility, sperm production and reproductive organ do not appear to be sensitive endpoints for assessment of the potential hazards of PAC-containing petroleum substances. Accordingly, it can be concluded that the most sensitive endpoints of reproductive toxicity for LOBs and other high-boiling, PAC-containing petroleum streams are likely to be the developmental toxicity effects (i.e., decreased fetal survival and growth) observed in developmental toxicity studies. Consequently, additional reproductive toxicity studies of LOBs are unnecessary since they would not be expected to identify reproductive endpoints more sensitive than those detected as a result of *in utero* exposure in developmental toxicity studies.

7.5.1 Conclusions (Reproductive Toxicity)

No complete reproductive toxicity studies of LOBs were identified; thus, a NOAEL from reproductive toxicity studies is not available. However, available data from four sources indicate that the NOAEL from reproductive toxicity studies of LOBs would not be lower than the NOAEL from developmental toxicity studies of LOBs.

1) Adverse effects on reproduction were not reported in dermal and oral studies with highly refined distillate LOBs, but these studies may be considered incomplete due to the lack of a concurrent/sham controls. Although these results may not be considered conclusive, they do indicate that the highly refined LOBs are likely to have little, if any, effects on reproductive parameters. The raw or mildly refined LOBs or other LOBs that are not highly refined have no similar data.
2) Data taken from multiple studies did not indicate treatment-related effects on weights of sex organs or histopathology of testes and ovaries with dermal dosing of LOBs.
3) In a large number of studies of developmental and repeated-dose toxicity studies of other PAC-containing, high-boiling petroleum substances, clear developmental toxicity was observed at doses that produced little evidence of effects on male and female reproductive organs (i.e., weight and histopathology) and on semen quality in repeated-dose toxicity studies (API, 2008).
4) The published NOAEL in a pair of dermal screening-level fertility studies of syntower bottoms, a refinery stream containing high amounts of PACs, was ≥ 250 mg/kg/day, a dose associated with a significant decrease in fetal survival in a dermal developmental toxicity study.

Thus, it can be concluded that the NOAEL for reproductive toxicity is not expected to be lower than the NOAEL for developmental toxicity because the most sensitive endpoints in either developmental or reproductive toxicity studies are expected to be effects on fetal survival and growth resulting from *in utero* exposure.

7.6. Health Effects Other

7.6.1. Carcinogenicity – Dermal

It has long been recognized that PACs in some petroleum streams can cause skin tumors with chronic dermal exposure. Current refining practices effectively eliminate the carcinogenic hazard from PACs in mineral basestocks by reducing the level of PACs and/or chemically altering them to inactive compounds (Kane et al, 1984; Mackerer, 1989; McKee et al, 1989 a, b). The PACs that cause the carcinogenicity are believed to be alkylated, 4-5 ring compounds (3 and 6 ring species may also contribute) and PACs substituted with S and N-hetero atoms. However, because the PAC fraction is extremely complex and individual chemical species exist at very low levels, it has not been possible to associate basestock carcinogenic activity with levels of individual PACs. Components of lube oils other than the PACs have not shown any carcinogenic activity.

IARC recognized that severe refining removes the biologically active PACs and results in lubricant basestocks that are not carcinogenic. Thus, classification of lubricant basestocks (called

mineral oils by IARC) was split into various categories depending on the severity of refining (IARC, 1984 and 1987). Mineral oils produced by major refiners today undergo relatively severe refining treatment and are recognized as having no evidence of carcinogenicity (Mackerer et al, 2003). These oils are considered highly refined. An additional bonus from removal of PACs and related aromatic compounds is increased performance of the final motor oil, i.e., an increase in viscosity index to help keep the oil fluid at low temperatures and to maintain viscosity at high temperatures.

Numerous carcinogenicity studies have been carried out on LOB samples that ranged from "raw" to "highly refined". Data from these studies have been reported and reviewed elsewhere (Bingham, et al., 1980; Blackburn, et al., 1984, 1996; CONCAWE, 1994; 1997; IARC, 1984; Roy, et al., 1988, EMBSI, 2001; Shoda, et al., 1997). The general conclusions that can be drawn from the animal carcinogenicity studies are:

1) Highly refined basestocks are not carcinogens, when given either orally or dermally.
2) Raw or mildly refined basestocks are potential skin carcinogens.
3) When applied repeatedly to the skin, carcinogenic basestocks are associated only with skin tumors and not with an increase in systemic tumors.
4) The potential dermal carcinogenicity of a basestock can be correlated with the oil's 3-7 ring PAC content, its mutagenicity index as determined in a modified Ames assay and the level of DMSO extractables (e.g. IP346 assay).

Most directly relevant are skin-painting studies in mice (Chasey and McKee, 1993; McKee and Freeman, 1993; Mackerer, et al, 2003; Dickson et al, 1997) which serve as the benchmark for carcinogenicity of lubricant basestocks; but such tests are too time-consuming to be practical for the large number of marketed mineral oils.

Short-term assays have been developed and carefully validated with chronic cancer bioassays in animals to screen many samples in a more timely manner than skin-painting assays. Two methods in particular are often used. The first, the optimized Ames assay, was designed specifically to evaluate the mutagenicity of petroleum samples using a bacterium, *Salmonella*. The original assay was developed by Bruce Ames and was called the Ames assay. This standard Ames assay was shown not to correlate well with chronic animal bioassays on petroleum-based samples due to the poor solubility of the oil in the water-based test system and also due to difficulties with the enzymatic activation systems of the bacteria. A modification to this assay was an initial extraction of PACs into DMSO so that adequate physical contact is made between the oily sample and the bacteria (TA-98, the most sensitive strain for this application).

Another short-term predictive method, the IP-346 assay, is a formalized analytical procedure for gravimetrically measuring the PAC-enriched fraction after extraction with DMSO and was developed by the Institute of Petroleum (IP, 1985). The European Union has endorsed this procedure for use in distinguishing between carcinogenic and non-carcinogenic basestocks. In the United States, both IP-346 and a modified Ames test (ASTM E 1687.98 are used to distinguish between potentially carcinogenic and non-carcinogenic oils (IP, 1985; ASTM, 2002b). An oil containing more than 3% of the PAC enriched fraction (according to IP-346) is considered carcinogenic for labeling purposes. Raw/mildly refined vacuum distillates typically

have IP-346 values above 3%, while highly refined oils have IP-346 values less than 3%. Very highly refined white oils have PAC levels approaching zero. Almost all basestocks used in the United States are highly refined and would not be skin carcinogens.

7.6.2. Carcinogenicity – Oral

As discussed previously, ingestion is not an expected route of exposure for LOBs except for white oils. Therefore, data on chronic studies were available only for white oils. Two-year feeding studies in F-344 rats were performed with P100H and P70H white oils (daily doses up to 1,200 mg/kg). No increased cancer or chronic effects were observed (Trimmer et al, 2004). An additional two-year dietary study with a white oil was also negative for cancer in F-344 rats. Dietary concentrations of the oil were 2.5% and 5%, approximately equivalent to 1,250 and 2,500 mg/kg, respectively (Shoda et al, 1997).

7.7. Assessment Summary for Health Effects

Multiple acute toxicity studies on a variety of LOBs have consistently shown these materials to have low acute toxicity by dermal, oral, and inhalation routes. Several repeated-dose dermal studies in both rabbits (3-4 week exposures) and rats (13-week exposures) with highly refined LOBs having a range of viscosities consistently demonstrated NOAELs for systemic toxicity in the range of 1,000 to 2,000 mg/kg/day, typically the highest dose tested. Repeated inhalation of highly refined distillates resulted primarily in local effects in the lung that were largely a response to the physical presence of particles with low toxicity. An overall NOAEL of 210 mg/m^3 for 90-day exposures is a reasonable choice based on the cited studies and previously published work. Repeated oral dosing of white oils at high doses resulted effects in the liver, lymph nodes, and spleen of F-344 rats. These effects were limited to the Fischer 344 rat and are not relevant to humans.

Studies have shown a consistent relationship among the degree and conditions of processing that a LOB undergoes, the associated 3-7 ring PAC content, and mutagenic potency of the LOB. Based on the large number of tests on various LOBs, the raw or mildly refined LOBs would be expected to be mutagenic *in vitro*. The highly refined LOBs would not be expected to be mutagenic, but testing or a thorough knowledge of the refining history of a given sample would be needed to confirm that premise. Otherwise the LOB could be considered potentially mutagenic.

Developmental toxicity studies with a highly refined distillate LOB showed a dermal NOAEL of 2000 mg/kg/day, an oral NOAEL of 5,000 mg/kg/day, and an inhalation NOAEC of 1,000 mg/m^3 for 6 hours/day. These NOAELs should also apply to highly refined residual LOBs and highly refined re-refined LOBs. Although no developmental studies were available on raw or mildly refined distillate LOBs, a NOAEL of 125 mg/kg/day from a dermal study with heavy vacuum gas oil was considered to provide an appropriate read-across value to these LOBs.

Adverse effects on reproduction were not reported in dermal and oral studies with highly refined LOBs, but these studies were incomplete. Although these results are not conclusive, they do indicate that the highly refined LOBs are likely to have little, if any, effects on reproductive

parameters. The raw or mildly refined LOBs could have greater reproductive toxicity, but that possibility is unlikely for reasons previously presented in the section on reproductive toxicity.

Regarding cancer, there is a large body of toxicity data relating to raw and mildly refined LOBs that dates back over 50 years. These LOBs produce skin cancer in the mouse and can possibly cause cancer of the respiratory tract upon inhalation of aerosols of the material. Highly refined LOBs are not expected to be carcinogenic.

8. HUMAN EXPOSURE SUMMARY

8.1 Occupational Exposure

Due to their physical and chemical properties as well as their low toxicity, lubricant oil basestocks are used in a wide variety of marketed lubricants including engine oils, automotive transmission fluids, hydraulic fluids, gear oils, metalworking fluids, greases, and additional applications. Nonlubricant products that contain mineral oils include cleaning fluid, heat transfer oils, and others. Dermal exposures are common in the workplace and both inhalation and oral exposures occur also depending on the application and the nature of the product. IARC (1984) is among the various sources that provide further information on uses that lead to human exposures.

An enforceable occupational exposure limit of 5 mg/m^3 for mineral oil mist has been established for inhalation exposures (OSHA, 2011). A voluntary standard for occupational exposure to mineral oil (pure, highly and severely refined) of 5 mg/m^3 (8-hour time weighted average) has been recommended by ACGIH (2010). Hazard evaluation and workplace labeling of lubricating base oils and products containing lubricating oils is regulated by the Occupational Health and Safety Administration in the Department of Labor.

The long history of petroleum refining has resulted in the development of recommended practices (RP) and standards (STD) to improve safety within the facilities. API has been a leader in developing these standards for both Upstream and Downstream operations. Listed below are groups of STDs and RPs that help ensure safe operation of the plant and reduce exposures to workers and the surrounding community.

