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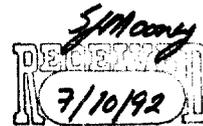
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(Identification No. FYI not assigned) API Mineral Oil Review. Report from the White Oil Workgroup of the American Petroleum Institute.

This document does not contain confidential information. If you have any questions about it, please communicate with me.

Sincerely,

Robert T. Drew, Ph.D.

# **API Mineral Oil Review**

**Health and Environmental Sciences Department**

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**JANUARY 1992**

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## EXECUTIVE SUMMARY

White mineral oils are viscous liquids derived from petroleum. They are complex mixtures of saturated hydrocarbons including straight chain, branched, and ring structures, and molecules containing all three configurations. The relative concentration of saturated ring structures (termed "naphthenes") and straight or branched chain structures (termed "paraffinic") in the oil will determine whether the oil is identified as naphthenic or paraffinic in nature. The chemical and physical properties of white mineral oils are defined by a number of national and international standard-setting groups dealing with food, medical and cosmetic specifications, as well as by individual trade associations representing particular applications. Approved uses are identified by national regulatory agencies along with the material specifications set up for those uses.

A complex series of processing steps is necessary to produce white mineral oils with the physical properties and the level of purity required. First, atmospheric and vacuum distillation are required to isolate fractions with the desired boiling range and viscosity. Unwanted constituents, such as polar compounds, aromatics, and waxes are then removed by solvent extraction and dewaxing. Hydrotreating or hydrogenation of the oils may then be used to produce a finished lubricating oil base stock or with additional treatment, white mineral oils. Two methods, separately or in combination, are used to produce finished white mineral oils. The older method involves treating the oil with fuming sulfuric acid (oleum) to sulfonate aromatics and polynuclear aromatics, which are removed after neutralization. The more common method today, two-stage hydrotreating, completely saturates all double bond containing compounds. These treatments may be repeated under different levels of severity until the desired degree of purity is attained.

In February 1989, the United Kingdom Ministry of Agriculture, Fisheries and Food (MAFF) recommended a ban on almost all direct food applications of mineral

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hydrocarbons including white mineral oil. This decision was based, in part, on the results of two 90-day toxicity studies in rats conducted by Shell Research Limited using white oils prepared by hydrotreatment and oleum treatment. These studies demonstrated accumulation of oil in the mesenteric lymph nodes and livers, accompanied by micro-granuloma formation at the highest dose levels. Other animal studies with white mineral oils have not shown such effects. A literature review performed in developing this document revealed that absorption of white mineral oil has been documented frequently in the past in both animals and humans. There has been no indication that such absorption has had any adverse effect on humans despite the many years white mineral oil has been used in pharmaceutical preparations and food.

It is the position of the work group that the majority of the data generated to date on mineral oils indicate that current uses can be continued safely in direct and indirect food applications.

Section I  
MINERAL OIL DEFINITIONS

For purposes of this discussion, the term "mineral oil" will refer to very highly refined liquid hydrocarbons derived from petroleum distillates, which are used in medicine, pharmaceutical applications, cosmetic applications, food packaging applications, food contact applications, and food itself. Other terms often used interchangeably with mineral oil include "liquid petrolatum," "liquid paraffin," "paraffin oil," "medicinal oil," "medicinal white oil," "white oil," "white mineral oil," "food grade oil," "food grade white oil" and "technical white oil." The term mineral oil as used in this paper does not include petroleum wax, petrolatum, lubricating base oils used in other applications, or oil derived from shale (also sometimes referred to as "mineral oil").

Mineral oils are manufactured from either naphthenic or paraffinic type crude oils. After initial processing in the refinery, they are intensely refined to remove constituents that impart color, odor, taste and potential toxicological properties. These constituents include aromatics; olefins; and sulfur-, oxygen-, nitrogen-, and metal-containing compounds. Additionally, they are made to comply with the purity requirements of the countries in which they are marketed. They consist almost entirely of saturated hydrocarbons and are manufactured in a variety of viscosity grades (viscosity being defined as a measure of time for a fixed amount of liquid to flow by gravity through a capillary or orifice under set conditions). Viscosity grades are determined, in part, by the distillation cut or boiling range initially used in processing. The distillation range will also determine the carbon number and molecular weight range of the finished product. The choice of either naphthenic or paraffinic crude will determine the predominant nature of the hydrocarbon species in the final product: cycloparaffinic or paraffinic hydrocarbon molecules. The number of molecular species present in a mineral oil is in the thousands, given all the possible arrangements of carbon and hydrogen atoms.

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While mineral oils can vary in viscosity, distillation range, molecular weight, carbon number and molecular arrangement, they are manufactured to comply with the regulations set forth in the countries in which they are to be marketed. These regulations begin to establish constraints on the range of variability for mineral oils. The following discussion will define mineral oils from the regulatory point of view.

The Toxic Substances Control Act Substance Inventory and the European Core Inventory define white mineral oil as follows:

CAS Registry Number 8042-47-5 "- a highly refined petroleum mineral oil consisting of a complex combination of hydrocarbons obtained from the intensive treatment of a petroleum fraction with sulfuric acid or 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 in the range of C15 to C50."

The World Health Organization defines medicinal white oil as:

" - highly refined, colorless oils free of all unsaturated compounds, aromatic compounds and other constituents that influence color, odor, taste and acceptability as a pharmaceutical and food grade material."

While these definitions describe some of the processes involved in the manufacture of mineral oil and the type and size of hydrocarbon molecules present, they do not establish specific analytical or purity criteria for mineral oils.

Analytical criteria and purity are prescribed by the various world pharmacopeias and by government agencies which are responsible for food and drug safety. In many instances, the analytical criteria and levels of purity are based on the end use application. This is true in the United States. The United States Pharmacopeia (U.S.P.), the National Formulary (N.F.), and the United States Cosmetic, Toiletry and Fragrance Association have established analytical criteria for mineral oils to be used in medical, pharmaceutical and cosmetic applications. The United States Food and Drug Administration (FDA) has set analytical criteria for mineral oil to be used in food and in food applications (direct and indirect contact).

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The U.S. Pharmacopeia and National Formulary (U.S.P. XXII and N.F. XVII) requirements are found in Appendix 1. U.S.P. Mineral Oil may be used as a laxative (oral and rectal) and in pharmaceutical applications that involve ingestion of the finished preparation, e.g., suspending agent. N.F. Light Mineral Oil or U.S.P. Topical Light Mineral Oil may be used in pharmaceutical preparations approved for dermal applications.

The U.S. Cosmetic, Toiletry and Fragrance Association (CTFA) requires mineral oils to be free of foreign materials; to be odorless at room temperature and after heating; to meet buyer's specification for viscosity at 38°C; and to meet U.S.P. requirements for readily carbonizable substances, solid paraffins and polynuclear aromatic compounds. Additionally, CTFA has established tests for water soluble acids and alkalis, sulfur and sulfides, and has set limits for lead (20 ppm), arsenic (3 ppm) and ash (0.005 percent maximum). Mineral oils meeting these requirements are suitable for use in a variety of cosmetic and toiletry applications, e.g., baby oil and make-up base.

The U.S. Food and Drug Administration has promulgated regulations defining criteria for mineral oils approved for specified uses in either direct or indirect food contact. Direct food contact mineral oils and their prescribed applications as set forth in 21 CFR 172.878 are found in Appendix 2. The regulations for indirect food contact (21 CFR 178.3620) are divided into four categories [(a) to (d)], each establishing analytical criteria and designated uses. Appendix 3 contains the requirements for oils a, b, and c.

The above examples demonstrate the complexity of mineral oil requirements and regulations in one country only. It is beyond the scope of this paper to try and encompass the definitions that may be used in other countries around the world.

An important part of defining mineral oil is understanding the manufacturing processes used to prepare them for distribution in commerce. The next section provides a basic description of the refining of mineral oils.

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## Section II

### MANUFACTURING AND PROCESSING

The manufacture of mineral oils begins with the type of crude oil. While crude oils vary widely in appearance and consistency around the world, ranging from light brown, mobile liquids to black, viscous semi-solids, they all consist primarily of hydrocarbons. The differences are due to the different proportions of the various molecular types and sizes of molecular species.

Crude oils are usually divided into two broad categories: (1) paraffinic- (straight and branched chain hydrocarbons) and (2) naphthenic- (cyclic hydrocarbons) base crude oil. A third category of mixed-base crude is also sometimes used. Either paraffinic or naphthenic crude may contain predominantly light hydrocarbons with dissolved gases, or may consist mostly of heavy hydrocarbons with little or no dissolved gas. Paraffin-base crudes contain paraffin wax and consist mostly of paraffinic hydrocarbons. Naphthenic-base crudes consist mostly of naphthenes and little or no paraffin wax. Both types of crude contain varying amounts of aromatic compounds.

The nature of the crude oil governs, to a certain extent, the nature of the products that can be manufactured from it and their suitability for special applications. For example, a naphthenic crude will be more suitable for the production of asphaltic bitumen, and a paraffinic crude for wax.

The refinery processes can be divided into three main categories: physical separation, chemical conversion, and treating. Physical separation includes distillation (differences in boiling points), absorption (differences in size or type of molecule), solvent extraction (differences in solubility in a solvent), crystallization (differences in melting points), and adsorption (differences in adhesion to porous surfaces). Chemical conversion includes reduction of molecular size (cracking); change of molecular

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structure (catalytic reforming) and increase in molecular size (alkylation). Finally, treating includes a variety of processes designed to purify or otherwise bring the material up to product specifications (hydrotreating and acid treating). The manufacture of a mineral oil generally undergoes only two of the three major process categories: physical separation and treating.

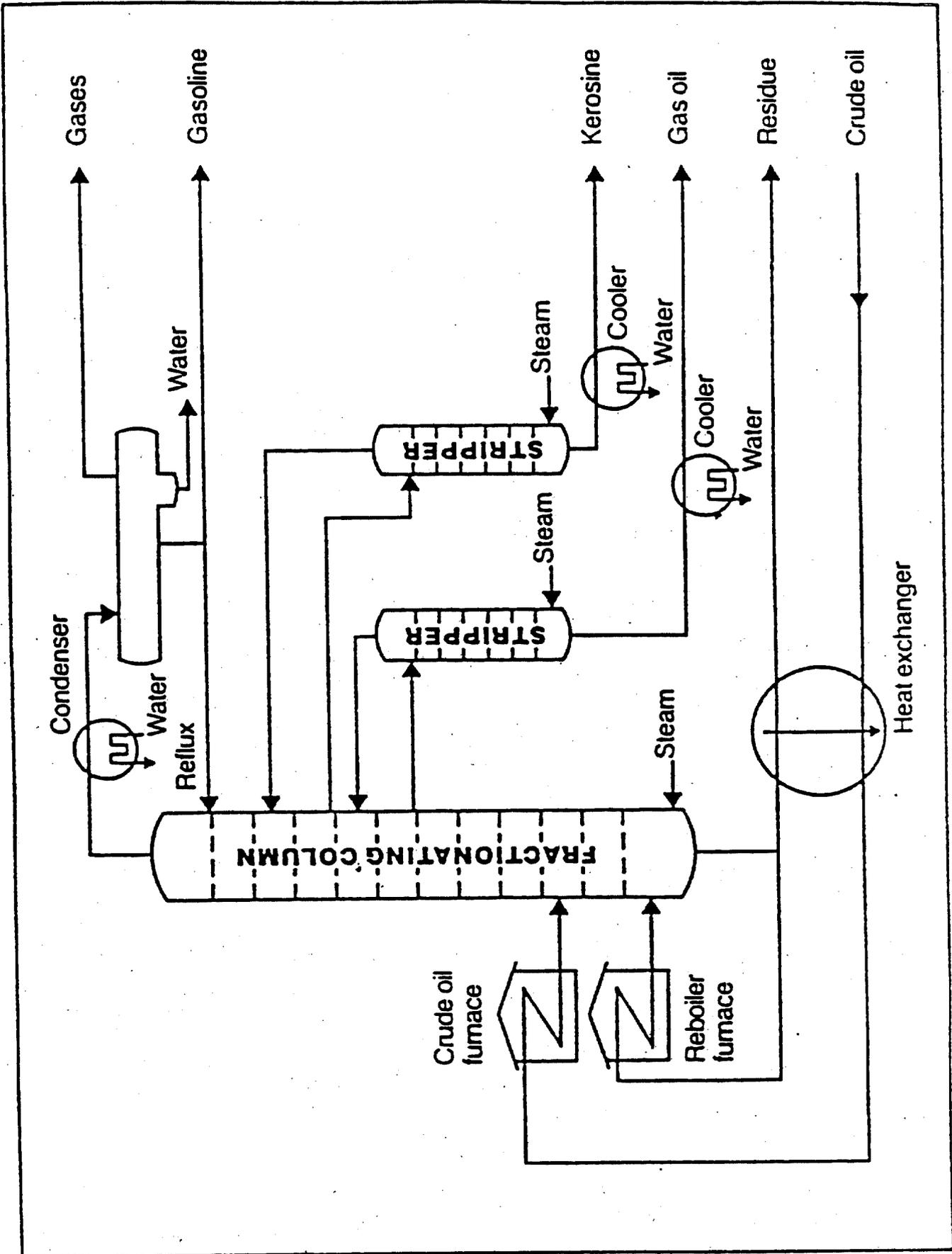
Crude oil is first separated into its main fractions by distillation in the primary distillation column (Figure 1). Here the crude oil is heated to boiling at atmospheric pressure and the various boiling range fractions are separated by fractional condensation. This unit provides the lighter petroleum components, which go on to other refinery processes to produce the components of motor fuels (gasoline, jet fuel, and diesel) and heating fuels (kerosine and fuel oils). Light lubricating oils, called "mineral seal oils," and other specialty oils can also be manufactured from atmospheric distillates.

The fraction that will not boil at temperatures easily achieved at atmospheric pressure, called atmospheric residuum or "long residue," is further distilled by vacuum distillation (Figure 2). In this unit, higher temperatures can be reached under reduced pressure. Distillates from this unit go on to produce feedstocks for other refinery units (e.g., cracking units), bitumens, waxes and feedstocks for the manufacture of lubricating base oils. Lubricating base oils are the feedstocks for the production of mineral oils.

Lubricating base oil high-vacuum units are specifically designed to produce high-quality distillate fractions for lube oil manufacture. Special precautions are taken to prevent thermal degradation of the distillates produced. The distillates from this unit are further processed by a variety of methods to produce the finished lubricating base oils. These processes might include solvent extraction, hydrotreating, one of several dewaxing methods, solvent deasphalting, acid treating, chemical neutralization, clay

Figure 1. Simplified Flow Diagram of a Primary Crude Distillation Unit

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treating or combinations of processes. Two of the most important of these processes are solvent extraction and hydrotreating.

Solvent extraction (Figure 3) is based on the use of a solvent that will preferentially dissolve polar and aromatic compounds in the feedstock. After dissolution has occurred, the solvent and solute, now called the "extract," can be separated and removed, leaving behind the undissolved phase, called the "raffinate." The raffinate now consists primarily of saturated hydrocarbons, which are desirable for lubricating base oils. The solvents most commonly used for lube oil extraction are furfural, phenol and N-methyl-2-pyrrolidone, since they all have a high selectivity for aromatics. The depth of solvent extraction can be controlled by 1) the solvent selected, 2) the solvent-to-feed ratio, 3) the temperature of solvent extraction, and 4) the contact time between solvent and feedstock. Solvent extraction in many instances may precede additional processing steps, such as hydrotreating or acid treatment.