API PERSONNEL SAFETY SET

PERSONNEL SAFETY INCLUDES THE FOLLOWING API STANDARDS: STD 2217A, RP 2016, STD 2220RP 2221, RP 54, RP 74, STD 2015

API PROCESS SAFETY SET

PROCESS SAFETY INCLUDES THE FOLLOWING API STANDARDS: PUBL 770, PUBL 9100, RP 751 RP 752

API SAFETY & FIRE SET

SAFETY AND FIRE - INCLUDES THE FOLLOWING API STANDARDS: 54, 74, 751, 752, 770, 2001, 2003, 2009, 2015, 2016, 2021, 2021A, 2023, 2026, 2027, 2028,

2030, 2201, 2207, 2210, 2214, 2216, 2217A 2218, 2219, 2220, 2221, 2350, 2510A, 9100

8.2 Consumer Exposure

Many lubricant products are available to the general consumer, i.e., automotive products such as motor oil. Labeling and packaging of many consumer products containing lubricating oils in the USA is regulated by the Consumer Product Safety Commission (CPSC). Any use of lubricating oils in pesticide products as a carrier is regulated by EPA under FIFRA. Transportation of lubricating base oils or products containing lubricating oils would be regulated by the Department of Transportation.

Nonlubricant products that contain mineral oils include cosmetics, preservatives, medicinal applications, cleaning fluid, baby oils, and many others. The cosmetic and pharmaceutical uses of lubricating base oils result in dermal and oral exposures from the intended applications. Food-grade white oils are approved for uses resulting in direct or indirect food contact. These uses are regulated under various national and international laws which set strict limits for the content of impurities, particularly extractable aromatic compounds which include PAHs. The U.S. FDA regulations covering white oils, waxes and petrolatum are found in 21CFR 172.

Dietary exposures to food-grade mineral hydrocarbons (MHC) which include white oils, waxes and petrolatum were estimated for the U.S. population in an extensive study by Heimbach *et al*. (2002). This study covered both direct-additive uses in which the MHC is intentionally applied to the food and indirect uses in which the MHC become components of the food due to migration from food-contact surfaces. Exposures were primarily based on a food consumption approach in which MHC concentrations in foods were multiplied by the amount of these foods consumed. This resulted in conservative estimates because it assumed that all foods that might contain MHC in fact do so at maximum estimated concentrations. Exposures from food packaging uses were estimated using the FDA's food-factor approach which takes into account the volumes and kinds of food packaged with specific types of materials. A conservative estimate of mean total exposure to all MHC types was 0.875 mg/kg/day. Half of this, 0.427 mg/kg/day, was white mineral oils used as pan-release lubricants in baking, for de-dusting of stored grain, in confectionaries and in fruit and vegetable coatings. Nearly all the remainder, 0.404 mg/kg/day, was petrolatum, primarily from its use in bakeries. Exposure to paraffin and microcrystalline waxes combined was estimated at 0.044 mg/kg/day.

8.3 Exposure to Children

There is no specific data on exposure to lubricating oils to children, however they will share most of the same exposure situations that general consumers do.

9. MATRIX OF DATA FOR LUBRICATING OIL BASESTOCKS CATEGORY

The data matrix for LOBs is divided into the following five tables.

Table 18 Physical and chemical properties of lubricating oil basestocks
Table 19 Environmental fate of lubricating oil basestocks
Table 20 Environmental effects of lubricating oil basestocks
Table 21 Matrix of data on mammalian toxicity for raw and mildly refined LOBs.
Table 22 Matrix of data on mammalian toxicity for "other LOBs" and white oils.

Table 18. Physical-Chemical Properties of Lubricating Oil Basestocks.

Endpoint	**Raw and Mildly Refined LOBs** Multiple CAS No.	**Other LOBs** Multiple CAS No.	**White Mineral Oil** CAS No. 8042-47-5	**Read-Across to Untested Category Members (Raw/Mildly Refined)**	**Read-Across to Untested Category Members (Highly Refined)**
Pour Point (°C)				-60 to +15.5°C	-60 to +15.5°C
Boiling Range (°C)				ca. 232°C to 800°C	ca. 232°C to 800°C
Vapor Pressure (Pa)				Negligible	Negligible
Partition Coefficient				>4	>4
Water Solubility (mg/L)				<1	<1

Table 19. Environmental Fate of Lubricating Oil Basestocks.

Endpoint	**Raw and Mildly Refined LOBs** Multiple CAS No.	**Other LOBs** Multiple CAS No.	**White Mineral Oil** CAS No. 8042-47-5	**Read-Across to Untested Category Members (Raw/Mildly Refined)**	**Read-Across to Untested Category Members (Highly Refined)**
Biodegradation				Not readily biodegradable	Not readily biodegradable
Photodegradation	Constituents of lubricating oil basestocks have low vapor pressure and would not likely partition readily to the atmosphere. However, if conditions permit this to occur, these compounds are shown to readily undergo indirect photodegradation and not persist in the atmosphere. Estimate half-life values for individual compounds ranged from 0.053 days to 0.66 days.				
Stability in Water	Constituent compounds in lubricating oil basestocks do not possess chemical linkages known to undergo hydrolysis reactions. Therefore these substances will be stable in water.				
Environmental Transport	Lubricating oil basestocks are complex substances comprised of hydrocarbons having low vapor pressure and low water solubility. When these substances enter the environment, they are expected to partition mostly to soil, with only the lowest molecular weight constituents partitioning to the air. Very little will partition to water as the constituents that comprise the lubricating oil basestocks are highly water insoluble.				

Table 20. Environmental Effects of Lubricating Oil Basestocks

Endpoint	**Raw and Mildly Refined LOBs** Multiple CAS No.	**Other LOBs** Multiple CAS No.	**White Mineral Oil** CAS No. 8042-47-5	**Read-Across to Untested Category Members (Raw/Mildly Refined)**	**Read-Across to Untested Category Members (Highly Refined)**
Acute Fish					
96-h LL50		>1,000 mg/L		>1,000 mg/L	>1,000 mg/L
96-h LL0		1,000 mg/L		1,000 mg/L	1,000 mg/L
NOELR		1,000 mg/L		1,000 mg/L	1,000 mg/L
Acute Daphnia					
48-h EL50		>10,000 mg/L		>10,000 mg/L	>10,000 mg/L
48-h EL0		10,000 mg/L		10,000 mg/L	10,000 mg/L
NOELR		10,000 mg/L		10,000 mg/L	10,000 mg/L
Algae					
72-h E_bL50		>50% WAF		>50% WAF	>50% WAF
72-h E_rL50		--		--	--
$NOELR_{biomass}$		50% WAF		50% WAF	50% WAF
$NOELR_{growth\ rate}$		--		--	--
Chronic Daphnia					
21-d survival EL50		>1,000 mg/L		>1,000 mg/L	>1,000 mg/L
21-d survival NOELR		1,000 mg/L		1,000 mg/L	1,000 mg/L
21-d reproduction EL50		>1,000 mg/L		>1,000 mg/L	>1,000 mg/L
21-d reproduction NOELR		1,000 mg/L		1,000 mg/L	1,000 mg/L

Table 21. Matrix of data on mammalian toxicity for raw and mildly refined LOBs. Data are from testing of one sample with given CAS number unless otherwise noted.

CAS Number	Oral LD_{50} (mg/kg)	Dermal LC_{50} (mg/kg)	LC_{50} (mg/L)	Repeated Dermal Dose (mg/kg)		In vitro Genotoxicity	In vivo Genotoxicity	Developmental Toxicity with Dermal Dosing (mg/kg)		Reproductive Toxicity
64741-50-0	>5,000	>2,000		NOAEL				NOAEL		
				PDR_{10}	2,000			PDR_{10}	2,000	
64741-51-1				NOAEL				NOAEL		
				PDR_{10}	62 to >2,000 (1)			PDR_{10}	59 to >2,000 (1)	
64741-52-2				NOAEL				NOAEL		
				PDR_{10}	480			PDR_{10}	1,842	
64741-53-3				NOAEL				NOAEL		
				PDR_{10}	38			PDR_{10}	28	
64742-18-3										
64742-19-4										
64742-34-3										
64742-35-4										
Read-across to untested raw or mildly refined LOBs	>5,000	>2,000			38 (2)	(3)	(3)		28 (2)	$\geq$NOAEL for developmental toxicity

1) Range of PDR10s for 10 samples.
2) The lowest PDR10 for raw or mildly refined LOBs can be assumed to apply to an untested sample unless refining history, data on PAC content, or other information suggests otherwise.
3) Raw or mildly refined LOBs are expected to be mutagenic *in vitro*. Some specific samples may not be mutagenic, but testing is needed to establish the lack of mutagenicity.

Table 22. Matrix of data on mammalian toxicity for highly refined "other LOBs" and white oils. Data are from testing of one sample with given CAS number unless otherwise noted. NOAELs with repeated-dose dermal studies are for systemic effects.

CAS Number	Oral LD_{50} (mg/kg)	Dermal LC_{50} (mg/kg)	LC_{50} (mg/L)	Repeated Dose	In vitro Genotoxicity	In vivo Genotoxicity	Developmental Toxicity	Reproductive Toxicity
Other LOBs								
64741-76-0								
64741-88-4			>5.53	1,000 mg/kg dermal NOAEL				
64741-89-5								
64741-95-3								
64741-96-4	>5,000	>5,000						
64741-97-5	>5,000	>5,000						
64742-01-4								
64742-37-6								
64742-44-5								
64742-52-5	>5,000	>2,000						
64742-53-6	>5,000	>2,000						
64742-54-7	>15,000	>5,000		2,000 mg/kg dermal NOEL 210 mg/m^3 90-day NOAEC				1,000 mg/kg/day oral NOAEL (limited data)
64742-55-8								
64742-56-9	>5,000	>5,000	>5.4	1,000 mg/kg dermal NOAEL				
64742-57-0								
64742-62-7				1,000 mg/kg dermal NOAEL				
64742-63-8								
64742-65-0	>5,000 (1) >15,000	>5,000 (2)	>2.4	2,000 mg/kg (1) 1,000 mg/kg (1) Dermal NOAELs				
64742-67-2								
64742-70-7	>15,000	>5,000	>2.46	1,720 mg/kg dermal NOAEL 210 mg/m^3 90-day NOAEC			2,000 mg/kg/day dermal NOAEL	

Table 22 Continued.

CAS Number	Oral LD_{50} (mg/kg)	Dermal LC_{50} (mg/kg)	LC_{50} (mg/L)	Repeated Dose	In vitro Genotoxicity	In vivo Genotoxicity	Developmental Toxicity	Reproductive Toxicity
64742-71-8								
72623-83-7				2,000 mg/kg dermal NOAEL				
72623-84-8								
72623-85-9								
72623-86-0								
72623-87-1								
Read-across to untested "other LOBs"	>5,000	>5,000	>5	>1,000 mg/kg/day Dermal NOAEL	(3)	(3)	2,000 mg/kg/day if highly refined	≥NOAEL for developmental toxicity
White Mineral Oil								
8042-47-5	>5,000 (5)	>5,000 (5)	>2.46	210 mg/m^3 90-day NOAEC	(4)	(4)	2,000/kg/day dermal NOAEL 1,000 mg/m^3 NOAEC 5,000 mg/kg/day oral NOAEL	2,000 mg/kg/day dermal NOAEL (limited data)

1) Value (the highest dose tested) was the same in tests on three separate samples.
2) Value (the highest dose tested) was the same in tests on four separate samples.
3) Expected to be highly refined and therefore not mutagenic. However, testing or thorough knowledge of refining history is needed for specific samples to establish the lack of mutagenicity.
4) Considered to be highly refined and not mutagenic.
5) Based on read-across from other highly refined LOBs.

10. CATEGORY ANALYSIS CONCLUSIONS

Lubricating Oil Basestocks are a family of complex hydrocarbon substances with variable composition. LOBs have typical pour points between –60°C and +15.5°C. Boiling points of constituent hydrocarbons vary with the type of basestock, but may range between 232°C and 600°C for distillate basestocks and up to 800°C for residual basestocks. These substances have negligible vapor pressure and partition coefficients of >4 for constituent hydrocarbons. Water solubility is < 1 ppm.

The available acute toxicity test data for aquatic organisms show that no acute effects would be expected from exposure to substances in the lubricating oil basestocks category. With the principal hydrocarbons in these substances falling within the range of C15 to C50, no acute toxicity effects would be anticipated. This is because acute toxicity reported for alkanes and alkylbenzenes is not expressed for molecular weight compounds representative of ≥C10 and ≥C15, respectively. In chronic exposures to freshwater invertebrates, toxicity is typically not observed, and the weight of the scientific evidence leads to the conclusion that these substances do not cause chronic toxicity in aquatic organisms.

Because LOBs are a family of substances with variable composition, the amount and profile of PACs can differ among different samples. As a result, mammalian toxicity with repeated exposures, mutagenicity, and carcinogenicity has been shown to vary with the PACs in the samples. Marketed, highly refined LOBs would not be considered hazardous. Testing or a thorough knowledge of refining history is needed to verify this demarcation as nonhazardous for samples within the group of "other LOBs". Raw or mildly refined distillate LOBs would be considered hazardous, although some individual samples could have very low PAC levels and be considered highly refined based on toxicity tests.

Multiple acute toxicity studies on a variety of LOBs have consistently shown these materials to have low acute toxicity by dermal, oral, and inhalation routes. Experimental data were not available for repeated-dose dermal studies with raw or mildly refined LOBs, but the lowest (sample) PDR_{10}s ranged from 38 to 2,000 mg/kg. For highly refined LOBs, several repeated-dose dermal studies in both rats (13-week exposures) and rabbits (3-4 week exposures) with LOBs of various CAS numbers and ranges of viscosities consistently demonstrated NOAELs for systemic toxicity in the range of 1,000 to 2,000 mg/kg/day, typically the highest doses tested. Effects of highly refined LOBs in repeated-dose inhalation studies were similar to those of particles with low toxicity; the overall NOAEL was 210 mg/m^3 for 90-day exposures. Repeated oral dosing of white oils led to changes that were limited to the Fischer 344 rat and are not relevant to humans.

Studies have shown a consistent relationship among the degree and conditions of refining, the associated 3-7 ring PAC content, and mutagenic potency of the LOB. Raw or mildly refined LOBs would be expected to be mutagenic *in vitro* and possibly *in vivo*. The highly refined LOBs would not be expected to be mutagenic, but testing or a thorough knowledge of the refining history of a given sample would be needed to confirm that premise. Regarding cancer, there is a large body of toxicity data relating to raw and mildly refined LOBs that dates back over 50 years showing that these LOBs produce skin cancer in the mouse and can possibly cause cancer of the respiratory tract upon inhalation of aerosols of the material. Highly refined LOBs are not expected to be carcinogenic.

Experimental data on the dermal developmental toxicity of raw or mildly refined distillate LOBs were not available, but sample PDR_{10}s ranged from 28 to 2000 mg/kg/day In contrast, NOAELs in dermal studies with highly refined LOBs and a white mineral oil were 900 to 2,000 mg/kg (the highest dose tested in a given study). Similarly, an inhalation study with a highly refined distillate LOB showed a NOAEC of 1,000 mg/m^3 and an oral study with a white mineral oil showed a NOAEL of 5,000 mg/kg/day.

Adverse effects on reproduction were not reported in dermal and oral studies with highly refined LOBs, but these studies were incomplete. Although these results are not conclusive, they do indicate that the highly refined LOBs are likely to have little, if any, effects on reproductive parameters. The raw or mildly refined LOBs or other LOBs that are not highly refined are unlikely to have greater reproductive toxicity.

Regarding cancer, there is a large body of toxicity data relating to raw and mildly refined LOBs that dates back over 50 years and shows that these LOBs produce skin cancer in the mouse and can possibly cause cancer of the respiratory tract upon inhalation of aerosols of the material. In contrast, highly refined LOBs are not expected to be carcinogenic.

Links to websites with additional background and information on petroleum refining and petroleum substances are in Appendix 5.

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12. LIST OF APPREVIATIONS AND ACRONYMS

API – American Petroleum Institute
BOD – biological oxygen demand
AUGC – area under the growth curve
CAS RN/CAS #/CAS No. - Chemical Abstract Service Registry Number
^{o}C – degrees Celsius
CIR – Cosmetics Ingredients Review Panel
CONCAWE – Conservation of Clean Air and Water in Europe
d - day
DMSO – Dimethyl sulfoxide
EINECS – European Inventory of Existing Commercial Chemical Substances
EL_{50} – effective loading rate lethal to 50% of the test population
E_bL_{50} – effective loading rate that causes 50% reduction in algal cell biomass
E_rL_{50} – effective loading rate that causes 50% reduction in algal growth rate
EPA/US EPA – United States Environmental Protection Agency
g/cm^3 – grams per cubic centimeter
h - hour
HLS – Huntingdon Life Sciences
HPV – High Production Volume
HSDB – Hazardous Substances Data Bank
IRDC – International Research and Development Corporation
^{o}K – degrees Kelvin
kPa - kilopascal
LC_{50} – lethal concentration for 50% of the test population
LC_{50}– lethal dose level for 50% of the test population
LL_{50} – lethal loading rate for 50% of the test population
Loading Rate – total amount of test substance added to dilution water to prepare water accommodated fractions (WAFs) for ecotoxicity testing
LOAEL – lowest observable adverse effect level
mg/kg – milligrams per kilogram
mg/L – milligrams per liter
mg/m^3 – milligrams per cubic meter
mL - milliliter
mm - millimeter
nm - nanometer
NOAEL – no observable adverse effect level
NOEC – no observable effect concentration
NOELR – no observable effect loading rate
NTP – National Toxicology Program
OECD – Organization for Economic Cooperation and Development
OPPTS – US EPA Office of Prevention, Pesticides and Toxic Substances
PAC - Polycyclic aromatic compound
PAH – polycyclic aromatic hydrocarbon
PNA – polynuclear aromatic

ppm – part per million
SIDS – Screening Information Data Set
UNEP – United Nations Environment Program
US EPA – United States Environmental Protection Agency
UV - ultraviolet
WAF – water accommodated fraction
wt% - weight percent
μg - microgram
μg/L – microgram/liter
> greater than
< less than

13. GLOSSARY

NOTE: The following terms are used in this document. To the extent possible, definitions were taken from relevant authoritative sources such as EPA, OECD, ASTM and IUPAC.

Acute Toxicity: The adverse effects occurring within a short time-frame of administration of a single dose of a substance, multiple doses given within 24 hours, or uninterrupted exposure over a period of 24 hours or less. Exposure may be via oral, dermal or inhalation routes as described in OECD Guidelines 401, 402, 403, and 420 in OECD Guidelines for the Testing of Chemicals.

Alga, Growth Inhibition Test: In a three-day exposure, growth inhibition is defined by the EC_{50}, the concentration of test substance in growth medium which results in a 50% reduction in either alga cell growth or growth rate relative to a control group. Test methodology is described in OECD Guideline 201, in OECD Guidelines for the Testing of Chemicals.

ARC: Aromatic ring class that reflects the weight percent of PACs that have a given number of aromatic rings (1 through 7) within the total analyzed sample.

Bioavailability: The state of being capable of being absorbed and available to interact with the metabolic processes of an organism. Typically a function of chemical properties, physical state of the material to which an organism is exposed, and the ability of the individual organism to physiologically take up the chemical. Also, the term used for the fraction of the total chemical in the environmental which is available for uptake by organisms. (AIHA, 2000)

Biodegradation: Breakdown of a substance catalyzed by enzymes *in vitro* or *in vivo*. As an endpoint in EPA's HPV program, biodegradation is measured by one of six methodologies described in OECD Guidelines 301A-F, in OECD Guidelines for the Testing of Chemicals.

BMD: The Benchmark Dose is the dose producing a predetermined change in response and is calculated from a dose-response model statistically fitted to experimental data. (Gephart, et al, 2001)

Category Member: The individual chemical or substance entities that constitute a chemical category.

Category: A chemical category, for the purposes of the HPV Challenge Program, is a group of chemicals whose physicochemical and toxicological properties are likely to be similar or follow a regular pattern as a result of structural similarity. These structural similarities may create a predictable pattern in any or all of the following parameters: physicochemical properties, environmental fate and environmental effects, and/or human health effects. (US EPA, 2007)

***Daphnia* sp., Acute Immobilization Test:** In a one or two-day exposure, acute toxicity is defined by the EC_{50}, the concentration of test substance in water which causes immobilization to 50% of the test population of invertebrates. Test methodology is described in OECD Guideline 202, Part 1, in OECD Guidelines for the Testing of Chemicals.

Developmental Toxicity: Adverse effects on the developing organism that may result from exposure prior to conception (either parent), during prenatal development, or postnatally until the time of sexual maturation. The major manifestations of developmental toxicity include death of the developing organism, structural abnormality, altered growth, and functional deficiency. (US NLM, 2007)

Dose: The amount of a substance available for interactions with metabolic processes or biologically significant receptors after crossing the outer boundary of an organism. The **potential dose** is the amount ingested, inhaled, or applied to the skin. The **applied dose** is the amount presented to an absorption

barrier and available for absorption (although not necessarily having yet crossed the outer boundary of the organism). The **absorbed dose** is the amount crossing a specific absorption barrier (e.g., the exchange boundaries of the skin, lung, and digestive tract) through uptake processes. **Internal dose** is a more general term denoting the amount absorbed without respect to specific absorption barriers or exchange boundaries. The amount of the chemical available for interaction by an particular organ or cell is termed the delivered or **biologically effective dose** for that organ or cell (US EPA, 2002).