Hydrotreating is the process where either distillate feedstocks or raffinates are treated with hydrogen at elevated temperatures and pressure in the presence of a catalyst (Figure 4). The feedstock is mixed with hydrogen-rich make-up gas. The mixture is heated by heat exchange or furnace and enters a reactor containing catalyst. In the reactor, sulfur and nitrogen compounds in the feedstock are converted to hydrogen sulfide and ammonia, respectively. Olefins are saturated with hydrogen and the aromatics are partially hydrogenated to naphthenes (saturated ring compounds). The severity of hydrotreatment can be controlled by 1) the pressure of the hydrogen, 2) the temperature of the reaction, 3) the type of catalyst, and 4) the contact time among the hydrogen, feedstock and catalyst.

A third process of diminishing importance in the manufacture of lubricating base oils is that of acid treatment. Because of its availability and versatility, sulfuric acid treatment was for many years the most important refining process for mineral oils. For conventional acid treatment of lubricant base oils, 98 percent strength sulfur mixed

Figure 3. Simplified Flow Diagram of a Solvent Extraction Unit

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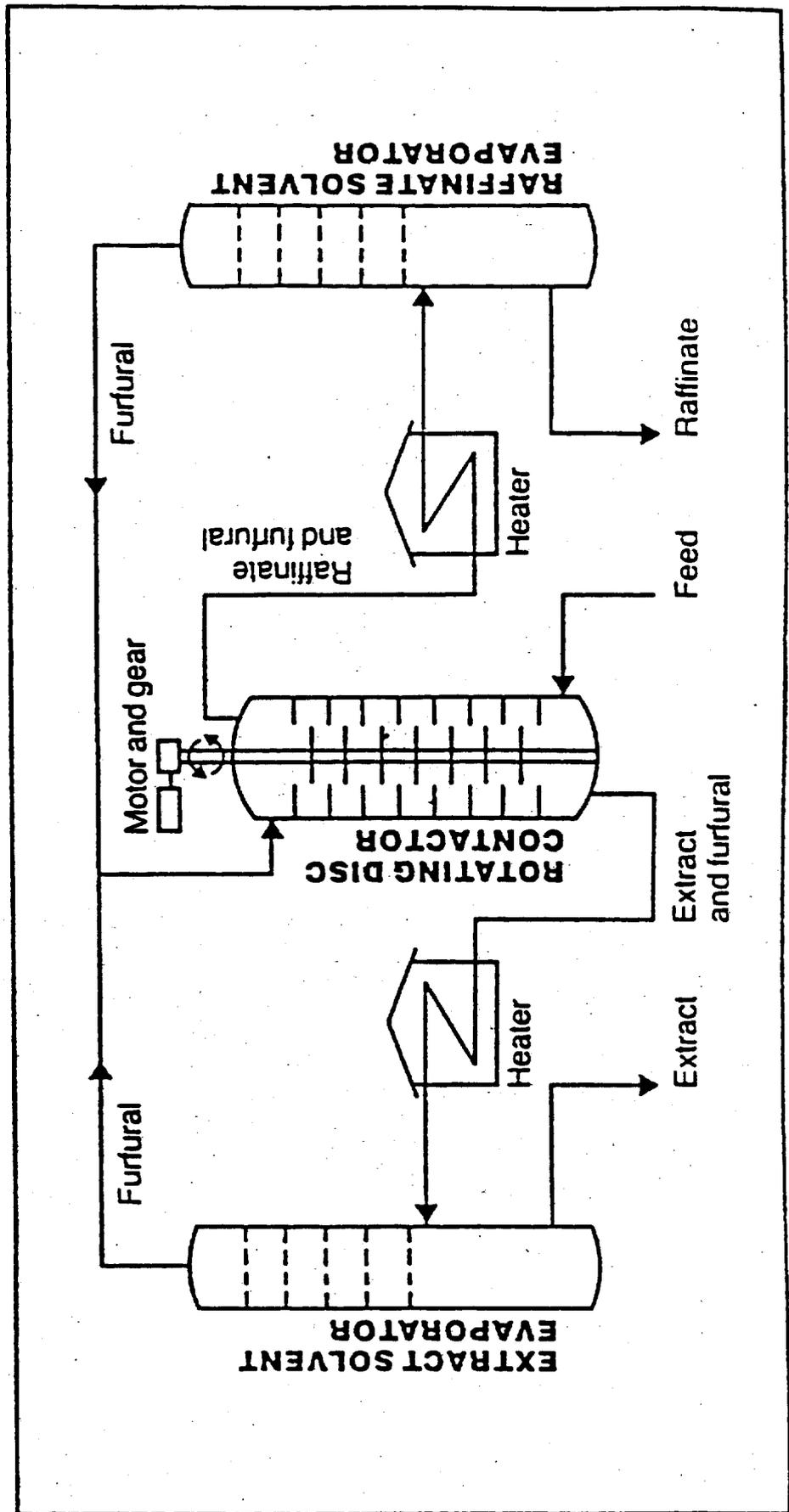
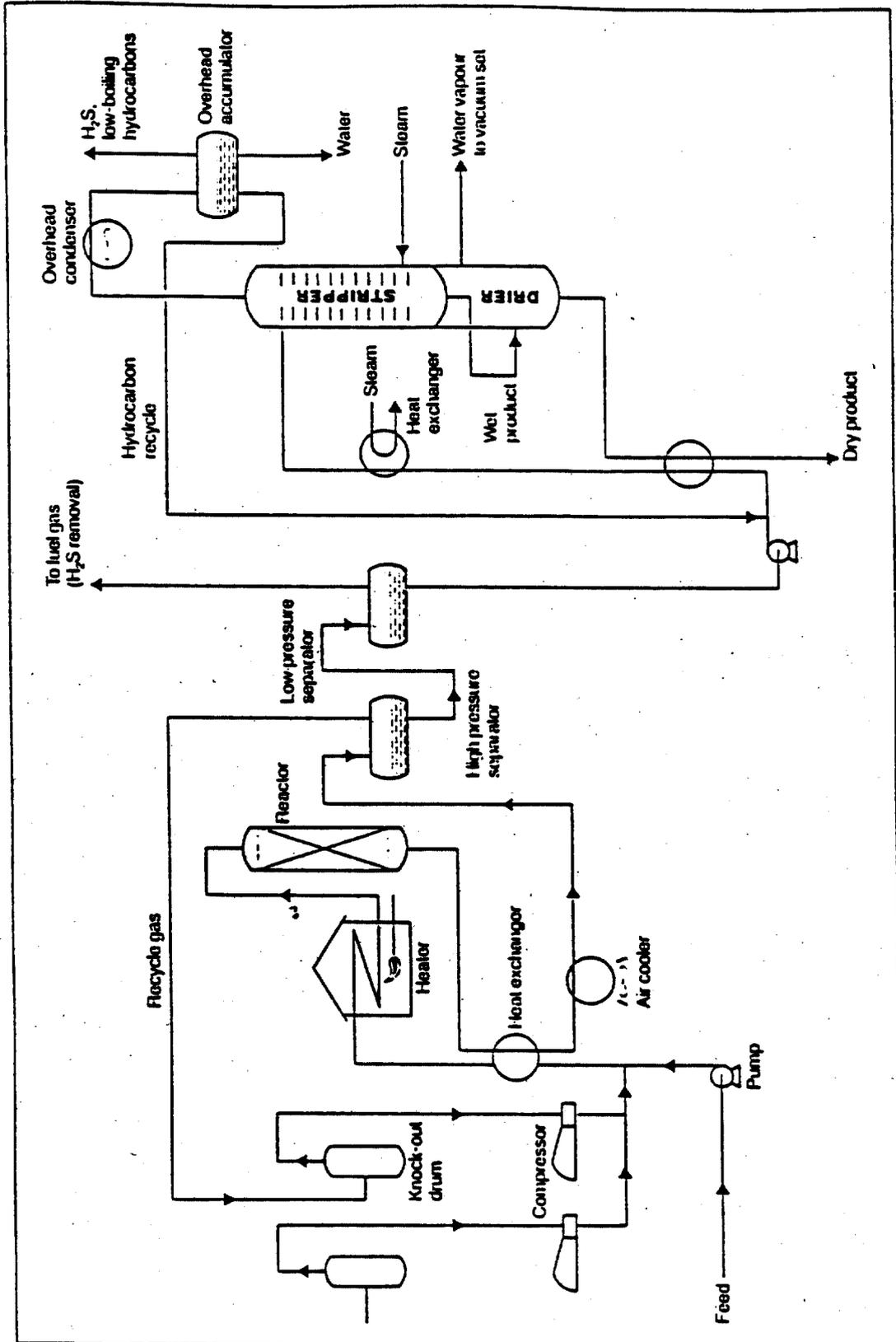


Figure 4. Simplified Flow Diagram of a Lube Hydrotreater



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with the feedstock and agitated for a specified period of time. The intensity of the treatment can be controlled by increasing 1) the strength of the acid, 2) the acid-to-feedstock ratio, 3) the temperature of the acid, 4) the number of consecutive treatments with acid, and 5) the contact time with the acid. The acid sludge is then separated. The treated feedstock is generally neutralized with calcium or sodium hydroxide and then filtered over a clay bed (chemical neutralization and clay treatment).

Lubricating base oils suitable for a variety of applications are manufactured from vacuum distillates by one or more of the above processes (base oils derived from paraffinic crudes will generally also undergo a dewaxing process). Depending on the intensity of treatment, some lubricating base oils, as produced, meet the requirements for certain grades of mineral oil, while others may require additional treatment.

#### WHITE MINERAL OIL MANUFACTURE

U.S.P./N.F. or food grade white mineral oils are manufactured from selected lubricating base oils by either severe hydrotreating or by intensive acid treatment with fuming sulfuric acid (oleum) or anhydrous sulfuric acid (SO<sub>3</sub>). A combination of severe hydrotreating and acid treatment is sometimes used in the processing as well.

In either the hydrotreating or acid treatment process, the objective is to obtain a nonreactive, saturated hydrocarbon liquid. Hydrotreating accomplishes the task by reacting hydrogen with the undesirable unsaturated, largely aromatic compounds, converting them to saturated hydrocarbons and removing sulfur and nitrogen. Sulfuric acid reacts with the same components and converts them into compounds that can be extracted from the saturated hydrocarbons in the feedstock.

## HYDROTREATING PROCESS

In the case of white oil production by severe hydrotreating, a two-stage process is most often used. Figure 5 is typical for two-stage hydrotreating processes used for white mineral oil manufacturing.

The first stage consists of the following steps:

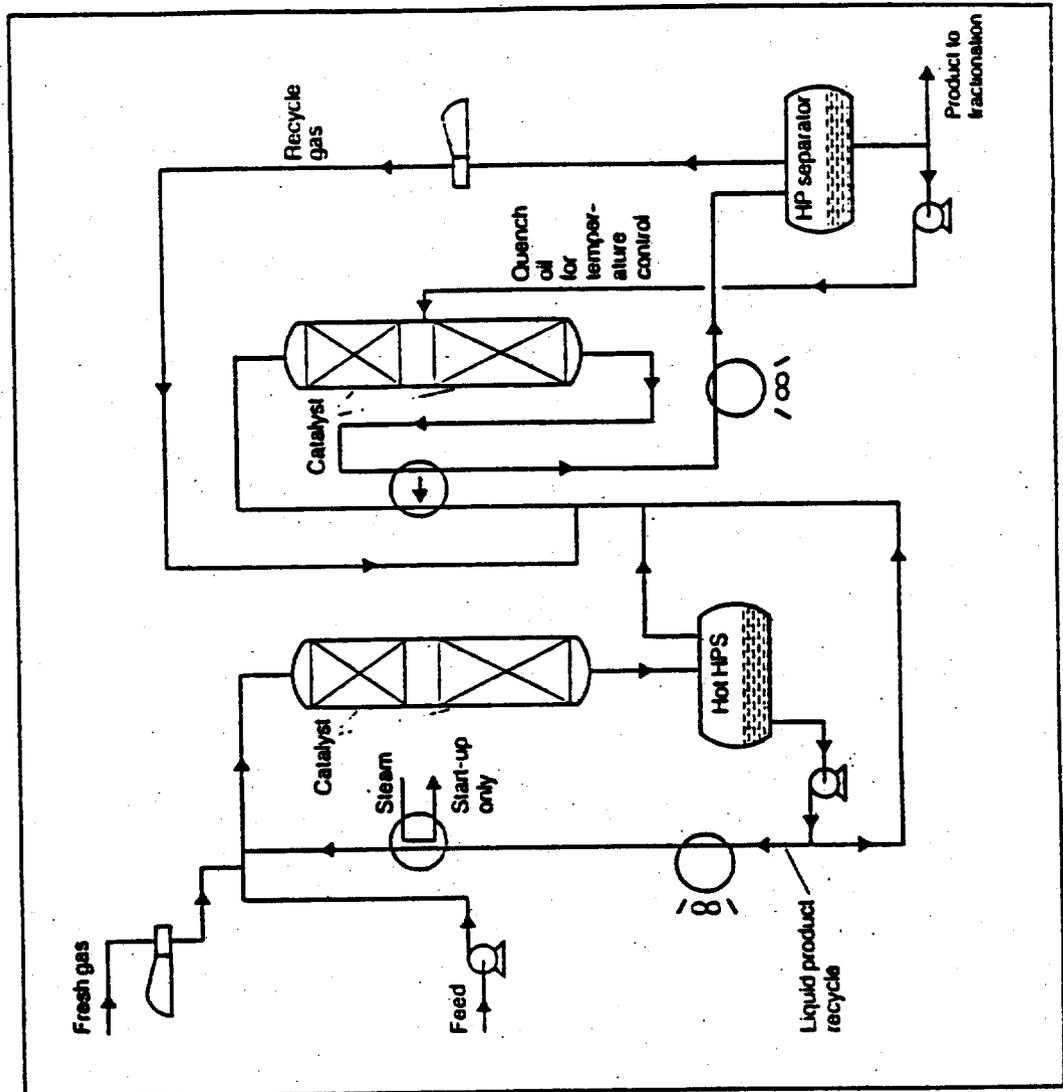
- 1) A selected oil feedstock is pumped into the hydrotreating circuit where it is pressurized and mixed with a high pressure hydrogen gas stream. Pressure is typically greater than 2500 pounds per square inch actual (psia). The gas/oil mixture is passed through heat exchangers and heaters to raise the temperature to 250-375° C.
- 2) At the correct feed temperature and feed rate, the hydrogen/oil mix is passed over the first-stage catalyst in a reactor. Hydrodesulfurization, denitrification and saturation of aromatics occur. The catalyst is chosen primarily for its ability to react hydrogen with sulfur and nitrogen in the feedstock.
- 3) Effluent from the reactor is passed through the feed/product heat exchanger and fed to a liquid/gas separation vessel, where hydrogen flash-gas is removed from the oil. The hydrogen from this separation is repressurized and blended with fresh make-up hydrogen to use again in the reaction.
- 4) The oil is passed on to a second, lower pressure, liquid/gas separator. The purge gas from this vessel is high in hydrogen sulfide and ammonia content and must be cleaned before reuse or disposal.
- 5) From the second gas/oil separation, the oil is sent to a fractionation tower to remove the remaining dissolved gases and to adjust the oil's physical properties and volatility. With suitable operating conditions, a technical white mineral oil meeting the requirements in 21 CFR 178.3620(b) or a type c mineral oil meeting 21 CFR 178.3620(c) requirements can be produced.