Dose-Response Relationship: The relationship between a quantified exposure (dose) and the proportion of subjects demonstrating specific biological changes in incidence or in degree of change (response) (US EPA, 2002).

Ecological Effects – all endpoints (OECD definitions)

Endpoint: In the context of the EPA High Production Volume Challenge Program, an endpoint is a physical-chemical, environmental fate, ecotoxicity, and human health attribute measurable by following an approved test methodology (e.g., OECD Guidelines for Testing of Chemicals). Melting point, biodegradation, fish acute toxicity, and genetic toxicity are examples of endpoints that are measured by an approved test method. (US EPA, 1999)

Environmental Fate Effects – all endpoints (OECD definitions)

Exposure: Contact made between a chemical, physical, or biological agent and the outer boundary of an organism. Exposure is quantified as the amount of an agent available at the exchange boundaries of the organism (e.g., skin, lungs, gut). (US EPA, 2002).

Feedstock: A refinery product that is used as the raw material for another process; the term is also generally applied to raw materials used in other industrial processes. (Speight, 2007).

Female Mating Index: Number of females with confirmed mating (sperm and/or vaginal plug)/number of females placed with males. (US EPA, 1996)

Fish, Acute Toxicity Test: In a four-day exposure, acute toxicity is defined by the LC_{50}, the concentration of test substance in water which kills 50% of the test population of fish. Test methodology is described in OECD Guideline 203, in OECD Guidelines for the Testing of Chemicals.

Genetic Toxicity *in vitro* (Gene Mutations): The assessment of the potential of a chemical to exert adverse effects through interaction with the genetic material of cells in cultured mammalian cells. Genotoxicity may be studies in cultured cells using methods described in OECD Guideline 476, in OECD Guidelines for the Testing of Chemicals.

Genetic Toxicity *in vivo* (Chromosomal Aberrations): The assessment of the potential of a chemical to exert adverse effects through interaction with the genetic material of cells in the whole animal. Genotoxicity may be studies in the whole animal using methods described in OECD Guideline 475, in OECD Guidelines for the Testing of Chemicals.

Hazard: A potential source of harm (US EPA, 2002).

Hazard Assessment: The process of determining whether exposure to an agent can cause an increase in the incidence of a particular adverse health effect (e.g., cancer, birth defect) and whether the adverse health effect is likely to occur in humans (US EPA, 2002).

Hazard Characterization: A description of the potential adverse health effects attributable to a specific environmental agent, the mechanisms by which agents exert their toxic effects, and the associated dose, route, duration, and timing of exposure (US EPA, 2002).

Health Effects : all endpoints (OECD definitions, unless otherwise specified)

Highly Refined: a descriptor for those lubricant oil basestocks that are not expected to be mutagenic or dermally carcinogenic based on knowledge of refining history or results from tests such as the optimized Ames assay, IP346 assay, skin-painting tests in mice, and analysis of PAC content by GC (such as PAC-2 method).

Lowest-Observed-Adverse-Effect Level (LOAEL): The lowest exposure level at which there are statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control group (US EPA, 2002).

Modified Ames Test: A modification of the Ames test used for petroleum materials and designed to facilitate physical contact between the test substance and the bacteria as well as enhance the reactions among the bacteria. Also referred to as the optimized Ames test.

Mutagenicity Index: The primary endpoint in the modified Ames test indicating the slope for the linear portion of the dose-response curve (number of revertant colonies vs dose of test substance per plate.

No-Observed-Adverse-Effect Level (NOAEL): The highest exposure level at which there are no biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control group; some effects may be produced at this level, but they are not considered adverse or precursors to adverse effects (US EPA, 2002).

Optimized Ames Test: See modified Ames test.

PAC Profile: The listing of the weight percent of each of the DMSO-extractable 1- through 7-ring polycyclic aromatic compounds from a test material. (API, 2008)

PAC 2: A single analytical method that involves solvent extraction (DMSO) and an analysis of the DMSO-extracted concentrate of PACs by gas chromatography with an FID or MS detector. The DMSO extraction procedure is selective for the less polar PAC species, so that highly alkylated PACs are excluded from measurement. (API, 2008)

PDR_{10}: The Predicted Dose for a Response that is a 10% change from control. The prediction is based on models developed from a series of exposure-response studies. (API, 2008)

Photodegradation: The photochemical transformation of a molecule into lower molecular weight fragments, usually in an oxidation process. This process may be measured by Draft OECD Guideline, "*Phototransformation of Chemicals in Water – Direct and Indirect Photolysis*". This process also may be estimated using a variety of computer models.

Portal-of- Entry Effect: A local effect produced at the tissue or organ of first contact between the biological system and the toxicant (US EPA, 1994).

Read-Across: Read-across can be regarded as using data available for some members of a category to estimate values (qualitatively or quantitatively) for category members for which no such data exist. (OECD, 2007)

Repeated Dose Toxicity: The adverse effects occurring due to repeated doses that may not produce immediate toxic effects, but due to accumulation of the chemical in tissues or other mechanisms, produces delayed effects. Repeated dose toxicity may be studied following methods described in OECD Guidelines 407, 410, or 412 in OECD Guidelines for the Testing of Chemicals.

Reproductive Toxicity: The occurrence of biologically adverse effects on the reproductive systems of females or males that may result from exposure to environmental agents. The toxicity may be expressed as alterations to the female or male reproductive organs, the related endocrine system, or pregnancy outcomes. The manifestation of such toxicity may include, but not be limited to, adverse effects on onset of puberty, gamete production and transport, reproductive cycle normality, sexual behavior, fertility, gestation, parturition, lactation, developmental toxicity, premature reproductive senescence, or modifications in other functions that are dependent on the integrity of the reproductive systems. (US EPA, 1996)

Stability in Water: This environmental fate endpoint is achieved by measuring the hydrolysis of the test substance. Hydrolysis is defined as a reaction of a chemical RX with water, with the net exchange of the group X with OH at the reaction center. Test methodology for hydrolysis is described in OECD Guideline 111, in OECD Guidelines for the Testing of Chemicals.

Systemic Effects or Systemic Toxicity: Toxic effects as a result of absorption and distribution of a toxicant to a site distant from its entry point (US EPA, 2002).

Target Organ: The biological organ(s) most adversely affected by exposure to a chemical or physical agent (US EPA, 2002).

Transport Between Environmental Compartments: This endpoint describes the distribution of a chemical between environmental compartments using fugacity-based computer models. The results of the model algorithms provide an estimate of the amount of the chemical within a specific compartment. The environmental compartments included in many models are air, water, soil, sediment, suspended sediment, and aquatic biota.

APPENDIX 1. CAS Numbers and Definitions of Category Members

The following list of CAS numbers and their definitions are sponsored in the HPV Challenge program in the Lubricating Base Oils Category. Because of the lack of process history detail in the CAS definitions, it is not always possible to determine the degree of refining for many of the basestocks. Nonetheless, the CAS numbers are grouped here based on the most likely degree of refining. The degree of refining for specific samples would need to be determined based on processing history and/or tests for PAC content or biological activity.

Distillate Basestocks Derived from Crude Oil (Raw and Mildly Refined)

64741-50-0 Distillates (petroleum), light paraffinic
A complex combination of hydrocarbons produced by vacuum distillation of the residuum from atmospheric distillation of crude oil. It consists of hydrocarbons having carbon numbers predominantly in the range of C_{15} through C_{30} and produces a finished oil with a viscosity of less than 100 SUS at 100°F (19cSt at 40°C). It contains a relatively large proportion of saturated aliphatic hydrocarbons normally present in this distillation range of crude oil.

64741-51-1 Distillates (petroleum), heavy paraffinic
A complex combination of hydrocarbons produced by vacuum distillation of the residuum from atmospheric distillation of crude oil. It consists of hydrocarbons having carbon numbers predominantly in the range of C_{20} through C_{50} and produces a finished oil with a viscosity of at least 100 SUS at 100°F (19cSt at 40°C). It contains a relatively large proportion of saturated aliphatic hydrocarbons.

64741-52-2 Distillates (petroleum), light naphthenic
A complex combination of hydrocarbons produced by vacuum distillation of the residuum from atmospheric distillation of crude oil. It consists of hydrocarbons having carbon numbers predominantly in the range of C_{15} through C_{30} and produces a finished oil with a viscosity of less than 100 SUS at 100°F (19cSt at 40°C). It contains relatively few normal paraffins.

64741-53-3 Distillates (petroleum), heavy naphthenic
A complex combination of hydrocarbons produced by vacuum distillation of the residuum from atmospheric distillation of crude oil. It consists of hydrocarbons having carbon numbers predominantly in the range of C_{20} through C_{50} and produces a finished oil with a viscosity of at least 100 SUS at 100°F (19cSt at 40°C). It contains relatively few normal paraffins.

64742-18-3 Distillates (petroleum), acid-treated heavy naphthenic
A complex combination of hydrocarbons obtained as a raffinate from a sulfuric acid treating process. It consists of hydrocarbons having carbon numbers predominantly in the range of C_{20} through C_{50} and produces a finished oil with a viscosity of at least 100 SUS at 100°F (19cSt at 40°C). It contains relatively few normal paraffins.

64742-19-4 Distillates (petroleum), acid-treated light naphthenic
A complex combination of hydrocarbons obtained as a raffinate from a sulfuric acid treating process. It consists of hydrocarbons having carbon numbers predominantly in the range of C_{15} through C_{30} and produces a finished oil with a viscosity of less than 100 SUS at 100°F (19cSt at 40°C). It contains relatively few normal paraffins.

64742-34-3 Chemically neutralized heavy naphthenic distillate (petroleum)
A complex combination of hydrocarbons produced by a treating process to remove acidic materials. It consists of hydrocarbons having carbon numbers predominantly in the range of C_{20} through C_{50} and produces a finished oil with a viscosity of at least 100 SUS at 100°F (19cSt at 40°C). It contains relatively few normal paraffins.

64742-35-4 Chemically neutralized light naphthenic distillate (petroleum)
A complex combination of hydrocarbons produced by a treating process to remove acidic materials. It consists of hydrocarbons having carbon numbers predominantly in the range of C_{15} through C_{30} and produces a finished oil with a viscosity of less than 100 SUS at 100°F (19cSt at 40°C). It contains relatively few normal paraffins.

Distillate Basestocks Derived from Crude Oil (Other LOBs)[1]

64741-76-0 Distillates (petroleum), heavy hydrocracked
A complex combination of hydrocarbons from the distillation of the products from a hydrocracking process. It consists predominantly of saturated hydrocarbons having carbon numbers in the range of C_{15} through C_{39} and boiling in the range of approximately 260°C to 600°C (500°F to 1112°F).

64741-88-4 Distillates (petroleum), solvent-refined heavy paraffinic
A complex combination of hydrocarbons obtained as the raffinate from a solvent extraction process. It consists predominantly of saturated hydrocarbons having carbon numbers predominantly in the range of C_{20} through C_{50} and produces a finished oil with a viscosity of at least 100 SUS at 100°F (19cSt at 40°C).