The second stage consists of the following steps:

- 1) When medicinal or food grade white oil is desired, the product from the first stage is pumped into the second stage circuit. The oil is again pressurized and mixed with a high-pressure/high-purity hydrogen gas stream. Pressure is typically greater than 2500 psia. Temperatures may run from 100°C to 375°C depending on catalyst choice.

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Figure 5. Simplified Flow Diagram of a Two-Stage Hydrotreater



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- 2) The catalyst for the second stage is chosen for the hydrogen activity needed to achieve complete aromatic-bond saturation. Feed rate and temperature are adjusted to meet food or medicinal grade white oil requirements for the limit of polynuclear aromatic compounds and readily carbonizable substances.
  - 3) Once the oil/gas separation is made in the second-stage circuit, the oil meets food/medicinal grade white oil purity (21 CFR 172.878).

### ACID TREATING PROCESS

A schematic representing the production of white mineral oil by oleum treatment is presented in Figure 6. The process involves the following steps:

- 1) Feedstocks similar and many times identical to those used in two stage hydrotreating are mixed with either fuming sulfuric acid (oleum) or anhydrous sulfuric acid ( $\text{SO}_3$ ) through a proportioning system. The ratio and temperature control are set to the individual operating parameters of the manufacturer and are typically based on laboratory evaluation of the feedstock. Typical ratio is 1:6 acid:oil and temperature is 35-95°C. Contact time with the acid is typically 1-30 minutes, but may be much longer.
- 2) The mixture of acid and oil is then moved to a gravity settling tank or centrifuge where the spent acid sludge is removed from the oil. Spent acid sludge is a mixture of sulfuric acid and sulfonic acids that is not oil soluble. Acid sludge is typically reclaimed as fuming sulfuric acid or anhydrous sulfuric acid in an acid manufacturing plant.
- 3) Acidified oil, a mixture of the treated feedstock oil and oil soluble sulfonic acid, is then neutralized with sodium hydroxide or sodium carbonate. This step can be a batch or a continuous operation depending on the manufacturer's equipment.
- 4) Once neutralized, the resulting sodium sulfonates are extracted from the oil mixture using a polar solvent, typically an alcohol or alcohol/water solution. Extraction can occur in batch or continuous operating equipment, with the extracting solvent carrying away the crude sodium sulfonate from the oil. The extracted sodium sulfonates from each of the treatment steps are typically accumulated, purified and marketed as sodium petroleum sulfonates.



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- 5) Traces of solvent are removed from the partially treated oil by heating and distillation. At this point, the saturated hydrocarbon content is higher than the initial level in the feedstock because of the removal of the sulfuric acid reactants, resulting in an intermediate oil.
  - 6) Intermediate oil is reprocessed through steps 1-5 until all unsaturated components have been removed from the oil. The number of times that reprocessing is necessary depends on how the lube base oil feedstock was processed and the quantity and type of nonsaturated components that are present in the feedstock. Typically the number of treatments is 2-5.
  - 7) When the quantity of nonsaturated components in the intermediate oil is negligible, the oil is contacted with an adsorbent clay. This can be accomplished by either percolation of the oil over a relatively coarse mesh clay or by mixing a fine mesh clay into the oil and then removal of the clay by filtration. The activated clay will adsorb any residual moisture, extraction solvent and trace quantities of aromatic hydrocarbons. At this point, the oil meets the food/medicinal grade white oil requirements (21 CFR 172.878).

The use of oleum treatment for the manufacture of mineral oil has been declining because of economic and environmental concerns. The use of severe hydrotreating has largely replaced oleum treatment for the production of mineral oil because it overcomes these disadvantages.

As noted earlier, many of the established specifications for mineral oils are set in reference to their intended use; therefore, the various applications of mineral oils become an important area for discussion.

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Section III  
MAJOR USES OF MINERAL OILS

**FOOD AND AGRICULTURE**

The direct use of white mineral oil in food products in the U.S. is covered by federal regulation 21 CFR 172.878. The regulation is shown in Appendix 2. Although a variety of applications are cited, only a few involve large volumes of white oils. White mineral oils are used in pan oils where they are usually mixed with vegetable oils. They are also used as "divider oils" to lubricate the blades of machines that slice dough. White mineral oils and petrolatums are used in making "trough greases," which are sprayed on the interior of troughs. Dough is allowed to ferment in the troughs and the "trough grease" permits easy release when it is moved to the next operation. Bakery products may contain up to 0.15% white mineral oil as a result of these applications.

Another large-scale application of white mineral oil in food products is its use as a dust control agent for grain. The application was approved in 1983 by the FDA for grains intended for human consumption. The limitation is 0.02% white mineral oil on the grains specified. This has proven to be a safe and practical method of controlling grain dust.

Smaller quantities of white mineral oils are used as defoamers in foods, on raw fruits and vegetables, and in the manufacture of confectionary. Other applications permitted in 21 CFR 172 regulations involve very little white mineral oil in actual practice.

The applications cited above are for direct use in food. To meet the regulations for direct food additives, it is necessary that white oils be refined to meet certain purity requirements specified in 21 CFR 172.878. These requirements establish limits on polynuclear aromatic compounds (PNAs), readily carbonizable substances and sulfur.

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Polynuclear aromatic compounds are limited by the UV absorbance of a DMSO extract from the oil being tested. Although this test does not determine actual compounds, it effectively limits the total PNAs by specifying maximum absorbances over wavelengths from 260nm to 350nm. The test and a description of its development are shown in Appendix 4. The Readily Carbonizable Substance Test limits aromatics and other impurities in a white oil by specifying a maximum color change when the oil is mixed with sulfuric acid. The test for sulfur limits mercaptans and sulfides.

White mineral oils also find numerous applications in food packaging and processing facilities. The U.S. Department of Agriculture (USDA) lists approved products for use in meat and poultry plants. These are usually mineral oils meeting the 172.878 regulation or technical white oils meeting 178.3620(b). The approved products are permitted for use as lubricants where "incidental food contact" may occur. This is the USDA's H1 category. The coating of shell-eggs with mineral oil is another application that falls under the responsibility of the USDA.

Mineral oil is used in soybean oil extraction for the recovery of the extraction solvent. The mineral oil does not contact soybean oil directly. White oils may also be used as heat transfer fluids and as hydraulic fluids in various food processors. These are applications where there is normally no direct contact with food, but process engineers build in a safety margin by using a "food grade oil."

Technical white mineral oils are used in large volumes for dedusting animal feed. A specific regulation, 21 CFR 573.680, must be met for this application. Another agricultural use of white oils is in citrus sprays. They are typically applied as an emulsion to control scale insects, spider mites, etc. This application is regulated by the pesticide division of the Environmental Protection Agency (EPA) under the Fungicide Insecticide and Rodenticide Act (FIFRA).

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## **FOOD PACKAGING MATERIAL**

The largest application of mineral oil in packaging materials is in polystyrene. This application generally makes use of high viscosity white oils at levels of 0.5 to 4.0% in the polymer. The oil acts as an internal plasticizer that enables molders and extruders to operate their machines efficiently. Examples of food packaging includes hamburger half shells and beverage containers.

Styrene-rubber block copolymers also make use of significant amounts of mineral oil. Some grades of these thermoplastic elastomers are oil extended and may be used in food or medical applications.

Mineral oils may also find their way into polyethylene and polyethylene copolymers via an indirect route. Ethylene compressors are lubricated with specially formulated products that are based on white mineral oils. The amount of oil entering polyethylene products by this route is very small.

## **COSMETIC AND PHARMACEUTICAL**

White mineral oils have been used in topical preparations for most of this century. White mineral oil production began in the U.S. in the 1920s and the industry very quickly found markets in cosmetics and pharmaceuticals.

White mineral oils are excellent moisturizers and emollients. They are used in a multitude of cosmetic products. A few examples are listed below:

- Baby oils
- Formulated creams and lotions
- Bath oils
- Lipsticks and lip gloss
- Sunscreens and suntan oil
- Make-up bases and removers
- Hair products

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Cosmetic and pharmaceutical companies require that white oils meet United States Pharmacopeia/National Formulary specifications as well as the food additive regulations. The monographs for Mineral Oil, U.S.P. and Light Mineral Oil, N.F. in the current edition (U.S.P. XXII/N.F. XVII) are shown in Appendix 1.

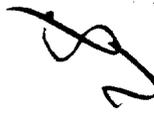
All products meeting the U.S.P./N.F. requirements for Mineral Oil and Light Mineral Oil also meet the most stringent FDA regulation, 21 CFR 172.878. The FDA purity tests are the same as the U.S.P./N.F., and they are the same for both Mineral Oil and Light Mineral Oil. The differences in the two Mineral Oil categories are viscosity and specific gravity.

In the pharmaceutical industry, white oils provide a convenient anhydrous base for prescription and over-the-counter drugs. White oils may also be formulated into creams or lotions containing active ingredients.

Mineral Oil, U.S.P. has been used as a laxative in the U.S. for more than 80 years. The question of interference with absorption of fat-soluble vitamins has been studied and debated in the literature. Although this has resulted in cautionary labeling requirements, Mineral Oil, U.S.P. has been regarded as a safe and effective laxative for adults.

The U.S.P. has taken precautions to assure that only the higher viscosity white oils are used as laxatives. They require that Light Mineral Oil be labeled "not intended for internal use." The primary concern with low viscosity oils is accidental aspiration into the lungs, which could result in chemical pneumonitis.

Veterinary products include applications similar to those used in human pharmaceuticals. These mostly involve topical remedies, but mineral oils are also used in animal laxatives. One application, not permitted in humans, makes use of Light Mineral Oil N.F. as an adjuvant in vaccines. The vaccines are primarily used in poultry inoculations.



## OTHER APPLICATIONS

Mineral Oils are permitted in numerous applications involving indirect food contact. A partial listing taken from Title 21 of the Code of Federal Regulations follows (Appendix 3).

- 173.340 Defoaming agents  
(White Mineral Oil conforming with 172.878 only)
- 175.105 Adhesives
- 175.210 Acrylate ester copolymer coatings
- 175.230 Hot melt strippable food coatings  
(White Mineral Oil conforming with 172.878 only)
- 175.300 Resinous and polymeric coatings  
(As surface lubricants)
- 176.170 Components of paper and paperboard in contact with aqueous  
and fatty foods
- 176.200 Defoaming agents used in coatings
- 177.1200 Cellophane
- 177.2260 Fibers, resin-bonded
- 177.2600 Rubber articles intended for repeated use
- 177.2800 Textiles and textile fibers
- 178.3570 Lubricants with incidental food contact
- 178.3740 Plasticizers in polymeric substances
- 178.3910 Surface lubricants used in the manufacture of metallic articles
- 179.45 Packaging materials for irradiated foods  
(Mineral Oil conforming to 178.3620(a) and (b) only)

Unless specifically noted, the regulations permit oils meeting parts (a), (b) and (c) of 178.3620.

Naphthenic oils meeting 21 CFR 178.3620(c) are used in large volumes in rubber and adhesive formulations. The naphthenic character of these oils enhance their compatibility with amorphous polymers found in rubber and adhesives. The pulp and paper industry also uses large volumes of naphthenic and paraffinic oils as defoamers. Many other applications exist for white mineral oils which do not require adherence to

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government regulations. Two important examples are mentioned briefly. The nonstaining and inert nature of white minerals oils makes them ideal lubricants in the fiber industry. Significant volumes of white mineral oils are used primarily by synthetic fiber manufacturers. Refrigeration systems, such as heat pumps, require low-pour-point white mineral oils for lubrication.

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## Section IV

### TYPICAL MINERAL OIL PROPERTIES AND COMPOSITION

Mineral oil producers provided data to the American Petroleum Institute (API) on the lowest and highest viscosity paraffinic and naphthenic mineral oils supplied for direct and indirect food contact applications. The information supplied included typical data for physical properties, composition, and impurities.

#### WHITE MINERAL OIL

Tables 1 through 4 present data on fully refined white mineral oils processed by hydrogenation (H/H), acid treatment (A) or a combination of the two methods (H/A) to meet the requirements of 21 CFR 172.878 and 178.3620(a). Tables 5 and 6 present data on technical white oils [21 CFR 178.3620(b)] and mineral oils [21 CFR 178.3620(c)].

The physical properties of white mineral oils are fixed by boiling range and the ratio of naphthenics to paraffinics. For a given boiling range, a paraffinic oil would have a lower viscosity, specific gravity, and refractive index than a naphthenic oil. In many applications, however, oils are selected by viscosity rather than boiling range. For a given viscosity, a paraffinic oil would have a higher viscosity index, boiling range and molecular weight, and a lower refractive index and specific gravity than a naphthenic oil. Viscosity index is a measure of change of viscosity with temperature. The higher the viscosity index, the smaller the viscosity decrease as temperature increases.

Tables 1 through 4 list viscosities at 40°C, 100°C, and 100°F. White mineral oil viscosities are usually specified at 40°C. Viscosities at 100°C and 100°F are provided for reference and for the calculation of compositional data (molecular weight and carbon type).

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Viscosities at 40°C ranged from 4.56 to 107 cSt for the paraffinic oils and from 7.42 to 73.5 cSt for the naphthenic oils. Viscosity index ranged from 95 to 115 for the paraffinic oils and from 60 to 89 for the naphthenic oils.

Flash point is valuable in establishing safe handling and operating temperatures and correlates with boiling range. Flash points ranged from 285 to 515°F for paraffinic oils and from 285 to 420°F for naphthenic oils.

Boiling ranges are reported using American Society for Testing Materials (ASTM) D2887, simulated distillation by gas chromatography. The boiling range covered temperatures from 425 to 1189°F for paraffinic oils and 426 to 1018°F for naphthenic oils. Boiling range is directly related to molecular weight. The average molecular weight by ASTM D2502 ranged from 240 to 550 for paraffinic oils and from 263 to 417 for naphthenic oils.

Carbon type analysis was done by ASTM D3238. This method calculates the percentage of naphthenic carbon atoms ( $C_N$ ), paraffinic carbon atoms ( $C_p$ ), and aromatic carbon atoms ( $C_A$ ) from the refractive index, density and molecular weight. White mineral oils are virtually free of aromatics. However, because of the error of the method, small values - often negative - are obtained for  $C_A$ . For Tables 1 through 5,  $C_A$  has been set at zero, and any value obtained for  $C_A$  has been included in the  $C_N$  result.

All mineral oils contain both naphthenic and paraffinic carbon; no oil is either 100%  $C_N$  or  $C_p$ . The highest  $C_p$  value obtained was 70%; the highest  $C_N$  value obtained was 52%.

The nitrogen, sulfur, and heavy metals content of white mineral oils would be expected to be extremely low. The values reported for these impurities were at or below the low ppm range. The variation in the data likely reflects differences in the detection limits for the different laboratories rather than differences in the impurity levels in the oils.

Overall, the naphthenic types of white mineral oils supplied for food applications in the U.S. had higher values for specific gravity and refractive index, and lower values for viscosity index than the paraffinic types. However, the ranges of values for viscosity, flash point, boiling range, and average molecular weight for the naphthenic types were within the range of values reported for the paraffinic types for these same properties.

#### TECHNICAL WHITE MINERAL OILS

Table 5 presents data on technical white mineral oil meeting 21 CFR 178.3620(b). Oils designated by reference numbers 17-22 are low-boiling products with a narrow boiling range. Oils 23 to 25 are paraffinic oils, and oils 26 to 29 are naphthenic oils. The properties of the latter two groups are very similar to the analogous fully refined white mineral oils. Aromatics, sulfur, and nitrogen content are low. Technical white mineral oils, however, are not required to meet the readily carbonizable substances test specified for fully refined white mineral oils, and have less stringent requirements for FDA ultraviolet absorbance.

#### TYPE C MINERAL OIL

Table 6 presents data for mineral oil meeting 21 CFR 178.3620(c). These products have physical properties similar to the more refined oils discussed earlier. Aromatics content is elevated ranging from 0.6 to 7% C<sub>A</sub>. Nitrogen, ranging from 10 to 350 ppm, and sulfur ranging from 100 to 2900 ppm, are also higher.

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Table 1. Low Viscosity Paraffinic White Mineral Oils

<u>Reference Number</u>	(1)	(1.1)	(2)	(3)	(4)	(5)	(6)
Method of Refining <sup>(a)</sup>	H/H	H/H	H/A	H/H	H/A	H/H	H/H
Visc., cSt @ 40°C	4.56	7	7.34	8.04	9.83	12.4	12.8
Visc., cSt @ 100°C	1.62	2.2	2.16	2.30	2.7	3.0	3.12
Visc., SUS @ 100°F	41.8	50	51.6	54.0	60.9	71.3	73.6
Visc. Index	NA <sup>(b)</sup>	100	101	95	102	96	108
Specific Gravity @ 60°F	0.8207	0.835	0.8358	0.8505	0.8579	0.8448	0.8406
Refractive Index @ 20°C	1.4503	1.458	1.4602	1.4640	1.4680	1.4651	1.4640
Flash Point, °F	285	310	310	306	340	385	365
<u>Boiling Range, °F</u>							
Initial	425	480	475	451	529	480	524
5%	500	530	550	502	566	581	600
50%	575	640	641	634	645	716	717
95%	675	740	729	796	739	825	809
End Point	725	780	878	947	831	NDA <sup>(c)</sup>	887
Avg. Molecular Weight	240	270	269	269	313	356	328
<u>Carbon Type</u>							
% C <sub>N</sub>	33.9	36	35.7	42.7	34	30.4	33.9
% C <sub>P</sub>	66.1	64	64.3	57.3	66	69.6	66.1
Nitrogen, ppm	<1	<1	0.5	<1	<2	<1	<1
Sulfur, ppm	<1	<1	<1	<1	NDA	<1	<1
<u>Heavy Metals, ppm</u>							
Arsenic	<0.1	<0.1	<0.1	<1	<3	<5 ppb	<0.1
Cadmium	<0.1	<0.1	<0.1	<1	<2	<0.1	<0.1
Mercury	<0.1	<0.1	<0.1	<1	NDA	<44 ppb	<0.1
Lead	<0.1	<0.1	<0.1	<1	<3	<0.2	<0.1

- (a) H/H indicates two-stage hydrogenation  
H/A indicates hydrogenation followed by acid treatment  
A indicates acid treatment
- (b) Not Applicable
- (c) No Data Available

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Table 2. High Viscosity Paraffinic White Mineral Oils

<u>Reference Number</u>	(7)	(7.1)	(8)	(9)	(10)	(11)
Method of Refining <sup>(a)</sup>	H/H	H/H	H/H	H/H	H/A	H/A
Visc., cSt @ 40°C	69.3	70	77.7	92.1	101	107
Visc., cSt @ 100°C	8.72	8.9	9.63	11.0	12.4	11.8
Visc., SUS @ 100°F	360	360	403	478	528	556
Visc. Index	97	100	101	104	115	97
Specific Gravity @ 60°F	0.8673	0.8700	0.8676	0.8697	0.8690	0.8745
Refractive Index @ 20°C	1.4640	1.476	1.4749	1.4761	1.4760	1.4786
Flash Point, °F	435	480	475	500	510	515
<u>Boiling Range, °F</u>						
Initial	640	720	679	682	635	752
5%	711	780	784	811	757	837
50%	865	900	945	954	938	940
95%	1002	1000	1031	1086	1055	1030
End Point	1018	1060	NDA <sup>(b)</sup>	1189	1136	1067
Avg. Molecular Weight	472	480	550	525	550	534
<u>Carbon Type</u>						
% C <sub>N</sub>	37.5	32	30.2	30	31	31.7
% C <sub>p</sub>	62.5	68	69.8	70	69	68.3
Nitrogen, ppm	<1	<1	2	<1	NDA	0.5
Sulfur, ppm	<1	<1	<15	<1	<2	<1
<u>Heavy Metals, ppm</u>						
Arsenic	<1	<0.1	<5 ppb	<0.1	<3	<0.1
Cadmium	<1	<0.1	<0.1	<0.1	<2	<0.1
Mercury	<1	<0.1	<44 ppb	<0.1	NDA	<0.1
Lead	<1	<0.1	<0.2	<0.1	<3	<0.1

- (a) H/H indicates two-stage hydrogenation  
 H/A indicates hydrogenation followed by acid treatment  
 (b) No Data Available

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Table 3. Low Viscosity Naphthenic White Mineral Oils

<u>Reference Number</u>	(12)	(13)	(14)
Method of Refining <sup>(a)</sup>	H/H	A	H/H
Visc., cSt @ 40°C	7.42	12.7	22.0
Visc., cSt @ 100°C	2.2	3.01	4.0
Visc., SUS @ 100°F	NDA <sup>(b)</sup>	72.4	122
Visc. Index	NDA	89	60
Specific Gravity @ 60°F	0.8665	0.8555	
0.8816			
Refractive Index @ 20°C	1.4711	1.4677	
1.4781			
Flash Point, °F	285	345	355
<u>Boiling Range, °F</u>			
Initial	426	472	477
5%	474	548	564
50%	604	687	718
95%	706	830	851
End Point	NDA	927	934
Avg. Molecular Weight	263	316	340
<u>Carbon Type</u>			
% C <sub>N</sub>	52	38.9	48.6
% C <sub>p</sub>	48	61.1	51.4
Nitrogen, ppm	2	0.3	<1
Sulfur, ppm	<15	<1	<1
<u>Heavy Metals, ppm</u>			
Arsenic	<5 ppb	<0.1	<0.1
Cadmium	<0.1	<0.1	<0.1
Mercury	<44 ppb	<0.1	<0.1
Lead	<0.2	<0.1	<0.1

(a) H/H indicates two-stage hydrogenation  
 H/A indicates hydrogenation followed by acid treatment  
 A indicates acid treatment  
 (b) No Data Available

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Table 4. High Viscosity Naphthenic White Mineral Oils

<u>Reference Number</u>	(15)	(16)
Method of Refining <sup>(a)</sup>	H/H	H/A
Visc., cSt @ 40°C	67.0	73.5
Visc., cSt @ 100°C	7.4	7.93
Visc., SUS @ 100°F	351	385
Visc. Index	60	63
Specific Gravity @ 60°C	0.8911	0.8877
Refractive Index @ 20°C	1.4833	1.4831
Flash Point, °F	400	420
<u>Boiling Range, °F</u>		
Initial	601	614
5%	678	720
50%	799	817
95%	912	936
End Point	982	1018
Avg. Molecular Weight	400	417
<u>Carbon Type</u>		
% C <sub>N</sub>	47.6	43.6
% C <sub>p</sub>	52.4	56.4
Nitrogen, ppm	<1	0.5
Sulfur, ppm	<1	<1
<u>Heavy Metals, ppm</u>		
Arsenic	<0.1	<0.1
Cadmium	<0.1	<0.1
Mercury	<0.1	<0.1
Lead	<0.1	<0.1

(a) H/H indicates two-stage hydrogenation  
 H/A indicates hydrogenation followed by acid treatment

Table 5. Technical White Mineral Oils (Part b)

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Reference Number	(17)	(18)	(19)	(20)	(21)	(22)	(23)	(24)	(25)	(26)	(27)	(28)	(29)
Type	---	---	---	---	---	---	---	Paraffinic	Paraffinic	Paraffinic	Paraffinic	Paraffinic	Naphthenic
Visc., cSt @ 40°C	1.5	1.5	2.2	2.3	6.0	2.61	4.56	17.8	77.7	101	4.46	7.42	67.5
Spec. Grav. @ 60°F	0.751	0.790	0.907	0.771	0.814	0.808	0.821	0.850	0.868	0.869	0.838	0.866	0.883
<u>Boiling Range, °F</u>													
Initial	370	396	469	486	491	375	425	552	679	635	416	426	613
50%	392	414	480	502	518	500	575	739	945	938	564	604	829
End Point	423	450	498	531	563	623	725	916	NDA <sup>(a)</sup>	1136	747	NDA	1017
<u>Carbon Type</u>													
% C <sub>N</sub>	---	---	---	---	---	29.8	33.9	33.8	30.2	31	42.6	52	43
% C <sub>P</sub>	---	---	---	---	---	70.2	66.1	66.9	69.8	69	57.0	48	57
Nitrogen, ppm	<1	NDA	NDA	1	NDA	<1	<1	<1	2	NDA	<1	2	<1
Sulfur, ppm	<1	3	3	5	1	<1	<1	0.5	<15	<2	<1	<15	<1

(a) Paraffinic or isoparaffinic products with low unsaturated content.  
 (b) No Data Available

Table 6. Mineral Oils (Part c)

Reference Number	(30)	(31)	(32)	(33)	(34)	(35)	(36)	(37)	(38)	(39)
Type	Paraffinic					Naphthenic				
Visc., cSt @ 40°C	2.38	7.0	19.0	59.0	164	9.2	14.1	27.1	85.4	87.1
Spec. Grav. @ 60°F	0.813	0.843	0.867	0.885	0.898	0.865	0.875	0.892	0.910	0.890
Boiling Range, °F										
Initial	455	473	421	544	572	443	475	NDA <sup>(a)</sup>	604	626
50%	487	639	741	848	963	646	684	NDA	790	855
End Point	522	840	954	970	1274	867	890	NDA	975	1036
Carbon Type										
% C <sub>N</sub>	23.4	29	39	39	30	47	44	55.4	46	37
% C <sub>P</sub>	71.6	64	60	60	66	49	52	44.0	53	60
% C <sub>A</sub>	5.0	7	1	1	4	4	4	0.6	1	3
Nitrogen, ppm	<25	NDA	<30	<30	NDA	15	11	310	10	NDA
Sulfur, ppm	450	1600	100	400	NDA	750	2900	2600	300	900

(a) No Data Available

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Section V  
REGULATORY HISTORY

Many of the food regulations for white mineral oil incorporate specifications from national pharmacopeias. White mineral oil was first listed in the U.S. Pharmacopeia in 1894. Monographs on white mineral oil were included in the British and other European pharmacopeias as early as 1914.

The early pharmacopeias specified only physical properties, such as viscosity, specific gravity and color. However, by 1940 purity criteria such as Readily Carbonizable Substances began to be incorporated in white mineral oil monographs. Ultraviolet absorbance limits began to appear in white mineral oil monographs following the work of Haenni and Hall in the 1960s.

#### U.S. REGULATIONS

Early governmental regulation of white mineral oil in food was done on a case-by-case basis for each application. The Food and Drug Administration's Regulatory Announcement 22, Item 265, dated April 18, 1918, permitted the use of "high grade harmless mineral oil" as a "slab oil" or release agent for confectionary. In 1944, the U.S. District Court of Idaho ruled that the use of small quantities of U.S.P. White Mineral Oil as a binder for the salt coating of popcorn was acceptable.

On March 5, 1959, the Federal Food Additive Amendment to the Food, Drug and Cosmetic Act was passed. This regulation required that the FDA approve all non-nutritive substances directly or indirectly becoming a component of food through manufacturing, processing, preparing, or packing. Substances already in commercial use were not affected by the regulation until March of 1960.

The API, on behalf of the U.S. manufacturers of white mineral oil, submitted petitions to the FDA requesting regulations permitting direct and indirect uses of white mineral oil in food. After considerable discussion and work by both the API and the FDA, the FDA, in 1964, issued regulations 121.1146 covering the direct uses and 121.2589

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covering indirect uses of white mineral oil in food. These regulations are the basis of the current regulations 172.878 and 178.3620, respectively.

The original approved uses were:

- 1) as a release agent, binder, and lubricant in or on capsules and tablets containing concentrates of flavoring, spices, condiments, and nutrients intended for addition to food, excluding confectionery;
- 2) as a release agent, binder, and lubricant in or on capsules and tablets containing food for special dietary use;
- 3) as a float on fermentation fluids in the manufacture of vinegar and wine to prevent or retard access of air, evaporation, and wild yeast contamination during fermentation;
- 4) in bakery products, as a release agent and lubricant;
- 5) in dehydrated fruits and vegetables, as a release agent;
- 6) in egg white solids, as a release agent; and
- 7) on raw fruits and vegetables, as a protective coating.

A number of uses have been approved since the issue of the regulations in 1964.

New direct applications allow the use of white mineral oil:

- 1) as a defoamer in food;
- 2) in frozen meat as a component of hot-melt coating;
- 3) as a protective coat used in the curing of pickles;
- 4) in molding starch used in the manufacture of confectionary;
- 5) as a release agent, binder in the manufacture of yeast;
- 6) as an antidusting agent in sorbic acid for food use;
- 7) as a release agent and sealing and polishing agent in the manufacture of confectionary; and
- 8) as a dust control agent for wheat, corn, soybean, barley, rice, rye, oats, and sorghum.

## EUROPEAN REGULATIONS

Regulations on the use of white mineral oil in food are not consistent among the various European countries. For example, British regulations permit the use of white mineral oil in many of the same applications permitted in the U.S., whereas the only direct use allowed by West Germany is the use of white mineral oil in chewing compounds and snuff.

## BRITISH REGULATIONS

In 1949, the British Ministry of Foods issued the "Mineral Oil in Food Order" which permitted up to 0.2% mineral oil in food when used as a lubricant. In 1964, the "Mineral Hydrocarbons in Food Regulation" was enacted. This regulation included petrolatum and wax as well as white mineral oil. The regulation, as redrafted in 1966, remains in effect today.

The British regulation prohibits the use of mineral hydrocarbons in food except for certain specified applications. Permitted applications allow the presence of mineral hydrocarbons in food, as listed below:

- 1) in dried fruit to a maximum of 0.5%;
- 2) in citrus fruit to a maximum of 0.1%;
- 3) as a polishing/glazing agent to a maximum of 0.2%;
- 4) as a lubricant/greasing agent in confectionary to a maximum of 0.2%;
- 5) in any food resulting from the use of commodities in items 1 to 4;
- 6) in chewing compounds to a maximum of 60%;
- 7) in the rind of any whole cheese product; and
- 8) on the shells of whole eggs.