64741-89-5 Distillates (petroleum), solvent-refined light paraffinic
A complex combination of hydrocarbons obtained as the raffinate from a solvent extraction process. It consists predominantly of saturated hydrocarbons having carbon numbers predominantly in the range of C_{15} through C_{30} and produces a finished oil with a viscosity of less than 100 SUS at 100°F (19cSt at 40°C).

64741-96-4 Distillates (petroleum), solvent-refined heavy naphthenic
A complex combination of hydrocarbons obtained as the raffinate from a solvent extraction process. It consists of hydrocarbons having carbon numbers predominantly in the range of C_{20} through C_{50} and produces a finished oil with a viscosity of at least 100 SUS at 100°F (19cSt at 40°C). It contains relatively few normal paraffins.

64741-97-5 Distillates (petroleum), solvent-refined light naphthenic

A complex combination of hydrocarbons obtained as the raffinate from a solvent extraction process. It consists of hydrocarbons having carbon numbers predominantly in the range of C_{15} through C_{30} and produces a finished oil with a viscosity of less than 100 SUS at 100°F (19cSt at 40°C). It contains relatively few normal paraffins.

64742-37-6 Distillates (petroleum), clay-treated light paraffinic
A complex combination of hydrocarbons resulting from treatment of a petroleum fraction with natural or modified clay in either a contacting or percolation process to remove the trace amounts of polar compounds and impurities present. It consists of hydrocarbons having carbon numbers predominantly in the range of C_{15} through C_{30} and produces a finished oil with a viscosity of less than 100 SUS at 100°F (19cSt at 40°C). It contains a relatively large proportion of saturated hydrocarbons.

64742-44-5 Distillates (petroleum), hydrotreated heavy naphthenic
A complex combination of hydrocarbons obtained by treating a petroleum fraction with hydrogen in the presence of a catalyst. It consists of hydrocarbons having finished oil of at least 100 SUS at 100°F (19cSt at 40°C). It contains relatively few normal paraffins.

64742-52-5 Distillates, (petroleum), hydrotreated heavy naphthenic
A complex combination of hydrocarbons obtained by treating a petroleum fraction with hydrogen in the presence of a catalyst. It consists of hydrocarbons having carbon numbers predominantly in the range of C20 through C50 and produces a finished oil of at least 100 SUS at 100.degree.F (19cSt at 40°C). It contains relatively few normal paraffins.

64742-53-6 Distillates (petroleum), hydrotreated light naphthenic
A complex combination of hydrocarbons obtained by treating a petroleum fraction with hydrogen in the presence of a catalyst. It consists of hydrocarbons having carbon numbers predominantly in the range of C_{15} through C_{30} and produces a finished oil with a viscosity of less than 100 SUS at 100°F (19cSt at 40°C). It contains relatively few normal paraffins.

64742-54-7 Distillates (petroleum), hydrotreated heavy paraffinic
A complex combination of hydrocarbons obtained by treating a petroleum fraction with hydrogen in the presence of a catalyst. It consists of hydrocarbons having carbon numbers predominantly in the range of C_{20} through C_{50} and produces a finished oil of at least 100 SUS at 100°F (19cSt at 40°C). It contains a relatively large proportion of saturated hydrocarbons.

64742-55-8 Distillates (petroleum), hydrotreated light paraffinic
A complex combination of hydrocarbons obtained by treating a petroleum fraction with hydrogen in the presence of a catalyst. It consists of hydrocarbons having carbon numbers predominantly in the range of C_{15} through C_{30} and produces a finished oil with a viscosity of less than 100 SUS at 100°F (19cSt at 40°C). It contains a relatively large proportion of saturated hydrocarbons.

64742-56-9 Distillates (petroleum), solvent-dewaxed light paraffinic
A complex combination of hydrocarbons obtained by removal of normal paraffins from a petroleum fraction by solvent crystallization. It consists predominantly of hydrocarbons having carbon numbers predominantly in the range of C_{15} through C_{30} and produces a finished oil with a viscosity of less than 100 SUS at 100°F (19cSt at 40°C).

64742-63-8 Distillates (petroleum), solvent-dewaxed heavy naphthenic
A complex combination of hydrocarbon obtained by removal of normal paraffins from a petroleum fraction by solvent crystallization. It consists of hydrocarbons having carbon numbers predominantly in the range of C_{20} through C_{50} and produces a finished oil of not less than 100 SUS at 100°F (19cSt at 40°C). It contains relatively few normal paraffins.

64742-65-0 Distillates (petroleum), solvent-dewaxed heavy paraffinic
A complex combination of hydrocarbons obtained by removal of normal paraffins from a petroleum fraction by solvent crystallization. It consists predominantly of hydrocarbons having carbon numbers predominantly in the range of C_{20} through C_{50} and produces a finished oil with a viscosity not less than 100 SUS at 100°F (19cSt at 40°C).

64742-67-2 Foots oil, petroleum
A complex combination of hydrocarbons obtained as the oil fraction from a solvent deoiling or a wax sweating process. It consists predominantly of branched chain hydrocarbons having carbon numbers predominantly in the range of C20 through C50. [Comment from API Work Group: Foots oil, obtained from the deoiling of wax made from vacuum distillate, is essentially a raw basestock that undergoes similar process as any of the vacuum tower fractions, each step removing impurities and improving product performance.]

64742-70-7 Paraffin oils (petroleum), catalytic dewaxed heavy
A complex combination of hydrocarbons obtained from a catalytic dewaxing process. It consists predominantly of hydrocarbons having carbon numbers predominantly in the range of C_{20} through C_{50} and produces a finished oil with a viscosity of at least 100 SUS at 100°F (19cSt at 40°C).

64742-71-8 Paraffin oils (petroleum), catalytic dewaxed light
A complex combination of hydrocarbons obtained from a catalytic dewaxing process. It consists predominantly of hydrocarbons having carbon numbers predominantly in the range of C_{15} through C_{30} and produces a finished oil with a viscosity of less than 100 SUS at 100°F (19cSt at 40°C).

72623-85-9 Lubricating oils (petroleum), C_{20-50}, hydrotreated neutral oil-based, high-viscosity
A complex combination of hydrocarbons obtained by treating light vacuum gas oil, heavy vacuum gas oil, and solvent deasphalted residual oil with hydrogen n the presence of a catalyst in a two stage process with dewaxing being carried out between the two states. It consists predominantly of hydrocarbons having carbon numbers predominantly in the range of C_{20} through C_{50} and produces a finished oil having a viscosity of approximately 112cSt at 40°C. It contains a relatively large proportion of saturated hydrocarbons.

72623-86-0 Lubricating oils (petroleum), C_{15-30}, hydrotreated neutral oil-based
A complex combination of hydrocarbons obtained by treating light vacuum gas oil and heavy vacuum gas oil with hydrogen in the presence of a catalyst in a two stage process and dewaxing being carried out between the two stages. It consists predominantly of hydrocarbons having carbon numbers predominantly in the range of C_{15} through C_{30} and produces a finished oil having a viscosity of approximately 15cSt at 40°C. It contains a relatively large proportion of saturated hydrocarbons.

72623-84-8 Lubricating oils (petroleum), C15-30, hydrotreated neutral oil-based, contg. solvent deasphalted residual oil
A complex combination of hydrocarbons obtained by treating light vacuum gas oil, heavy vacuum gas oil, and solvent deasphalted residual oil with hydrogen in the presence of a catalyst in a two stage process with dewaxing being carried out between the two stages. It consists predominantly of hydrocarbons having carbon numbers predominantly in the range of C15 through C30 and produces a finished oil having a viscosity of approximately 10cSt at 40° C (104°F). It contains a relatively large proportion of saturated hydrocarbons.

Distillate Basestocks Derived from Crude Oil (White Oils)

8042-47-5 White mineral oil (petroleum)
A highly refined petroleum mineral oil consisting of a complex combination of hydrocarbons obtained from the intensive treatment of a petroleum fraction with sulphuric acid and oleum, or by hydrogenation, or by a combination of hydrogenation and acid treatment. Additional washing and treating steps may be included in the processing operation. It consists of saturated hydrocarbons having carbon numbers predominantly in the range of C_{15} through C_{50}.

Residual Basestocks Derived from Crude Oil (Other LOBs) [1]

64741-95-3 Residual oils (petroleum), solvent deasphalted
A complex combination of hydrocarbons obtained as the solvent soluble fraction from C_3 through C_4 solvent deasphalting of a residuum. It consists of hydrocarbons having carbon numbers predominantly higher than C_{25} and boiling above approximately 400°C (725°F).

64742-01-4 Residual oils (petroleum), solvent-refined
A complex combination of hydrocarbons obtained as the solvent insoluble fraction from solvent refining of a residuum using a polar organic solvent such as phenol or furfural. It consists of hydrocarbons having carbon numbers predominantly higher than C_{25} and boiling above approximately 400°C (725°F).

64742-57-0 Residual oils (petroleum), hydrotreated
A complex combination of hydrocarbons obtained by removal of long, branched chain hydrocarbons from a residual oil by solvent crystallization. It consists of hydrocarbons having carbon numbers predominantly greater than C_{25} and boiling above approximately 400°C (752°F).

64742-62-7 Residual oils, petroleum, solvent-dewaxed
A complex combination of hydrocarbons obtained by removal of long, branched chain hydrocarbons from a residual oil by solvent crystallization. It consists of hydrocarbons having carbon numbers predominantly greater than C25 and boiling above approximately 400 degree C (752°F).

72623-83-7 Lubricating oils (petroleum)C_{25}, hydrotreated bright stock-based
A complex combination of hydrocarbons obtained by treating solvent deasphalted residual oil with hydrogen in the presence of a catalyst in two stages with dewaxing carried out between stages. It consists predominantly of hydrocarbons having carbon numbers predominantly greater than C_{25} and produces a finished oil with a viscosity of approximately 440cSt at 40°C. It contains a relatively large proportion of saturated hydrocarbons.

72623-87-1 Lubricating oils (petroleum), C_{20-50}, hydrotreated neutral oil-based
A complex combination of hydrocarbons obtained by treating light vacuum gas oil, heavy vacuum gas oil and solvent deasphalted residual oil with hydrogen in the presence of a catalyst in a two stage process with dewaxing being carried out between the two stages. It consists predominantly of hydrocarbons having carbon numbers predominantly in the range of C_{20} through C_{50} and produces a finished oil with a viscosity of approximately 32cSt at 40°C. It contains a relatively large proportion of saturated hydrocarbons.

Re-Refined Oil Distillate Basestocks (Other LOBs)[1]

64742-58-1 Lubricating oils (petroleum), hydrotreated spent
A complex combination of hydrocarbons obtained by treating a spent lube oil with hydrogen in the presence of a catalyst. It consists predominantly of hydrocarbons having carbon numbers predominantly in the range of C15 through C50.