In 1975, the British regulation was reviewed by the Food Additives and Contaminates Committee (FACC).

The FACC recommended:

- 1) that the FDA ultraviolet absorbance test for white mineral oil be adopted for all mineral hydrocarbons;

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- 2) reductions in permitted levels of mineral hydrocarbons in dried fruit (from 0.5 to 0.25%), confectioning (from 0.2 to 0.1%) and chewing compounds (from 60 to 15%); and
  - 3) that the provision for 0.2% mineral hydrocarbon in food due to the use of lubricant/grease agents be limited to 0.1% in bread and 0.2% in table jellies.

A proposal to modify the mineral hydrocarbon regulation to incorporate the FACC recommendations was made in 1978. However, the proposal was never adopted, and the regulation remains as written in 1966.

In February of 1989, the Ministry of Agriculture, Fisheries and Food (MAFF) proposed to ban the use of mineral hydrocarbons in food except in chewing compounds and food packaging materials, both of which were to be studied separately. MAFF's justification of the proposed ban was that there was inadequate toxicological information on the mineral oils in use, and that recent toxicological studies (see Section VI) indicated toxicity down to very low doses.

MAFF has indicated that it has not been swayed from its intended course by arguments and toxicological information submitted in the comment period following the proposal. However, the drafting of the regulation for the implementation of the ban has been delayed, and has not yet been submitted to Parliament.

#### JOINT FAO/WHO EXPERT COMMITTEE ON FOOD ADDITIVES (JECFA)

Prior to 1976, at its 14th and 17th meeting, JECFA had established an "ADI not limited" for white mineral oil. This classification would limit food use only by good manufacturing practice. At its 20th meeting in 1976, JECFA stated that insufficient information was available for white oils produced by catalytic hydrogenation (hydrotreating). For this reason, JECFA issued an "ADI not specified" for oleum-treated white mineral oils and did not classify hydrogenated white mineral oils.

At its 30th meeting in 1986, JECFA allocated a "temporary ADI not specified" to white mineral oils, but noted that safety data and specifications for hydrogenated oils were

inadequate. In its 33rd meeting in 1988, after reviewing the Shell studies, JECFA extended the "temporary ADI not specified" for mineral oil in use as lubricants and release agents in food. JECFA also called for further studies to characterize these materials by 1990.

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Section VI  
REVIEW OF SHELL STUDIES

Shell Research Limited, Sittingbourne Research Centre (U.K.) conducted two 90-day feeding studies using Fischer 344 (F344) rats to compare the toxicity of white mineral oils of naphthenic origin, one prepared by oleum treatment and the other by the newer hydrotreating process. The two oils tested were processed at different refineries and were representative of oils currently supplied to the food industry. Samples of the two oils were recently analyzed on behalf of API for physical properties and compositional data. Table 7 compares the data for the two Shell test oils with data for low and high viscosity paraffinic and naphthenic U.S. white mineral oils reported in Tables 1 through 4 in Section IV. The properties of the Shell test oils were well within the ranges reported for the naphthenic type U.S. white mineral oils.<sup>1</sup> There was a large difference between the viscosities of the two oils tested which, probably reflected a significant difference in average molecular weights.

In Shell's first study, male and female rats were exposed to each oil at concentrations of 5000 ppm (0.5%), 10,000 ppm (1.0%), and 20,000 ppm (2.0%) in the diet. Measurements of hematology, clinical chemistry, and complete histopathology were conducted. In the second study, only females were exposed to dietary concentrations of 10, 100, 500, 5000, 10,000 and 20,000 ppm. In this study group, histopathological examination was limited to liver and mesenteric lymph nodes with no hematological or clinical chemical measurements made.

In the first study, histopathological examination at exposure termination revealed effects in spleen, lymph nodes, and liver. In males, the splenic lesions (capsular adhesions, capsular inflammatory cell infiltrates) were present at all levels of oleum-treated oil administration (0.5 to 2.0%). In males fed hydrotreated oil, there were no

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<sup>1</sup> The one exception to this is the Readily Carbonizable Substances test. The Shell Ondina 68 sample failed this test. Shell reported that both test oils met national pharmacopeia and food regulations at the time the feeding studies were conducted, which include the Carbonizable Substances test. It is not known what caused the failure in the sample tested for the API; however, the test is extremely sensitive, and the failure may have been caused by contamination of the sample during storage or in transfer.

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such lesions at the 1% dietary level and only a few at 0.5% and 2%. In females, the splenic capsular lesions were scattered among all groups without any detectable dose response. Additionally, hematopoietic effects in the spleen (red cell congestion, erythropoiesis, and myelopoiesis) occurred in females at all treatment levels of the oleum-treated oil. Only the female animals in the 2% hydrotreated oil group showed consistent, significant hematopoietic effects.

The only clear histopathological evidence of liver effects in male rats occurred in the 2% oleum-treated group, where focal Kupffer-cell hypertrophy and very slight multifocal granulomas were noted. However, in females, liver granulomas occurred in both studies at the 0.5% dietary level or above, with greater incidences in the oleum-treated group. No granulomas were seen with either oil below 0.5%. Males were not used in the second study, since females were the more sensitive sex.

In the first study, male and female rats exposed to all levels (0.5 to 2%) of both oils showed granulomas, fat-like globules in granulomatous foci, and histiocytosis in mesenteric lymph nodes. The mesenteric lymph nodes might be expected to be the first collecting organ for absorbed oil and, therefore, may be the most sensitive organ in detecting physiological reactions to mineral oil ingestion. In the second study, frequent granulomatous macrophage syncytia were noted in one female rat after administration of 100 ppm oleum-treated oil; at 10 ppm, no such lesions were seen. Three out of five female rats given 5000 ppm hydrotreated oil demonstrated this lesion. No effects of this type were observed at doses below this level.

The effects of dietary white mineral oil on the hematological system were most obvious in females given oleum-treated oil. These consisted of increases in white cell count (WBC) and in the occurrence at all dose levels (0.5 to 2%) of what was termed a "hypochromic microcytic" anemia. Examination of the female hematology data indicates that the anemia can best be termed normochromic normocytic since the trends of red cell count, hematocrit and hematosiis all proceed in the same direction.

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The cellular parameters, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCEC) showed absolutely no change with dose. Even at the highest dietary levels, the decreases in hematological values were not evidence of a compromised hematopoietic system. Measurements of blood parameters were not done at levels below 0.5% dietary concentration. Slight increases in WBC were seen in males at the 2% level, but no other parameters were affected at high dietary levels. At high dietary levels, changes in the hematological values may reflect the inflammatory responses occurring in the liver and spleen (an accessory hematopoietic organ in rodents).

The increases in blood concentrations of liver enzymes (alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, and gamma glutamyl transpeptidase) in females at the 1% and 2% dietary levels of the oleum-treated oil are consistent with the histopathological findings of occasional necrotic foci in that organ. The absence of any increases at the 0.5% dietary level supports the view that the liver granulomas do not lead to parenchymal cellular damage at this level. Serum enzyme evidence of such damage is less clear in females exposed to the hydrotreated oil and completely absent in males.

In summary, the effects of dietary administration of white oil to F344 rats appear to be those expected from a poorly absorbed, insoluble liquid that is not metabolized rapidly. It may be hypothesized that, above a certain level, this leads to cellular changes associated with ingestion of oil by macrophages and formation of macrophage syncytia. At higher levels, this may progress to frank granuloma formation, and when high enough levels are reached, cellular damage can occur leading to the histopathological, hematological and clinical chemical alterations seen in the Shell studies.

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Table 7. Low and High Viscosity U.S. White Mineral Oils vs. Shell Oils

<u>Reference Number</u>	<u>Paraffinic</u>		<u>Naphthenic</u>		<u>Shell Study</u>	
	(1)	(11)	(12)	(16)	WOM 24	Ondina 68
Method of Refining <sup>(a)</sup>	H/H	H/A	H/H	H/A	A	H/H
Visc., cSt @ 40°C	4.56	107	7.42	73.5	26.2	68.4
Visc., cSt @ 100°C	1.62	11.8	2.2	7.93	4.42	7.72
Visc., SUS @ 100°F	41.8	556	NDA <sup>b</sup>	385	136	358
Visc. Index	NA <sup>c</sup>	97	NDA	63	60	68
Specific Gravity @ 60°F	0.8207	0.8745	0.8655	0.8877	0.8746	0.8778
Refractive Index @ 20°C	1.4503	1.4786	1.4711	1.4831	1.4758	1.4780
Flash Point, °F	285	515	285	420	NDA	NDA
<u>Boiling Range, °F</u>						
Initial	425	752	426	614	520	654
5%	500	837	474	720	605	705
50%	575	940	604	817	724	818
95%	675	1030	706	936	836	953
End Point	725	1067	---	1018	896	>1018
Avg. Molecular Weight	240	534	263	417	341	422
<u>Carbon Type</u>						
% C <sub>N</sub>	33.9	31.7	52	43.6	41.0	39.9
% C <sub>p</sub>	66.1	68.3	48	56.4	55.9	56.5
Nitrogen, ppm	<1	<0.5	2	0.5	<1	<1
Sulfur, ppm	<1	<1	<15	<1	4.7	0.2
FDA UVA	-----0.10 Max.-----			0.028	0.083	
Carbonizable Substances	-----Must pass-----			Pass	Fail	

- (a) H/H indicates two-stage hydrogenation  
     H/A indicates hydrogenation followed by acid treatment  
     A indicates acid treatment
- (b) No Data Available
- (c) Not Applicable

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Section VII  
SUMMARY OF THE TOXICOLOGY OF MINERAL OILS

Shell Oil Company and Exxon Biomedical Sciences, Inc., have prepared detailed review papers on the toxicology of mineral oils (Appendices 5 and 6, respectively). Exxon's review addresses all aspects of the current knowledge of mineral oil toxicology and related biological effects. Most notably, the Exxon review presents extensive data on subchronic dietary and oral gavage 90-day toxicity studies on four white mineral oils and a technical grade mineral oil. In addition to the Exxon data, results from an ARCO-sponsored 90-day feeding study in rats is appended as Appendix 7. Table 8 provides a comparison of the properties of the oils tested by Exxon, ARCO, and Shell, while Table 9 provides a summary of the experimental differences among these studies. Shell's literature review focuses primarily on the current knowledge surrounding the granulomatous response noted in the 90-day feeding studies conducted by Shell Research, Limited. Summaries of the above reviews and studies are presented below. The reader is directed to the reviews appended here as Appendix 5 and Appendix 6 for more detail.

**EXXON**

Subchronic dietary and oral gavage 90-day toxicity studies have been conducted by Exxon on four white mineral oils and a technical grade mineral oil. Four of these oils were paraffinic (one oleum-treated oil and three hydrogenated oils) and were evaluated in rats and dogs at dietary concentrations of 300 and 1500 ppm (w/w). No toxicity was observed with any oil, and none of the oils appeared to accumulate in the tissues of either species. Thus, the NOEL exceeded 1500 ppm in feed or dietary consumption rates of approximately 125 mg/kg/day in rats and 52 mg/kg/day in dogs. A fifth oil (medicinal grade) was an oleum-treated naphthenic product that was given to rats by oral gavage at a dose of 4350 mg/kg, 5 days per week, for 90 days. No toxicity was observed; thus, the NOEL exceeded 4350 mg/kg/day.

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White mineral oils and petrolatums have been tested in lifetime dietary feeding studies in rats. These studies also failed to establish any chronic toxicity or carcinogenic effects. The approximate NOELs exceeded 1200-6000 mg/kg/day in these studies.

Numerous studies indicate that white mineral oils from either paraffinic or naphthenic crude sources are not carcinogenic. These include studies conducted by the dermal and inhalation routes of exposure as well as the dietary feeding studies discussed above. Further studies indicate that white mineral oils are neither mutagenic nor developmental or reproductive toxicants.

The toxicity of technical mineral hydrocarbons has also been characterized. The technical mineral hydrocarbons discussed in the Exxon report are made by different processes than the white mineral oils and are typically of lower average molecular weight, lower final boiling point, lower viscosity, and higher volatility. All Exxon studies of technical mineral hydrocarbons were conducted by inhalation because this was considered to be the most relevant route of industrial human exposure. The specific studies included subchronic (i.e., 90 day) inhalation, teratology, and dominant lethal studies as well as acute toxicity tests.

None of the three tested technical mineral hydrocarbons produced evidence of acute health hazards. There was no evidence of cumulative toxicity in rats exposed to vapor concentrations of up to 900-1180 ppm, 6 hours/day, 5 days/week for 12 weeks, with the exception of effects on the kidneys. However, this specific renal effect, also known as light hydrocarbon nephropathy (LHN), is a phenomenon that occurs only in male rats and is not considered to be a toxic end point representing a human health concern (Kloss and Bus, 1985; see Appendix 6 References). Of particular note was the absence of pathologic evidence of mineral hydrocarbon accumulation or specific organ toxicity. Additionally, there was no evidence of testicular toxicity or genetic toxicity in dominant lethal studies which utilized the same exposure levels. The lack of

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effect in the dominant lethal study also indicates that these products are not male reproductive toxins. Corroborative findings can be found in the published literature.

#### ARCO

ARCO sponsored a subchronic (90-day) feeding study in male and female albino rats of the technical white mineral oil product Tufflo 6056 (Appendix 7). The study was conducted by Industrial BIO-TEST Laboratories, Inc. (IBT). While the raw data are not available and the study was not audited by ARCO, it is included here for the purpose of completeness.

The white oil was fed to male and female albino rats (15/sex/group) at dietary concentrations of 0 and 10,000 ppm. Evaluations for toxicity included clinical signs of toxicity, body weight measurements, food consumption, hematology, clinical chemistry, urinalysis, and histopathology. Liver specimens were treated with osmium tetroxide, a stain for unsaturated lipids. All results for white-oil-treated animals were considered comparable to control. Thus, under the conditions of this study, there was no evidence of white-oil-induced toxicity.

#### SHELL

Shell's review of the literature shows that mineral oil hydrocarbons are absorbed from the gastrointestinal tract; this absorption appears to be dependent upon molecular size and structure. Straight-chain compounds are better absorbed than branched or cyclic structures. Lower molecular weight (MW) compounds are better absorbed from the gastrointestinal tract than higher MW compounds; petroleum waxes do not appear to be absorbed. The absorbed oil is distributed to the liver, spleen, mesenteric lymph nodes, and lungs. The amount of mineral oil deposited and retained in the organs is dependent on dose.

Mineral oil induces a state of hyperphagocytosis by the macrophages of the liver and lungs, which can lead to microgranulomatous changes in these tissues. The hepatic

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granulomas are composed primarily of Kupffer cells and/or macrophages with infiltrating polymorphonuclear and mononuclear leukocytes. Pulmonary granulomas consist of oil-containing macrophages, lymphocytes, and fibroblasts, together with a slight amount of collagen fibers.

Species differ greatly in their response to mineral oil; dogs and rats are sensitive to the accumulation of white oil, while rabbits, hamsters, mice, and gerbils seem more resistant to these changes.

Case studies of individuals using or misusing mineral oil reveal a pattern of structural and functional cellular changes in the liver, lungs, spleen, and mesenteric lymph nodes. These changes have not been regarded as harmful in the medical literature.

Hepatic granulomatous reactions have been evoked under a variety of experimental conditions. Some involve reactions to metallic and other compounds; others involve occlusion of the hepatic vein, and yet others relate to familiar pathogens.

The granulomatous reactions described above are not considered to be toxicologically significant to functional changes in the organs.

Table 8. Comparison of Properties of Oils Evaluated in the Exxon, ARCO & Shell Studies

	<u>EXXON</u>			<u>ARCO</u>	<u>SHELL Study</u>	
	Marcol <sup>(1)</sup>	EZL 550 <sup>(2)</sup>		Tufflo <sup>(3)</sup>	Ondina <sup>(4)</sup>	WOM 24 <sup>(4)</sup>
Oil	82			6056	68	
Refining Method (5)	H/H	----H/H----		H/H	H/H	A
Oil Type	Para.	----Para.---		Para.	Naph.	Naph.
Saybolt Color	+30	+30	+30	+30	+30	+30
Density (Kg/l. @ 15°C)	0.843	0.866	0.864	0.872	0.8778	0.8746
Refractive Index, 20°C	1.4642	1.4754	1.4749	1.4778	1.4780	1.4758
Pour Point, °F	10	10	10	15	-25	-30
Visc., cSt @ 40°C	14.5	67.5	68.2	90.0	68.4	26.2
Visc. Index	104	101	103	100	68	60
<u>Boiling Range, °F</u>						
Initial	592	736	754	594	654	520
5%	633	801	815	797	705	605
10%	653	828	842	844	727	631
20%	680	862	873	NDA <sup>a</sup>	756	662
50%	745	918	923	914	818	724
95%	838	990	991	993	953	836
End Point	883	1040	1027	---	>1018	896
Avg. Molecular Weight	368	514	521	530	422	341
<u>Carbon Type</u>						
% C <sub>N</sub>	34	36	34	31	39.9	41
% C <sub>p</sub>	66	64	66	69	56.5	55.9
% C	85.79	86.06	86.05	NDA	86.39	86.20
% H	14.21	13.94	13.95	NDA	13.84	13.86
Nitrogen, ppm	<1	<1	<1	2	<1	<1
Sulfur, ppm	0.4	0.2	0.2	<10	0.2	4.7
FDA UVA	0.03	0.01	0.01	0.057	0.083	0.028
Carbonizable Substances	Pass	Pass	Pass	Fail <sup>(6)</sup>	Fail	Pass

(1) CONCAWE data

(2) CONCAWE data for product similar to Primol 352

(3) ARCO data

(4) API analysis of Shell oils

(5) H/H - Two-stage hydrogenation. A - Acid treatment

(6) Technical White Mineral Oil

a) No Data Available

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 4 Table 9. Comparison of Shell, Exxon, and ARCO 90-Day Studies

Studies Oil Type	Shell		Exxon					ARCO
	Naphthenic		Paraffinic		Naphth. (Gavage)			Para.
Vis, cSt	25.6	69.2	12.3	13.8	65.9	31.6	35.7	101
MW	352	415	365 <sup>a</sup>	368	518	423 <sup>a</sup>	362 <sup>a</sup>	530
C <sub>N</sub> % <sup>b</sup>	39.9	41.0		34	35			31
C <sub>p</sub> % <sup>c</sup>	56.5	55.9		66	65			69
Process <sup>d</sup>	ol.	hy.	ol.	hy.	hy.	hy.	ol.	hy.
Grade	Meet NP, food regs.		Med.	Med.	Med.	Tech.	Med.	Tech.
IBP, °F	520	654		592	745			594
BP 50%	724	818	734 <sup>a</sup>	745	921	811 <sup>a</sup>	718 <sup>a</sup>	914
FBP	896	1018		883	1035			993
Rat Strain	F-344		Long-Evans (Beagle Dogs)			S-D		S-D
Feed Conc.	0.001, 0.01, 0.05, 0.5, 1, and 2%		0.03 and 0.15%			gavage		1%
Dose, mg/kg/day	0.6, 5.7, 29, 285, 580, and 1150		Rats - 25 and 125 Dogs - 10 and 52			4350		580(est.)
Regimen	Daily 90 days		Daily 91-99 days			5 days/wk for 13 wks		Daily 90 days
Sacrifice	Exposure termination		Exposure termination			14 days post- termination		Exposure termination
Stain	Sudan IV at 2% level		Oil Red O, both levels			None		Osmium Tetroxide
Oil in organs	Measured at 2% level		Not measured			Not measured		Not measured

<sup>a</sup> Derived from lines plotted using CONCAWE data.

<sup>b</sup>% Naphthenic carbon atoms.

<sup>c</sup>% Paraffinic carbon atoms.

<sup>d</sup> ol. = oleum treated, hy. = hydrotreated.

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Section VIII  
SIGNIFICANCE OF THE SUBCHRONIC TOXICITY STUDIES  
OF WHITE MINERAL OILS

The summary of the toxicology of food grade mineral oils in Section VI indicates that these products have a low order of toxicity. A long history of safe use in humans supports this view. However, there is some disparity in the reported study results, specifically, between the Shell Sittingbourne and the Exxon studies. This section attempts to identify factors that may have contributed to these different findings.

Protocols and test material differences between the Shell Sittingbourne and the Exxon studies are summarized in Table 9. Those protocol differences which appear noteworthy included sample preparation, dose, species/strain and exposure regimen. The notable test material variables were crude type, process and viscosity.

There was a difference in sample preparation between the Shell and Exxon feeding studies. Hexane was added to the Shell oils before mixing with the powdered feed. The Exxon oil was added directly to the meal and mixed. Animals in both groups of studies were sacrificed for histopathological examination immediately after exposure.

The most important of the protocol differences was clearly dose. The Shell studies covered a wider range of doses and included much higher concentrations than the Exxon studies. However, where there were similar concentrations of oil in feed, biological responses were observed only in the Shell studies.

It is unknown whether the strain differences in the rats used in the different tests could have affected study outcome. There are no data available to indicate whether these strains are more or less sensitive with respect to foreign-body type granuloma formation.

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The most pronounced difference in exposure regimens among the various mineral oil studies was the use of oral gavage route, rather than feeding, in two of the Exxon studies. In the oral gavage studies, the terminal sacrifices of the animals occurred 14 days, rather than immediately, after completion of dosing. These methodological differences would have affected study outcome (compared to exposure via the feed) but cannot be quantitated.

Regarding differences in the test materials, it is intuitive that differences in hydrocarbon distribution (e.g., molecular size or weight) could result in differences in absorption, distribution, metabolism and elimination. Crude type, processing, and viscosity, for example, could each affect the distribution of hydrocarbons present in a product. However, the available information (summarized in Table 9) is insufficient to determine whether certain hydrocarbon species are indeed more likely to elicit granulomatous reactions. Thus, the critical production variables, if any, also cannot be identified.

The Shell and Exxon studies appear to have been conducted according to the best standards of the time and to have been interpreted objectively. From the information available, it is not possible to make a judgment concerning the causes of the different results obtained in the two series of studies.

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Section IX  
API WHITE MINERAL OIL WORK GROUP POSITION

Based on the information presented in this review, the API White Mineral Oil Workgroup has concluded:

- 1) The reviewed data indicate that, in general, mineral oils pose a low potential for toxicity. Published and unpublished subchronic and chronic studies of mineral oil conducted by feeding, oral gavage or inhalation routes of exposure have been mostly without significant toxic effect.
- 2) Highly refined mineral oils derived from vacuum distillates have been shown to be noncarcinogenic to experimental animals in lifetime skin painting studies.
- 3) The reviewed genetic toxicity studies of highly refined mineral oils indicate that these materials are not genotoxic.
- 4) The available animal data indicate that mineral oils do not pose a developmental or reproductive risk.
- 5) Mineral oil accumulation in the mesenteric lymph nodes, liver and spleens of humans is widely documented in the literature and is generally viewed as having no remarkable adverse effects on function or health. Indeed, hepatic granulomatous reactions can be evoked in experimental animals under a variety of circumstances, including the ingestion of high lipid diets.

It is the position of the work group that the majority of the data generated to date on mineral oils indicate that they can continue to be used safely in both direct and indirect food applications.

## Mineral Oil

➤ Mineral Oil is a mixture of liquid hydrocarbons obtained from petroleum. It may contain a suitable stabilizer.

**Packaging and storage**—Preserve in tight containers.

**Labeling**—Label it to indicate the name of any substance added as a stabilizer.

**Specific gravity (841)**: between 0.845 and 0.905.

**Viscosity (911)**—It has a kinematic viscosity of not less than 34.5 centistokes at 40.0°.

**Neutrality**—Boil 10 mL with an equal volume of alcohol: the alcohol remains neutral to moistened litmus paper.

**Readily carbonizable substances**—Place 5 mL in a glass-stoppered test tube that previously has been rinsed with chromic acid cleansing mixture (see *Cleaning Glass Apparatus* (1051)), then rinsed with water, and dried. Add 5 mL of sulfuric acid containing from 94.5% to 94.9% of H<sub>2</sub>SO<sub>4</sub>, and heat in a boiling water bath for 10 minutes. After the test tube has been in the bath for 30 seconds, remove it quickly, and, while holding the stopper in place, give three vigorous, vertical shakes over an amplitude of about 5 inches. Repeat every 30 seconds. Do not keep the test tube out of the bath longer than 3 seconds for each shaking period. At the end of 10 minutes from the time when first placed in the water bath, remove the test tube: the Oil may turn hazy, but it remains colorless, or shows a slight pink or yellow color, and the acid does not become darker than the standard color produced by mixing in a similar test tube 3 mL of ferric chloride CS, 1.5 mL of cobaltous chloride CS, and 0.5 mL of upric sulfate CS, this mixture being overlaid with 5 mL of Mineral Oil (see *Readily Carbonizable Substances Test* (271)).

**Limit of polynuclear compounds**—

**Methyl sulfoxide**—Use methyl sulfoxide that has an absorbance, compared to that of water, in a 1-cm cell, not greater than 1.0 at 264 nm, and that shows no extraneous impurity peaks in the wavelength region up to 350 nm.

**Standard solution**—Dissolve a suitable quantity of naphthalene, accurately weighed, in isooctane, and dilute quantitatively and stepwise with isooctane to obtain a solution having a concentration of 7.0 µg per mL. Determine the absorbance of this solution in a 1-cm cell at the maximum at about 275 nm, with a suitable spectrophotometer, using isooctane as the blank.

**Procedure**—Transfer 25.0 mL of Mineral Oil and 25 mL of n-hexane to a 125-mL separator, and mix. [NOTE—Use only n-hexane that previously has been washed by being shaken twice with one-fifth its volume of Methyl sulfoxide. Use no lubricants other than water on the stopcock, or use a separator equipped with a suitable polymeric stopcock.] Add 5.0 mL of Methyl sulfoxide, and shake the mixture vigorously for 1 minute. Allow to stand until the lower layer is clear, transfer the lower layer to another 125-mL separator, add 2 mL of n-hexane, and shake vigorously. Separate the lower layer, and determine its absorbance in a 1-cm cell, in the range of 260 nm to 350 nm, with a suitable spectrophotometer, using as the blank Methyl sulfoxide that previously has been shaken vigorously for 1 minute with n-hexane in the ratio of 5 mL of Methyl sulfoxide and 25 mL of n-hexane. The absorbance at any wavelength in the specified

range is not greater than one-third of the absorbance, at 275 nm, of the Standard solution.

**Solid paraffin**—Fill a tall, cylindrical, standard oil-sample bottle of colorless glass of about 120-mL capacity with Mineral Oil that has been dried previously in a beaker at 105° for 2 hours and cooled to room temperature in a desiccator over silica gel. Insert the stopper, and immerse the bottle in a mixture of ice and water for 4 hours: the Oil is sufficiently clear that a black line 0.5 mm in width, on a white background, held vertically behind the bottle, is clearly visible.

## Light Mineral Oil

➤ Light Mineral Oil is a mixture of liquid hydrocarbons obtained from petroleum. It may contain a suitable stabilizer.

**Packaging and storage**—Preserve in tight containers.

**Labeling**—Label it to indicate the name of any substance added as a stabilizer, and label packages intended for direct use by the public to indicate that it is not intended for internal use.

**Specific gravity (841)**: between 0.818 and 0.880.

**Viscosity (911)**—It has a kinematic viscosity of not more than 33.5 centistokes at 40°.

**Neutrality, Readily carbonizable substances, Limit of polynuclear compounds, and Solid paraffin**—It meets the requirements of the tests for *Neutrality, Readily carbonizable substances, Limit of polynuclear compounds, and Solid paraffin* under *Mineral Oil*.

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## Mineral Oil Enema

➤ Mineral Oil Enema is Mineral Oil that has been suitably packaged.

**Packaging and storage**—Preserve in tight, single-unit containers.

**Specific gravity (841)**: between 0.845 and 0.905.

**Viscosity (911)**—It has a kinematic viscosity of not less than 34.5 centistokes at 40.0°.

**Neutrality**—Boil 10 mL with an equal volume of alcohol: the alcohol remains neutral to moistened litmus paper.

Mineral Oil, Light—see Mineral Oil, Light NF

## Topical Light Mineral Oil

➤ Topical Light Mineral Oil is Light Mineral Oil that has been suitably packaged.

**Packaging and storage**—Preserve in tight containers.

**Labeling**—Label it to indicate the name of any substance added as a stabilizer, and label packages intended for direct use by the public to indicate that it is not intended for internal use.

**Specific gravity (841)**: between 0.818 and 0.880.

**Viscosity (911)**—It has a kinematic viscosity of not more than 33.5 centistokes at 40°.

**Neutrality, Readily carbonizable substances, and Solid paraffin**—It meets the requirements of the tests for *Neutrality, Readily carbonizable substances, and Solid paraffin* under *Mineral Oil*.

§ 172.878

21 CFR Ch. I (4-1-89 Edition)

§ 172.878 White mineral oil.

White mineral oil may be safely used in food in accordance with the following conditions:

(a) White mineral oil is a mixture of liquid hydrocarbons, essentially paraffinic and naphthenic in nature obtained from petroleum. It is refined to meet the following specifications:

(1) It meets the test requirements of the United States Pharmacopoeia XX (1980) for readily carbonizable substances (page 532).

(2) It meets the test requirements of U.S.P. XVII for sulfur compounds (page 400).

(3) It meets the specifications prescribed in the "Journal of the Association of Official Analytical Chemists," Volume 45, page 66 (1962), which is in-

corporated by reference, after correction of the ultraviolet absorbance for any absorbance due to added antioxidants. Copies of the material incorporated by reference are available from the Division of Food and Color Additives, Bureau of Foods (HFF-330), Food and Drug Administration, 200 C St. SW., Washington, DC 20204, or available for inspection at the Office of the Federal Register, 1100 L St. NW., Washington, DC 20408.

(b) White mineral oil may contain any antioxidant permitted in food by regulations issued in accordance with section 409 of the Act, in an amount not greater than that required to produce its intended effect.