Footnotes

1) The substances in this group currently marketed by major refiners are highly refined. However, the CAS numbers encompass a range of refining such that not all products would meet the criteria for being "highly refined" from a toxicological perspective. Therefore evaluation of these products is conducted to ensure that they meet the criteria for being highly refined.

Appendix 2. PAC content of representative raw or mildly refined LOBs

ID	CAS No.	DMSO wt%[1]	% ARC 1[2]	% ARC 2[2]	% ARC 3[2]	% ARC 4[2]	% ARC 5[2]	% ARC 6[2]	% ARC 7[2]
Distillate Basestocks Derived from Crude Oil (Raw or Mildly Refined)									
Site# 23, Sample# 11	64741-50-0	0.3	0.0	0.0	0.3	0.0	0.0	0.0	0.0
Site# 12, Sample# 22	64741-51-1	5.2	0.0	0.0	0.2	0.3	0.5	1.5	2.6
Site# 12, Sample# 26	64741-51-1	6.6	0.0	0.0	2.0	4.0	0.7	0.1	0.0
Site# 23, Sample# 9	64741-51-1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Site# 37, Sample# 3	64741-51-1	1.4	0.0	0.0	0.3	0.3	0.4	0.4	0.1
Site# 37, Sample# 4	64741-51-1	0.8	0.0	0.0	0.0	0.0	0.1	0.2	0.5
Site# 33, Sample# 3	64741-52-2	6.1	0.1	2.4	3.1	0.3	0.0	0.0	0.0
Site# 7, Sample# 4	64741-52-2	12.5	0.0	5.0	6.3	1.3	0.3	0.0	0.0
Site# 33, Sample# 2	64741-53-3	6.0	0.0	0.0	0.6	2.4	1.8	1.2	0.4

1) Percent of DMSO-extractable PACs as determined by PAC 2 Method as described by API (2008).
2) ARC is "aromatic ring class". "ARC 1 %" is the weight percent of PACs that have 1 aromatic ring within the total sample. "ARC 2 %" is the percent of PACs with 2 aromatic rings, and so forth to 7 aromatic rings. Percent of each ring class was determined by PAC2 Method as described by API, 2008.

Appendix 3. Correlation between PAC Profile and Selected Endpoints of Mammalian Toxicity

As explained in the section on category definition and justification, the mammalian toxicity of the substances found in the LOBs is expected to be related to their PAC profile; particularly the toxicity measured in repeat-dose, developmental, and *in vitro* mutagenicity studies. The PAC[1] profile is the weight percent of DMSO-extractable, aromatic compounds contained in each of seven separate ring classes.

The initial indication that PAC content could be used to predict the toxicity of untested substances in the LOBs was based on the publication by Feuston et al. (1994). Their research, based on thirteen refinery streams, examined the correlations between the weight percentage of several chemical classes of compounds and the magnitude of various effects produced in rats treated dermally with these substances in repeat-dose and developmental toxicity studies. In general, Feuston et al. found that the toxicity of the streams was correlated with the concentrations of the 3 to 7 ring PACs. The analyses were based on the ranks of several measures of toxicity and the individual PAC concentrations.

In 2004, the API Testing Group recognized the need to further evaluate the observations made by Feuston et al. (1994) and commissioned a Task Group (PAC Analysis Task Group, or TG) comprised of experts in the fields of petroleum chemistry, toxicology, and biostatistics. The TG issued a report describing the relationships between PAC profile and the repeat-dose, developmental toxicities of high-boiling petroleum substances, i.e. those with initial boiling points greater than approximately 300 °F (API, 2008). Predictive models for 7 selected repeat-dose and developmental dermal toxicity endpoints in the rat were developed and discussed (API, 2008). The report was reviewed in a peer consultation process and the report and results are publicly available (TERA, 2008). Reports are in preparation on the relationship between PACs and reproductive and genetic toxicities of high-boiling petroleum substances.

Four potential sources of information were reviewed for the project: the publication by Feuston et al (1994), other published literature on the toxicity of individual PAH and PAC containing materials, studies sponsored by the American Petroleum Institute (API), and unpublished company laboratory reports. The unpublished laboratory reports consisted of: (1) reports of repeat-dose toxicity studies, (2) reports of developmental toxicity studies, (3) two reproductive toxicity screening studies, one each with treated males and females, on a single substance containing a high concentration of PAC, (4) an exploratory dose range-finding study in non-pregnant female rats, (5) reports of mutagenesis tests, primarily results of optimized Ames tests, and (6) reports of compositional data on the tested substances. All unpublished company laboratory reports (repeat-dose, developmental toxicity, and analytical) were judged to be either "reliable without restrictions" or "reliable with restrictions, i.e. reliability scores of 1 or 2 (Klimsch, et al. 1997).

The relationship between acute toxicity and PAC was not investigated statistically since the reported oral LD_{50} values for high-boiling petroleum substances are generally greater than the maximum doses tested, typically 5 g/kg and 2 g/kg for oral and dermal exposures, respectively (API 2001, 2002, 2003a,

[1] Note that "polycyclic aromatic hydrocarbons" (PAH) refers to compounds of two or more fused-aromatic rings consisting of carbon and hydrogen only. Polycyclic aromatic compounds (PAC) is a more inclusive term than PAH since, in addition to the PAHs, PAC also includes compounds in which one or more atoms of nitrogen, oxygen or sulfur (a heteroatom) replaces one or more of the carbon atoms in a fused ring system and perhaps more importantly includes alkylated (methyl, ethyl, etc.) rings **(API, 2008)**.

b, c & d, 2004). These data demonstrate that the respective petroleum-derived streams are not toxic, at least within the operational definitions of the regulatory testing guidelines.

To model the outcomes of repeat-dose and developmental studies, sets of matched data of PAC composition and biological effects were selected. Each biological endpoint had an average of about 80 data points. The 7 biological endpoints that were selected for final statistical characterization were 4 repeat-dose measures (thymus weight, liver to body weight ratio, platelet count and, hemoglobin concentration), and 3 developmental measures (fetal weight, live fetal count, and percent resorptions). The endpoints selected for modeling are consistent with effects reported for both individual PACs and PAC containing substances (SCF, 2002, ATSDR, 1995; IPCS, 1998; IRIS 2007; RAIS, 2007). The endpoints selected are also supported by other studies on PAC-containing petroleum substances prepared and submitted by the Petroleum HPV Testing Group as robust study summaries to satisfy the USEPA HPV Challenge Program requirements for the Aromatic Extracts, Crude Oil, Gas Oils, Heavy Fuel Oils, Lubricating Oil Basestocks, and Waxes and Related Materials).

The PAC compositional data was developed using an analytical technique referred to as the "PAC-2 Method," or 'Mobil Oil PAC Method" or, simply "Method II" (Feuston et al., 1994; Roy et al., 1985; Roy et al., 1988), a variation of the Institute of Petroleum IP 346 method (IP, 1980). In the PAC-2 Method, the percent of sample mass is determined for each PAC ring class (1 through 7) contained in PAC-concentrated dimethyl sulfoxide (DMSO) extracts of the test material. The analysis was performed by gas chromatography with flame ionization detection (GC/FID) or mass spectrometry (GC/MS).

The dose-response relationships between the "PAC profile" and specific biologic effects were successfully predicted using linear regression models. The correlations between observed and model-predicted data were very high ($r > 0.90$). The predictive ability of the models was rigorously tested and the models were found to be accurate predictors when they were used for interpolated data. A test material that has its PAC profile and dose within the range of the PAC profiles and doses used to develop the model gives rise to an interpolated model prediction. Predictions from samples that do not meet this requirement are considered extrapolated predictions. Extrapolated predictions might not be accurate and are considered unreliable by the Testing Group.

Interpolated model results can be used to estimate the dose that would cause a 10% change in the response relative to the control group (PDR_{10}). The concept is similar to the Benchmark Dose (BMD) for continuous endpoints developed by Crump (Crump, 1984). Comparison of the PDR_{10} and BMD_{10} from a series of samples shows close agreement; this indicates the usefulness of the PDR_{10} when there is no biological enpoint testing data and only the PAC profile is available to assess toxicity.

While similar to the BMD, the PDR_{10} has several advantages:

- The PDR_{10} is based on one validated model, whereas the BMD can be developed from several competing models, making the BMD strongly dependent on the selected model (Gephart et al, 2001).
- The PDR_{10} can be applied to untested materials for which there are compositional data (ie, PAC profiles) but no response data, whereas the BMD cannot be used for untested materials.
- The PDR_{10} is based on the large amount of data accumulated over multiple studies, whereas the BMD is based on a single study, usually with only 3 to 5 data points.

A copy of the full report detailing the development and testing of the predictive models developed by the Testing Group can be obtained through either API or TERA (API, 2008; TERA, 2008).

Appendix 4. Summary of Mobil study 40921: one-generation and 13-week dermal studies on Stock 461 (80" white oil) and relevant data from studies on other LOBs

Summary

No adverse effects were noted on reproductive performance of female rats or on the *in utero* and postnatal survival or development of offspring in a one-generation study with dermal dosing of male and female rats with Stock 461 at doses up to 2,000 mg/kg/day beginning 10 weeks before mating. Only dermal irritation and lower body weight relative to sham-treated controls were seen with exposure to 500 and 2,000 mg/kg/day in a 13-week dermal toxicity study with Stock 461. Absolute organ weights, including those of sex organs, were unaffected by treatment. Histopathology was not available in these studies with Stock 461, but no treatment-related effects were seen in testes or ovaries during 13-week dermal studies with several other LOBs at comparable doses.

Endpoints that are particularly sensitive to PACs in petroleum substances with repeated dermal dosing were not significantly affected in the 13-week study with Stock 461 except for higher relative liver weights with 2,000 mg/kg/day. This increase in relative liver weight (as percent of body weight) appeared to be more related to decreased body weight in this group rather than to an actual change in liver weight.

A separate developmental toxicity screening study with dermal, oral, and inhalation dosing was performed with the same sample of Stock 461, as discussed in the CAD on LOBs. No treatment-related changes were seen in maternal or fetal endpoints, including maternal reproductive performance and survival or development of fetuses. The only exceptions to this statement were slight dermal irritation in treated dams at the site of dermal dosing and oily anal discharges in animals treated orally. The dermal NOAEL was 2000 mg/kg/day; the oral NOAEL was 5,000 mg/kg/day; and the inhalation NOAEC was 1,000 mg/m^3 for 6 hours/day (Mobil, 1987b).

These data provide support to the proposal that reproductive effects in rats are not expected from repeated dermal exposures to LOBs, even at doses as high as 2,000 mg/kg/day. Additional details are in API, 2010c.

Background

A one-generation dermal toxicity study and a 13-week dermal toxicity study were performed concurrently on the same sample of white oil. More specifically, animals were divided into 5 treatment groups at the beginning of the one-generation study and the study was started. Subsequently, during the 10-week premating period and the 3-week mating/postmating period of the one-generation study, a 13-week dermal toxicity study was added by assigning some of the animals from the respective groups in the one-generation study to 5 treatment groups in the 13-week toxicity study. The study numbers for the two studies are thus derived from the same initial study number (40921); a suffix of "A" or "B" designated the one-generation and the 13-week study, respectively.

Initial acclimation of the test animals to the laboratory for the one-generation study (Study No. 40921-A) was from 6-18-85 to 7-3-85 and the study was started on 7-8-85. The initial goals of this study were "1) to generate rat reproduction baseline data concerning the effects of Stock 461 (80" white oil) on

gonadal function, conception, parturition, and the growth and development of offspring; 2) to develop methods in: residue analysis of milk, male reproductive toxicity" (Mobil, 1985b).

On 8-21-85 the protocol was amended with the additional goal "to evaluate the toxic potential of dermal administration of Stock 461 to rats for five days a week for thirteen weeks" (Mobil, 1985b). For that purpose, some of the animals were assigned to the 13-week study (Study No.40921-B) and additional endpoints were included for those animals.

Reasons for the conduct of these studies included (1) the use of the white oil (Stock 461) as a diluent for other substances in other studies on developmental toxicity and (2) validation of the test protocol in a relatively new reproductive toxicity laboratory. When no untoward effects were seen in the biophase and necropsy periods of these studies, these goals were considered to be met and the subsequent histopathology and final reports were not prepared. Only the interim report for each study was written; those reports and data on organ weights taken from the original data sheets were the basis for the present summary.

Test Substance

The test substance was identified as "Stock 461 (80" White Oil)" and was obtained from Witco Chemical Company. The CAS number was 8042-47-5 for white mineral oil (petroleum). Viscosity of the sample was a nominal value of 80 SUS. The same sample was used for both the 13-week study and the one-generation study.

One-Generation Study: Design and Endpoints

Forty Sprague-Dawley rats (20/sex) were assigned to each treatment group. Those groups received doses of neat Stock 461 of 0 (untreated), 0 (sham-treated), 125, 500, or 2,000 mg/kg/day. Doses were administered for approximately 10 weeks during premating, 3 weeks for mating period, 3 weeks of gestation, and 3 weeks postpartum. Dams were sacrificed on day 21 of lactation. The frequency of dosing for females was 5 days/wk during premating and mating, daily on gestation days 0-20, and 5 days/wk during the postpartum period. Males were split into two subgroups within each dose group. Half of the males were dosed 5 days/wk during premating and mating. The other half of the males were dosed 5 days/wk during premating, mating, and postmating until sacrifice.

Stock 461 was applied to the dorsal skin of the rats. The application sites were not covered; therefore rats were fitted with Elizabethan collars to minimize ingestion of the test substance. During the mating period, the test material remained on the animals for a minimum of 4 hours. Excess material was then removed with a gauze pad before cohabitation. Untreated controls were not clipped to remove hair or collared. Sham-exposed controls were clipped, collared, and received mock dosing with an empty syringe.

Maternal body weights were measured weekly during premating and at intervals during gestation and lactation. Maternal food consumption was measured at intervals during premating and gestation. Females that did not deliver were sacrificed on GD 25 and necropsied. Females that delivered were sacrificed on postpartum day 21 and necropsied. At necropsy, ovaries and uterus were examined grossly, weighed, and preserved. The number of implantations and any remarkable findings were recorded. In

addition, the estrus cycle was followed 5 days/wk in 5 females in the untreated controls, sham-exposed controls, and rats dosed with 2,000 mg/kg for 2 weeks prior to mating and during mating until breeding activity began.

All offspring were observed individually for body weight, behavior, and appearance during the postpartum period until sacrifice. All viable neonates were examined as early as possible for sex and external anomalies. Litters of sufficient size were culled to 8 pups on postpartum day 4 (4/sex if possible). The number of open eyelids for each pup was recorded on postpartum day 10 and continued until both eyelids were open. All pups were tested for surface righting reflex on postpartum day 14. Pups were weaned on postpartum days 21 and then sacrificed and necropsied with gross observations on postpartum day 28.

Data from the gestation and postpartum phases were analyzed with ANOVA followed by group comparisons using Fisher's Exact or Dunnett's Test. Information on the design and endpoints was taken from the protocol and interim report (Mobil, 1985b, 1987c).

One-Generation Study: Results from Interim (Biophase) Report (Mobil, 1987c)

The estrus cycle was not affected by treatment in the limited number of animals examined. The fertility index among those females was 100% in the sham-exposed controls and 2,000 mg/kg/day groups and 80% in the untreated controls due to one female with an abnormal estrus cycle.

During gestation, erythema, scabs, and flaking were observed on the skin of nearly all animals treated with Stock 461. Similar findings were reported during lactation. Body weight gain during the gestation and postpartum periods appeared normal. Mean body weight of females in the 2,000 mg/kg/day group were significantly lower than the untreated control during the first half of gestation, but were similar to mean weights for the sham-exposed controls. (See Table 4-1.) Since the gain in body weight was not different in the treated groups, no treatment-related effect was apparent.

No effects of treatment with Stock 461 were noted at necropsies of dams. No effects were seen in dams on the percentage of pregnant females, duration of gestation, or number of implantation sites per dam. No adverse effects were noted among the litters for Liveborn Index, Day 4 Survival index, or Day 21 Survival Index. Mean pup weight was not affected by treatment during postpartum days 0 to 28. Eyelid dysjunction and surface righting reflex were not affected by treatment. Observations of offspring at birth and at necropsy were not affected by treatment.

The study director concluded that dermal application of Stock 461 at doses up to 2,000 mg/kg/day beginning 10 weeks before mating did not have any adverse effects on reproductive performance of female rats or on the *in utero* and postnatal survival or development of offspring (Mobil, 1987c). Given the lack of analyses on organ weights and histopathology, a NOAEL could not be established on the basis of the interim report alone.

13-Week Dermal Toxicity Study: Design and Endpoints

Twenty Sprague-Dawley rats (10 per sex) were assigned to each treatment group. Those groups received doses of neat Stock 461 of 0 (untreated), 0 (sham-treated), 125, 500, or 2000 mg/kg/day. Doses were administered 5 days/week (weekdays) for 13 weeks.

Hair was clipped from the dorsal skin of each rat as needed and the test substance was applied to the back of each animal with a syringe. The test substance was spread evenly over the back of each animal with the tip of the syringe. The treated skin was left uncovered and the rats were fitted with cardboard Elizabethan collars to minimize ingestion of the test substance. Excess test material was wiped from the skin with a gauze pad four hours after dosing. Sham-exposed controls were clipped and collared just as treated animals were and their dorsal skin was stroked with the tip of a syringe without application of any test material. Untreated controls were not clipped, collared, or given any treatments.

Endpoints during the biophase included daily observation of clinical signs and body weights measured weekly. Skin irritation was assessed weekly.

At sacrifice at week 13, animals were fasted overnight and weighed the following morning. Blood samples were taken for measurement of the following hematological endpoints: hematocrit, hemoglobin, number and morphology of red blood cells, platelet count, and the number and differential count of white blood cells. In addition, the following clinical chemistry parameters were analyzed: albumin, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, cholesterol, creatinine, glucose, lactate dehydrogenase, sorbitol dehydrogenase, total bilirubin, total protein, triglycerides, urea nitrogen, uric acid, calcium, chloride, iron, phosphorus, potassium, and sodium. Urine samples were also collected for analysis of specific gravity, pH, glucose, occult blood, ketone bodies, albumin, urobilinogen, and bilirubin.

All animals were then killed and necropsied. The following organs were weighed: adrenals, brain, epididymides, gonads, heart, kidneys, liver, prostate, seminal vesicles, spleen, thymus, thyroid, and uterus. Histological slides from the following organs of both control groups and the high-dose animals were to be prepared and examined by a pathologist: adrenals, bone and marrow, brain, epididymides, eyes and optic nerve, gonads, heart, duodenum, colon, kidneys, liver, lung, pancreas, prostate, salivary glands, seminal vesicles, skin (2 sections of treated skin), spleen, stomach, thymus, thyroid, urinary bladder, uterus, vagina, and any gross lesions.

Statistical analysis: Quantitative data from the biophase were analyzed by ANOVA followed by group comparisons using Fisher's Exact Test or Dunnett's test. Information on the design and endpoints was taken from the protocol and interim report (Mobil, 1985b, 1988b).

13-Week Dermal Toxicity Study: Results from Interim (Biophase) Report (Mobil, 1988b)

No treatment-related deaths occurred and no treatment-related abnormal clinical signs were noted except for the skin. Erythema, scabs, and flaking of the skin were observed in nearly all of the animals treated with Stock 461. A few sham-treated females also had flaking and scabs on the back.

Body weights in males were lower than weights in controls in a dose-related manner, with a 13% difference in the high-dose group for mean unfasted weight at week 13 relative to the sham-dosed controls. Body weight of only the high-dose females was lower than that of controls (9% difference from sham-treated controls at week 13). Selected examples of mean body weights are in Table 4-2.

Parameters of hematology and urinalysis were not affected by treatment. Among parameters of serum chemistry, serum albumin was slightly lower in males treated with 500 and 2,000 mg/kg/day compared to sham-treated controls and was also below the historical range of control values. Mean albumin concentrations were 3.8, 3.7, 3.6, 3.5, and 3.5 g/dL for untreated controls, sham-treated controls, and 125, 500, and 2,000 mg/kg, respectively. These same groups of treated males also have lower mean body weights relative to controls.

Dermal administration of Stock 461 to adult rats for 13 weeks resulted in dermal irritation and lower body weights. Although analyses of organ weights and histopathology were not available, a NOAEL of 125 mg/kg/day was assigned by the study director based on lower body weights with 500 and 2000 mg/kg/day relative to controls. Similar lower body weights relative to sham-treated controls have been observed sporadically in similar studies on other LOBs. This difference in body weight was not considered in the present document to be an adverse effect related to the test substance, as discussed in the section on subchronic dermal studies.

13-Week Dermal Toxicity Studies on Stock 461 and Related Substances: Organ Weights and Histopathology

Although the data on organ weights were not compiled in a formal report, the raw data still existed in the study files. Therefore these data were compiled for this summary and statistical analyses on the data were performed. Analyses were based on a parametric analysis of variance (ANOVA) followed by Dunnett's test for mean differences from sham control. Statistically significant differences from the sham-treated control were not reported at a level more significant than the ANOVA significance level.

The first step in the compilation of organ weights was obtaining the unique identification number for each animal in each treatment group. These numbers were copied from the Appendix 5 of the interim report (Mobil, 1988b). Measured organ weights were then copied from the raw data (copied into *Study_40921_summary.doc*) into an Excel spreadsheet for statistical analysis.