(c) White mineral oil is used or intended for use as follows:

Use	Limitation (inclusive of all petroleum hydrocarbons that may be used in combination with white mineral oil)
1. As a release agent, binder, and lubricant in or on capsules and tablets containing concentrates of flavoring, spices, condiments, and essences intended for addition to food, excluding confectionery.	Not to exceed 0.6% of the capsule or tablet.
2. As a release agent, binder, and lubricant in or on capsules and tablets containing food for special dietary use.	Not to exceed 0.6% of the capsule or tablet.
3. As a float on fermentation fluids in the manufacture of vinegar and wine to prevent or retard access of air, evaporation, and wild yeast contamination during fermentation.	In an amount not to exceed good manufacturing practice.
4. As a defoamer in food.	In accordance with § 172.340 of this chapter.
5. In bakery products, as a release agent and lubricant.	Not to exceed 0.15% of bakery products.
6. In dehydrated fruits and vegetables, as a release agent.	Not to exceed 0.02% of dehydrated fruits and vegetables.
7. In egg white solids, as a release agent.	Not to exceed 0.1% of egg white solids.
8. On raw fruits and vegetables, as a protective coating.	In an amount not to exceed good manufacturing practice.
9. In frozen meat, as a component of hot-melt coating.	Not to exceed 0.06% of meat.
10. As a protective float on brine used in the curing of pickles.	In an amount not to exceed good manufacturing practice.
11. In molding starch used in the manufacture of confectionery.	Not to exceed 0.3 percent in the molding starch.
12. As a release agent, binder, and lubricant in the manufacture of yeast.	Not to exceed 0.15 percent of yeast.
13. As an anti-caking agent in sorbic acid for food use.	Not to exceed 0.25 percent in the sorbic acid.
14. As release agent and as sealing and polishing agent in the manufacture of confectionery.	Not to exceed 0.2 percent of confectionery.
15. As a dust control agent for wheat, corn, soybean, barley, rice, rye, oats, and sorghum.	Applied at a level of no more than 0.02 percent by weight of grain.

(Secs. 201(s), 409, 72 Stat. 1784-1788 as amended (21 U.S.C. 321(s), 348); secs. 409, 701(e), 706, 70 Stat. 919 as amended, 72 Stat. 1784-1788 as amended, 74 Stat. 399-407 as amended (21 U.S.C. 348, 371(e), 376))

(42 FR 14491, Mar. 15, 1977, as amended at 47 FR 8784, Mar. 2, 1982; 47 FR 11838, Mar. 19, 1982; 48 FR 55728, Dec. 15, 1983; 49 FR 10105, Mar. 19, 1984)

§ 172.880 Petrolatum.

Petrolatum may be safely used in food, subject to the provisions of this section.

(a) Petrolatum complies with the specifications set forth in the United States Pharmacopoeia XX (1980) for white petrolatum or in the National Formulary XV (1980) for petrolatum.

Appendix 3. FDA Specifications for Types (a), (b), and (c) Mineral Oils

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Substances	Limitations
Zinc sulfide	For use at levels not to exceed 10 percent by weight of the lubricant.

(b) The lubricants are used on food-processing equipment as a protective antirust film, as a release agent on gaskets or seals of tank closures, and as a lubricant for machine parts and equipment in locations in which there is exposure of the lubricated part to food. The amount used is the minimum required to accomplish the desired technical effect on the equipment, and the addition to food of any constituent identified in this section does not exceed the limitations prescribed.

(c) Any substance employed in the production of the lubricants described in this section that is the subject of a regulation in Parts 174, 175, 176, 177, 178 and § 179.45 of this chapter conforms with any specification in such regulation.

[42 FR 14609, Mar. 15, 1977]

For FEDERAL REGISTER citations affecting § 178.3620, see the List of CFR Sections Affected in the Finding Aids section of this volume.

§ 178.3600 Methyl glucoside-coconut oil ester.

Methyl glucoside-coconut oil ester identified in § 172.816(a) of this chapter may be safely used as a processing aid (filter aid) in the manufacture of starch, including industrial starch-modified complying with § 178.3520, intended for use as a component of articles that contact food.

§ 178.3610  $\alpha$ -Methylstyrene-vinyltoluene resins, hydrogenated.

Hydrogenated  $\alpha$ -methylstyrene-vinyltoluene copolymer resins having a molar ratio of 1  $\alpha$ -methylstyrene to 3 vinyltoluene may be safely used as components of polyolefin film intended for use in contact with food, subject to the following provisions:

(a) Hydrogenated  $\alpha$ -methylstyrene-vinyltoluene copolymer resins have a drop-softening point of 125° to 165° C and a maximum absorptivity of 0.17 liter per gram centimeter at 266 nanometers, as determined by methods

titled "Determination of Softening Point (Drop Method)" and "Determination of Unsaturation of Resin 1977," which are incorporated by reference. Copies are available from the Division of Food and Color Additives, Bureau of Foods (HFF-330), Food and Drug Administration, 200 C St. SW., Washington, DC 20204, or available for inspection at the Office of the Federal Register, 1100 L St. NW., Washington, DC 20408.

(b) The polyolefin film is produced from olefin polymers complying with § 177.1520 of this chapter, and the average thickness of the film in the form in which it contacts food does not exceed 0.002 inch.

[42 FR 14609, Mar. 15, 1977, as amended at 47 FR 11847, Mar. 19, 1982]

§ 178.3620 Mineral oil.

Mineral oil may be safely used as a component of nonfood articles intended for use in contact with food, subject to the provisions of this section:

(a) White mineral oil meeting the specifications prescribed in § 172.878 of this chapter may be used as a component of nonfood articles provided such use complies with any applicable limitations in Parts 170 through 189 of this chapter. The use of white mineral oil in or on food itself, including the use of white mineral oil as a protective coating or release agent for food, is subject to the provisions of § 172.878 of this chapter.

(b) Technical white mineral oil identified in paragraph (b)(1) of this section may be used as provided in paragraph (b)(2) of this section.

(1) Technical white mineral oil consists of specially refined distillates of virgin petroleum or of specially refined distillates that are produced synthetically from petroleum gases. Technical white mineral oil meets the following specifications:

(i) Saybolt color 20 minimum as determined by ASTM method D156-82, "Standard Test Method for Saybolt

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Color of Petroleum Products (Saybolt Chromometer Method),” which is incorporated by reference. Copies may be obtained from the American Society for Testing Materials, 1916 Race St., Philadelphia, PA 19103, or may be examined at the Office of the Federal Register, 1100 L St. NW., Washington, DC 20408.

(ii) Ultraviolet absorbance limits as follows:

Wavelength (mμ)	Maximum absorbance per centimeter optical pathlength
280 to 290	4.9
290 to 300	3.3
300 to 320	2.3
320 to 350	0.8

Technical white mineral oil containing antioxidants shall meet the specified ultraviolet absorbance limits after correction for any absorbance due to the antioxidants. The ultraviolet absorbance shall be determined by the procedure described for application to mineral oil under "Specification" on page 66 of the *Journal of the Association of Official Agricultural Chemists*, Volume 45 (February 1962) (which is incorporated by reference; copies are available from the Division of Food and Color Additives, Bureau of Foods (HFF-330), Food and Drug Administration, 200 C St. SW., Washington, DC 20204, or available for inspection at the Office of the Federal Register, 1100 L St. NW., Washington, DC 20408), disregarding the last two sentences of that procedure and substituting therefor the following: Determine the absorbance of the mineral oil extract in a 10-millimeter cell in the range from 260-350 mμ, inclusive, compared to the solvent control. If the absorbance so measured exceeds 2.0 at any point in range 280-350 mμ, inclusive, dilute the extract and the solvent control, respectively, to twice their volume with dimethyl sulfoxide and remeasure the absorbance. Multiply the remeasured absorbance values by 2 to determine the absorbance of the mineral oil extract per centimeter optical pathlength.

(2) Technical white mineral oil may be used wherever mineral oil is permitted for use as a component of nonfood articles complying with §§ 175.105, 176.200, 176.210, 177.2260, 177.2600, and 177.2800 of this chapter and §§ 178.3570 and 178.3910.

(3) Technical white mineral oil may contain any antioxidant permitted in food by regulations issued in accordance with section 409 of the Act, in an amount not greater than that required to produce its intended effect.

(c) Mineral oil identified in paragraph (c)(1) of this section may be used as provided in paragraph (c)(2) of this section.

(1) The mineral oil consists of virgin petroleum distillates refined to meet the following specifications:

(i) Initial boiling point of 450°F minimum.

(ii) Color 5.5 maximum as determined by ASTM method D1500-82, "Standard Test Method for ASTM Color of Petroleum Products (ASTM Color Scale)," which is incorporated by reference. The availability of this incorporation by reference is given in paragraph (b)(1)(i) of this section.

(iii) Ultraviolet absorbance limits as follows as determined by the analytical method described in paragraph (c)(3) of this section:

Wavelength (mμ)	Maximum absorbance per centimeter optical pathlength
280 to 290	0.7
290 to 300	0.6
300 to 320	0.4
320 to 400	.09

(2) The mineral oil may be used wherever mineral oil is permitted for use as a component of nonfood articles complying with §§ 175.105 and 176.210 of this chapter and § 178.3910 (for use only in rolling of metallic foil and sheet stock), §§ 176.200, 177.2260, 177.2600, and 177.2800 of this chapter.

(3) The analytical method for determining ultraviolet absorbance limit is as follows:

GENERAL INSTRUCTIONS

Because of the sensitivity of the test, the possibility of errors arising from contamination is great. It is of the greatest importance that all glassware be scrupulously cleaned to remove all organic matter such as oil, grease, detergent residues, etc. Examine all glassware, including stoppers and stopcocks, under ultraviolet light to detect any residual fluorescent contamination. As a precautionary measure it is recommended practice to rinse all glassware with purified isooctane immediately before use. No grease is to be used on stopcocks or joints. Great care to avoid contamination of oil samples in handling and to assure absence of any extraneous material arising from inadequate packaging is essential. Because some of the polynuclear hydrocarbons sought in this test are very susceptible to photo-oxidation, the entire procedure is to be carried out under subdued light.

APPARATUS

**Separatory funnels.** 250-milliliter, 500-milliliter, 1,000-milliliter, and preferably 2,000-milliliter capacity, equipped with tetrafluoroethylene polymer stopcocks.

**Reservoir.** 500-milliliter capacity, equipped with a 24/40 standard taper male fitting at the bottom and a suitable ball-joint at the top for connecting to the nitrogen supply. The male fitting should be equipped with glass hooks.

**Chromatographic tube.** 180 millimeters in length, inside diameter to be 15.7 millimeters  $\pm 0.1$  millimeter, equipped with a coarse, fritted-glass disc, a tetrafluoroethylene polymer stopcock, and a female 24/40 standard tapered fitting at the opposite end. (Overall length of the column with the female joint is 238 millimeters.) The female fitting should be equipped with glass hooks.

**Disc.** Tetrafluoroethylene polymer 2-inch diameter disk approximately  $\frac{1}{8}$ -inch thick with a hole bored in the center to closely fit the stem of the chromatographic tube.

**Suction flask.** 250-milliliter or 500-milliliter filter flask.

**Condenser.** 24/40 joints, fitted with a drying tube, length optional.

**Evaporation flask (optional).** 250-milliliter or 500-milliliter capacity all-glass flask equipped with standard taper stopper having inlet and outlet tubes to permit passage of nitrogen across the surface of contained liquid to be evaporated.

**Spectrophotometric cells.** Fused quartz cells, optical path length in the range of 5.000 centimeter  $\pm 0.005$  centimeter; also for checking spectrophotometer performance only, optical path length in the range 1.000 centimeter  $\pm 0.005$  centimeter. With distilled water in the cells, determine any absorbance differences.

**Spectrophotometer.** Spectral range 250 millimicrons—400 millimicrons with spectral slit width of 2 millimicrons or less; under instrument operating conditions for these absorbance measurements, the spectrophotometer shall also meet the following performance requirements:

Absorbance repeatability,  $\pm 0.01$  at 0.4 absorbance.

Absorbance accuracy<sup>1</sup>  $\pm 0.05$  at 0.4 absorbance.

Wavelength accuracy,  $\pm 1.0$  millimicron.

**Nitrogen cylinder.** Water-pumped or equivalent purity nitrogen in cylinder equipped with regulator and valve to control flow at 5 p.s.i.g.

REAGENTS AND MATERIALS

**Organic solvents.** All solvents used throughout the procedure shall meet the specifications and tests described in this specification. The isooctane, benzene, acetone, and methyl alcohol designated in the list following this paragraph shall pass the following test:

To the specified quantity of solvent in a 250-milliliter Erlenmeyer flask, add 1 milliliter of purified n-hexadecane and evaporate on the steam bath under a stream of nitrogen (a loose aluminum foil jacket around the flask will speed evaporation). Discontinue evaporation when not over 1 milliliter of residue remains. (To the residue from benzene add a 10-milliliter portion of purified isooctane, reevaporate, and repeat once to insure complete removal of benzene.)

Alternatively, the evaporation time can be reduced by using the optional evaporation flask. In this case the solvent and n-hexadecane are placed in the flask on the steam bath, the tube assembly is inserted, and a stream of nitrogen is fed through the inlet tube while the outlet tube is connected to a solvent trap and vacuum line in such a way as to prevent any flow-back of condensate into the flask.

Dissolve the 1 milliliter of hexadecane residue in isooctane and make to 25 milliliters volume. Determine the absorbance in the 5-

<sup>1</sup>As determined by procedure using potassium chromate for reference standard and described in National Bureau of Standards Circular 484, Spectrophotometry, U.S. Department of Commerce (1949). The accuracy is to be determined by comparison with the standard values at 290, 345, and 400 millimicrons. Circular 484 is incorporated by reference. Copies are available from the Division of Food and Color Additives, Bureau of Foods (HFP-330), Food and Drug Administration, 200 C St. SW., Washington, DC 20204, or available for inspection at the Office of the Federal Register, 1100 L St. NW., Washington, DC 20408.

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centimeter path length cells compared to isooctane as reference. The absorbance of the solution of the solvent residue (except for methyl alcohol) shall not exceed 0.01 per centimeter path length between 280 and 400 m $\mu$ . For methyl alcohol this absorbance value shall be 0.00.

**Isooctane (2,2,4-trimethylpentane).** Use 180 milliliters for the test described in the preceding paragraph. Purify, if necessary, by passage through a column of activated silica gel (Grade 12, Davison Chemical Company, Baltimore, Maryland, or equivalent) about 90 centimeters in length and 5 centimeters to 8 centimeters in diameter.

**Benzene, A.C.S. reagent grade.** Use 150 milliliters for the test. Purify, if necessary, by distillation or otherwise.

**Acetone, A.C.S. reagent grade.** Use 200 milliliters for the test. Purify, if necessary, by distillation.

**Eluting mixtures:**

1. **10 percent benzene in isooctane.** Pipet 50 milliliters of benzene into a 250-milliliter glass-stoppered volumetric flask and adjust to volume with isooctane, with mixing.

2. **20 percent benzene in isooctane.** Pipet 50 milliliters of benzene into a 250-milliliter glass-stoppered volumetric flask and adjust to volume with isooctane, with mixing.

3. **Acetone-benzene-water mixture.** Add 20 milliliters of water to 380 milliliters of acetone and 200 milliliters of benzene, and mix.

**n-Hexadecane, 99-percent olefin-free.** Dilute 1.0 milliliter of n-hexadecane to 25 milliliters with isooctane and determine the absorbance in a 5-centimeter cell compared to isooctane as reference point between 280 m $\mu$ -400 m $\mu$ . The absorbance per centimeter path length shall not exceed 0.00 in this range. Purify, if necessary, by percolation through activated silica gel or by distillation.