Adrenals, brain, heart, kidneys, liver, spleen, and thymus were weighed in both sexes. In addition, epididymides, prostate and seminal vesicles (weighed together), and testes were weighed in males; the ovaries and uterus were weighed in females. No significant treatment-related effects were seen on absolute organ weights in either sex.

Mean body weight and sex-related organ weights are shown in Table 4-3. Final fasted body weight at the time of sacrifice was significantly lower in animals receiving 2,000 mg/kg/day than in the sham-dosed controls, as seen in the table. Several relative organ weights, expressed as a percent of final body weight, were greater than in sham-treated controls. Given the number of relative organ weights that were higher in treated animals (including relative brain weight), the lack of treatment-related effects on absolute organ weights, and the lower body weights in treated animals, the toxicological relevance of the differences in relative organ weights is very questionable.

The lack of effects on weights of reproductive organs seen in Mobil study 40921-B was supported by a similar lack of effects in other 13-week dermal toxicity studies in rats with other relevant lubricant basestocks. A summary of these data is presented in Table 4-3.

Testes were evaluated microscopically in controls and treated animals in all six studies in Table 4-3. Ovaries were examined microscopically following exposures to Stock 142 (Mobil, 1986). No treatment-related effects were seen microscopically in these organs in any of these studies, as summarized in Table 4-4.

13-Week Dermal Toxicity Study on Stock 461: Sensitive Endpoints

Hemoglobin, platelet count, thymus weight, and relative liver weight are the four endpoints that were determined to be most sensitive in rats treated dermally with petroleum substances that contain polycyclic aromatic compounds (PACs), as discussed in the CAD on LOBs. For that reason, mean values for these endpoints in the 13-week toxicity study on Stock 461 are presented in Table 4-5. Information on the results of the 13-week study was taken from the interim report (Mobil, 1988b) except for the liver weights, thymus weights, and relative liver weights. The only treatment-related effected were decreased body weights and increased relative liver weights.

Conclusions

1) In a one-generation study with dermal dosing of male and female rats with Stock 461 at doses up to 2,000 mg/kg/day beginning 10 weeks before mating, no adverse effects were noted on reproductive performance of female rats or on the *in utero* and postnatal survival or development of offspring (Mobil, 1987c).
2) In a 13-week dermal toxicity study with Stock 461, only dermal irritation and lower body weight relative to sham-treated controls were seen with exposure to 500 and 2,000 mg/kg/day. Absolute organ weights, including those of sex organs, were unaffected by treatment.
3) Histopathology was not available in these studies with Stock 461, but no treatment-related effects were seen in testes or ovaries during 13-week dermal studies with other LOBs at comparable doses.
4) Endpoints in the 13-week study that are particularly sensitive to PACs in petroleum substances were not significantly affected in the 13-week study with Stock 461 except for higher relative liver weights with 2,000 mg/kg/day. This increase in relative liver weight appeared to be more related to decreased body weight in this group rather than to an actual change in liver weight.
5) A separate developmental toxicity screening study with dermal, oral, or inhalation dosing was performed with the same sample of Stock 461 (CRU No. 85018). This study is discussed in the CAD on LOBs. No treatment-related changes were seen in maternal or fetal endpoints, including maternal reproductive performance and survival or development of fetuses. The only exceptions to this statement were slight dermal irritation in treated dams at the site of dermal dosing and oily anal discharges in animals treated orally. The dermal NOAEL was 2000 mg/kg/day; the oral NOAEL was 5,000 mg/kg/day; and the inhalation NOAEC was 1,000 mg/m^3 for 6 hours/day (Mobil, 1987b).
6) These data provide support to the proposal that reproductive effects in rats are not expected from repeated dermal exposures to LOBs, even at doses as high as 2,000 mg/kg/day.

Table 4-1. Mean maternal body weight (g) at intervals during gestation in one-generation study with Stock 461.					
Day	**Untreated**	**Sham-Treated**	**125 mg/kg**	**500 mg/kg**	**2000 mg/kg**
0	302	283[a]	288	300	276[b]
3	320	304	306	319	298[b]
6	328	317	314	329	310[a]
10	347	330	331	344	328[a]
13	360	347	344	358	344
16	377	364	360	376	363
18	402	391	385	405	389
20	431	421	412	438	418

Significantly different from untreated controls: a = P<0.05 b=P<0.01
Significantly different from sham-treated controls: c = P<0.05 d=P<0.01

Table 4-2. Mean unfasted body weight (g) at intervals during 13-week study with Stock 461.					
	Untreated	**Sham-Treated**	**125 mg/kg**	**500 mg/kg**	**2000 mg/kg**
Males					
Week 0	245	258	253	244	244
Week 4	425	414	410	379[bd]	354[bd]
Week 9	532	519	513	475[bd]	446[bd]
Week 13	565	560	550	512[bd]	486[bd]
Females					
Week 0	174	172	172	176	167
Week 4	252	238[b]	245	245	228[b]
Week 9	293	279[b]	289	287	272[b]
Week 13	320	312	325	306	285[a]

Significantly different from untreated controls: a = P<0.05 b=P<0.01
Significantly different from sham-treated controls: c = P<0.05 d=P<0.01

Table 4-3. Mean body weight and weights of reproductive organs in 13-week dermal studies with Stock 461 and related lubricant basestocks.

		Males					Females			
Sample (CASRN)	**Dose (mg/kg/day)**	**Body Weight**	**Testes**	**Prostate**	**Prostate & Seminal Vesicles**	**Epididymides**	**Body Weight**	**Ovaries**	**Uterus**	**Reference**
Stock 141 (64742-65-0)	0 (Sham-dosed)	366	3.42	ND		ND	252	0.21	ND	Mobil, 1983i
	2,000	372	3.23	ND		ND	239	0.19	ND	
Stock 300 (64742-65-0)	0 (Sham-dosed)	366	3.42	ND		ND	252	0.21	ND	Mobil, 1983j
	2,000	369	3.34	ND		ND	247	0.18	ND	
Stock 335 (64742-65-0)	0 (Sham-dosed)	379	3.74	ND		ND	252	0.22	ND	Mobil, 1982c
	2,000	378	3.62	ND		ND	250	0.23	ND	
Stock 345 (72623-83-7)	0 (Sham-dosed)	379	3.74	ND		ND	252	0.22	ND	Mobil, 1982c
	2,000	353	3.66	ND		ND	243	0.19	ND	
Stock 142 (64742-70-7)	0 (Sham-dosed)	443	3.884	ND		ND	234	0.073	ND	Mobil, 1986
	2,000	392*	3.919	ND		ND	233	0.079	ND	
Ssangyong 150N (64742-54-7)	0 (Sham-dosed)	488.4	3.441	0.835		1.320	257.8	0.078	0.568	Mobil, 1987e
	800	444.8*	3.469	0.968		1.340	259.0	0.082	0.568	
	2,000	440.5*	3.324	0.806		1.314	253.8	0.081	0.630	
Stock 461 (8042-47-5)	0 Untreated)	556.2	3.395		2.930	1.383	325.7	0.090	0.557	Mobil, 1988b and raw data
	0 (Sham-dosed)	552.7	3.505		3.133	1.406	300.6	0.079	0.575	
	125	531.6	3.415		2.697	1.382	302.3	0.086	0.544	
	500	525.0	3.458		3.122	1.407	280.9	0.084	0.548	
	2,000	488.4*	3.529		2.727	1.325	268.3*	0.102	0.534	

* Significantly different from sham-dosed controls ($p<0.05$) ND = Not determined

Table 4-4. Summary of histopathological evaluations of testes and ovaries from multiple dermal 13-week studies in rats

Sample (CASRN)	Dose (mg/kg/day)	Testes	Ovaries	Reference
Stock 141 (64742-65-0)	2,000	No effect	NE	Mobil, 1983i
Stock 300 (64742-65-0)	2,000	No effect	NE	Mobil, 1983j
Stock 335 (64742-65-0)	2,000	No effect	NE	Mobil, 1982c
Stock 345 (72623-83-7)	2,000	No effect	NE	Mobil, 1982c
Stock 142 (64742-70-7)	2,000	No effect	No effect	Mobil, 1986
Ssangyong 150N (64742-54-7)	2,000	No effect	NE	Mobil, 1987e

No effect = no treatment-related effect
NE = not evaluated microscopically

Table 4-5. Mean fasted body weight (BW) and mean values of selected sensitive endpoints from 13-week study with Stock 461.

	Untreated Controls	Sham-Exposed Controls	125 mg/kg/day	500 mg/kg/day	2,000 mg/kg/day
Males					
Body weight (BW, g)	556.2	552.7	531.6	525.0	488.4*
Liver weight (g)	16.663	16.193	15.690	18.476	17.233
Liver weight/BW (%)	2.989	2.934	2.943	2.762	3.528**
Thymus weight (g)	0.303	0.530	0.275	0.268	0.245
Platelets (10^9/L)	1062	960	1003	1009	1099
Hemoglobin (g/dL)	16.2	15.8	15.7	16.0	16.2
Females					
Body weight (g)	325.7	300.6	302.3	280.9	268.3*
Liver weight (g)	11.608*	10.009	9.246	9.234	9.950
Liver weight/BW (%)	3.565	3.323	3.068	3.285	3.694*
Thymus weight (g)	0.251	0.278	0.264	0.259	0.212
Platelets (10^9/L)	1074	1000	874	1051	900
Hemoglobin (g/dL)	15.0	15.7	16.6	15.0	15.8

Significantly different from sham-treated controls : * P<0.05 **<0.01

Appendix 5. Links to Additional Resources

General Descriptions of Refining Processes

http://www.chevron.com/about/learning_center/refinery
http://www.lubrizol.com/lubetheory/default.htm
http://www.orionrefining.com/flow.htm
http://www.osha-slc.gov/dts/osta/otm/otm_toc.html
http://www.shellglobalsolutions.com/base_oils/library/library.htm
http://www.shell-lubricants.com/learningcenter/aboutoil.html
http://www.shellus.com/welcome/history/hist_oil_main.html
http://www.epa.gov/compliance/resources/publications/assistance/sectors/notebooks/petrefsnpt1.pdf
http://www.mts.net/~dbrad1/base_oil.htm

Petroleum-Related Glossaries

http://www.caltex.com.au/products_glo.asp
http://www.citgo.com/CommunityInvolvement/Classroom/Glossary.jsp
http://www.epplp.com/gloss.html
http://www.prod.exxon.com/exxon_productdata/lube_encyclopedia/
http://www.hellenic-petroleum.gr/english/glossary/gl_main.htm
prod.exxon.com/exxon_productdata/lube_encyclopedia/
http://www.oilanalysis.com/dictionary
http://www.orionrefining.com/glossary.htm
http://www.gedolbear.com/glossary.htm
http://www.shellglobalsolutions.com/base_oils/glossary/a_g.htm
http://www.ursa-texaco.com/English/glossary_a.html
http://www.eia.doe.gov/pub/oil_gas/petroleum/data_publications/petroleum_marketing_annual/current/pdf/glossary.pdf