**Methyl alcohol, A.C.S. reagent grade.** Use 10.0 milliliters of methyl alcohol. Purify, if necessary, by distillation.

**Dimethyl sulfoxide, Spectrophotometric grade (Crown Zellerbach Corporation, Camas, Washington, or equivalent).** Absorbance (1-centimeter cell, distilled water reference, sample completely saturated with nitrogen).

Wavelength	Absorbance (maximum)
281.5	1.00
270	.20
275	.08
280	.06
300	.015

There shall be no irregularities in the absorbance curve within these wavelengths.

**Phosphoric acid, 85 percent A.C.S. reagent grade.**

**Sodium borohydride, 98 percent.**

**Magnesium oxide (See Sorb 43, Food Machinery Company, Westvaco Division, distributed by chemical supply firms, or equivalent).** Place 100 grams of the magnesium oxide in a large beaker, add 700 milliliters of distilled water to make a thin slurry, and heat on a steam bath for 30 minutes with intermittent stirring. Stir well initially to insure that all the adsorbent is completely wetted. Using a Buchner funnel and a filter paper (Schleicher & Schuell No. 597, or equivalent) of suitable diameter, filter with suction. Continue suction until water no longer drips from the funnel. Transfer the adsorbent to a glass trough lined with aluminum foil (free from rolling oil). Break up the magnesia with a clean spatula and spread out the adsorbent on the aluminum foil in a layer about 1 centimeter to 2 centimeters thick. Dry for 24 hours at 180° C  $\pm$  1° C. Pulverize the magnesia with mortar and pestle. Sieve the pulverized adsorbent between 60-180 mesh. Use the magnesia retained on the 180-mesh sieve.

**Cellite 545, Johns Mansville Company, diatomaceous earth, or equivalent.**

**Magnesium oxide-Cellite 545 mixture (2+1) by weight.** Place the magnesium oxide (60-180 mesh) and the Cellite 545 in 2 to 1 proportions, respectively, by weight in a glass-stoppered flask large enough for adequate mixing. Shake vigorously for 10 minutes. Transfer the mixture to a glass trough lined with aluminum foil (free from rolling oil) and spread it out on a layer about 1 centimeter to 2 centimeters thick. Reheat the mixture at 180° C  $\pm$  1° C for 2 hours, and store in a tightly closed flask.

**Sodium sulfate, anhydrous, A.C.S. reagent grade, preferably in granular form.** For each bottle of sodium sulfate reagent used, establish as follows the necessary sodium sulfate prewash to provide such filters required in the method: Place approximately 35 grams of anhydrous sodium sulfate in a 30-milliliter coarse, fritted-glass funnel or in a 65-millimeter filter funnel with glass wool plug; wash with successive 15-milliliter portions of the indicated solvent until a 15-milliliter portion of the wash shows 0.00 absorbance per centimeter path length between 280 m $\mu$  and 400 m $\mu$  when tested as prescribed under "Organic solvents." Usually three portions of wash solvent are sufficient.

Before proceeding with analysis of a sample, determine the absorbance in a 5-centimeter path cell between 250 millimicrons and 400 millimicrons for the reagent blank by carrying out the procedure, without an oil sample, recording the spectra after the extraction stage and after the complete procedure as prescribed. The absorbance per centimeter pathlength following the extraction stage should not exceed

0.02 in the wavelength range from 280  $m\mu$  to 400  $m\mu$ ; the absorbance per centimeter pathlength following the complete procedure should not exceed 0.02 in the wavelength range from 280  $m\mu$  to 400  $m\mu$ . If in either spectrum the characteristic benzene peaks in the 250  $m\mu$ -260  $m\mu$  region are present, remove the benzene by the procedure under "Organic solvents" and record absorbance again.

Place 300 milliliters of dimethyl sulfoxide in a 1-liter separatory funnel and add 75 milliliters of phosphoric acid. Mix the contents of the funnel and allow to stand for 10 minutes. (The reaction between the sulfoxide and the acid is exothermic. Release pressure after mixing, then keep funnel stoppered.) Add 150 milliliters of isooctane and shake to pre-equilibrate the solvents. Draw off the individual layers and store in glass-stoppered flasks.

Weigh a 20-gram sample of the oil and transfer to a 500-milliliter separatory funnel containing 100 milliliters of pre-equilibrated sulfoxide-phosphoric acid mixture. Complete the transfer of the sample with small portions of pre-equilibrated isooctane to give a total volume of the oil and solvent of 75 milliliters. Shake the funnel vigorously for 2 minutes. Set up three 250-milliliter separatory funnels with each containing 30 milliliters of pre-equilibrated isooctane. After separation of liquid phases, carefully draw off lower layer into the first 250-milliliter separatory funnel and wash in tandem with the 30-milliliter portions of isooctane contained in the 250-milliliter separatory funnels. Shaking time for each wash is 1 minute. Repeat the extraction operation with two additional portions of the sulfoxide-acid mixture and wash each extractive in tandem through the same three portions of isooctane.

Collect the successive extractives (300 milliliters total) in a separatory funnel (preferably 2-liter) containing 480 milliliters of distilled water; mix, and allow to cool for a few minutes after the last extractive has been added. Add 80 milliliters of isooctane to the solution and extract by shaking the funnel vigorously for 2 minutes. Draw off the lower aqueous layer into a second separatory funnel (preferably 2-liter) and repeat the extraction with 80 milliliters of isooctane. Draw off and discard the aqueous layer. Wash each of the 80-milliliter extractives three times with 100-milliliter portions of distilled water. Shaking time for each wash is 1 minute. Discard the aqueous layers. Filter the first extractive through anhydrous sodium sulfate prewashed with isooctane (see Sodium sulfate under "Reagents and Materials" for preparation of filter) into a 250-milliliter Erlenmeyer flask (or optionally into the evaporation flask). Wash the first separatory funnel with the second 80-milliliter isooctane extractive and pass

through the sodium sulfate. Then wash the second and first separatory funnels successively with a 20-milliliter portion of isooctane and pass the solvent through the sodium sulfate into the flask. Add 1 milliliter of *n*-hexadecane and evaporate the isooctane on the steam bath under nitrogen. Discontinue evaporation when not over 1 milliliter of residue remains. To the residue, add a 10-milliliter portion of isooctane, re-evaporate to 1 milliliter of hexadecane, and repeat this operation once.

Quantitatively transfer the residue with isooctane to a 200-milliliter volumetric flask, make to volume, and mix. Determine the absorbance of the solution in the 1-centimeter pathlength cells compared to isooctane as reference between 280  $m\mu$ -400  $m\mu$  (take care to lose none of the solution in filling the sample cell). Correct the absorbance values for any absorbance derived from reagents as determined by carrying out the procedure without an oil sample. If the corrected absorbance does not exceed the limits prescribed in this paragraph, the oil meets the ultraviolet absorbance specifications. If the corrected absorbance per centimeter pathlength exceeds the limits prescribed in this paragraph, proceed as follows: Quantitatively transfer the isooctane solution to a 125-milliliter flask equipped with 24/40 joint, and evaporate the isooctane on the steam bath under a stream of nitrogen to a volume of 1 milliliter of hexadecane. Add 10 milliliters of methyl alcohol and approximately 0.3 gram of sodium borohydride. (Minimize exposure of the borohydride to the atmosphere. A measuring dipper may be used.) Immediately fit a water-cooled condenser equipped with a 24/40 joint and with a drying tube into the flask, mix until the borohydride is dissolved, and allow to stand for 30 minutes at room temperature, with intermittent swirling. At the end of this period, disconnect the flask and evaporate the methyl alcohol on the steam bath under nitrogen until the sodium borohydride begins to come out of the solution. Then add 10 milliliters of isooctane and evaporate to a volume of about 2-3 milliliters. Again, add 10 milliliters of isooctane and concentrate to a volume of approximately 5 milliliters. Swirl the flask repeatedly to assure adequate washing of the sodium borohydride residues.

Fit the tetrafluoroethylene polymer disc on the upper part of the stem of the chromatographic tube, then place the tube with the disc on the suction flask and apply the vacuum (approximately 136 millimeters Hg pressure). Weigh out 14 grams of the 2:1 magnesium oxide-Celite 545 mixture and pour the adsorbent mixture into the chromatographic tube in approximately 3-centimeter layers. After the addition of each layer, level off the top of the adsorbent with

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a flat glass rod or metal plunger by pressing down firmly until the adsorbent is well packed. Loosen the topmost few millimeters of each adsorbent layer with the end of a metal rod before the addition of the next layer. Continue packing in this manner until all the 14 grams of the adsorbent is added to the tube. Level off the top of the adsorbent by pressing down firmly with a flat glass rod or metal plunger to make the depth of the adsorbent bed approximately 12.5 centimeters in depth. Turn off the vacuum and remove the suction flask. Fit the 500-milliliter reservoir onto the top of the chromatographic column and prewet the column by passing 100 milliliters of isooctane through the column. Adjust the nitrogen pressure so that the rate of descent of the isooctane coming off the column is between 2-3 milliliters per minute. Discontinue pressure just before the last of the isooctane reaches the level of the adsorbent. (Caution: Do not allow the liquid level to recede below the adsorbent level at any time.) Remove the reservoir and decant the 5-milliliter isooctane concentrate solution onto the column and with slight pressure again allow the liquid level to recede to barely above the adsorbent level. Rapidly complete the transfer similarly with two 5-milliliter portions of isooctane, swirling the flask repeatedly each time to assure adequate washing of the residue. Just before the final 5-milliliter wash reaches the top of the adsorbent, add 100 milliliters of isooctane to the reservoir and continue the percolation at the 2-3 milliliters per minute rate. Just before the last of the isooctane reaches the adsorbent level, add 100 milliliters of 10 percent benzene in isooctane to the reservoir and continue the percolation at the aforementioned rate. Just before the solvent mixture reaches adsorbent level, add 25 milliliters of 20 percent benzene in isooctane to the reservoir and continue the percolation at 2-3 milliliters per minute until all this solvent mixture has been removed from the column. Discard all the elution solvents collected up to this point. Add 300 milliliters of the acetone-benzene-water mixture to the reservoir and percolate through the column to eluate the polynuclear compounds. Collect the eluate in a clean 1-liter separatory funnel. Allow the column to drain until most of the solvent mixture is removed. Wash the eluate three times with 300-milliliter portions of distilled water, shaking well for each wash. (The addition of small amounts of sodium chloride facilitates separation.) Discard the aqueous layer after each wash. After the final separation, filter the residual benzene through anhydrous sodium sulfate pre-washed with benzene (see Sodium sulfate under "Reagents and Materials" for preparation of filter) into a 250-milliliter Erlenmeyer flask (or optionally into the evaporation flask). Wash the se-

paratory funnel with two additional 20-milliliter portions of benzene which are also filtered through the sodium sulfate. Add 1 milliliter of n-hexadecane and completely remove the benzene by evaporation under nitrogen, using the special procedure to eliminate benzene as previously described under "Organic solvents." Quantitatively transfer the residue with isooctane to a 200-milliliter volumetric flask and adjust to volume. Determine the absorbance of the solution in the 1-centimeter pathlength cells compared to isooctane as reference between 250 m $\mu$ -400 m $\mu$ . Correct for any absorbance derived from the reagents as determined by carrying out the procedure without an oil sample. If either spectrum shows the characteristic benzene peaks in the 250 m $\mu$ -280 m $\mu$  region, evaporate the solution to remove benzene by the procedure under "Organic solvents." Dissolve the residue, transfer quantitatively, and adjust to volume in isooctane in a 200-milliliter volumetric flask. Record the absorbance again. If the corrected absorbance does not exceed the limits proposed in this paragraph, the oil meets the proposed ultraviolet absorbance specifications.

(d) Mineral oil identified in paragraph (d)(1) of this section may be used as provided in paragraph (d)(2) of this section.

(1) The mineral oil consists of virgin petroleum distillates refined to meet the following specifications:

(i) Distillation endpoint at 760 millimeters pressure not to exceed 371° C, with a maximum residue not to exceed 2 percent, as determined by ASTM method D86-82, "Standard Method for Distillation of Petroleum Products," which is incorporated by reference. The availability of this incorporation by reference is given in paragraph (b)(1)(1) of this section.

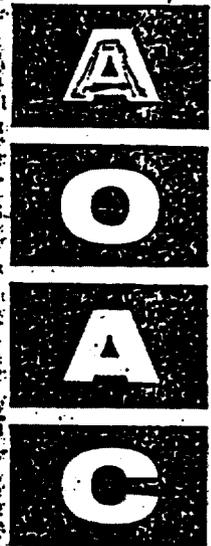
(ii) Ultraviolet absorbance limits as follows as determined by the method described in paragraph (d)(3) of this section.

Wavelength (m $\mu$ )	Maximum absorbance per centimeter optical pathlength
280 to 290	2.3
300 to 310	1.2
320 to 330	.8
340 to 400	.3

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All of the analytical methods which were evaluated produce results biased above the true value. They should be studied and the causes of the high results eliminated.

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## FOOD ADDITIVES

## A More Sensitive and Selective Ultraviolet Absorption Criterion for Mineral Oil\*

By EDWARD O. HAENNI, FRANK L. JOE, Jr., JOHN W. HOWARD, and RUDOLPH L. LEIBEL† (Division of Food, Food and Drug Administration, Washington 25, D.C.)

One of the major concerns in the regulation of food additives under the Food Additives Amendment to the Food, Drug, and Cosmetic Act is the potential contamination of food by some carcinogenic polynuclear hydrocarbons which may be present in additives of petroleum origin. The first food additive petition to require evaluation of this problem involved migration of mineral oil from a packaging material to meat at a level of about 200 ppm. The mineral oil specification suggested by the petitioner was inadequate, and in 1959, Haenni and Hall (1) proposed a tentative direct ultraviolet absorption criterion. This specification was a rapid, practical test designed to limit the possibility of any potentially carcinogenic polynuclear hydrocarbons being present in the oil. The specification has been adopted officially (2) to control the quality of oil permitted under extension of a number of uses of food additives pending issuance of regulations, or until January 1, 1962.

The sensitivity of the Haenni-Hall test is

adequate for low migration levels, but the test is quite restrictive in excluding from food additive use many U.S.P. and N.F. oils containing appreciable quantities of similar aromatic hydrocarbons that absorb strongly, but are inconsequential. In 1959, Druceker, Schmal, and Preussman (3) proposed a direct fluorescence test designed to detect the presence of benz(a)pyrene, 3-methyl cholanthrene, or dibenz(a,h)anthracene down to 0.3 ppm in mineral oil. However, the fluorescence test is unsatisfactory for several reasons. Not only is the claimed sensitivity dependent on the absence of self-quenching or of any fluorescence-quenching substances, but the presence of such substances may render the test entirely invalid. The test is not at all selective, and although the three aforementioned carcinogens show relatively strong fluorescence, the fluorescence of other hydrocarbons of concern shows a great range of intensities, spectral characteristics, and excitation maxima. For example, Sawicki, Hauser, and Stanley (4) reported activation and fluorescence maxima and their intensities as well as the ultraviolet absorbances for over forty polynuclear hydrocarbons including the major carcinogens. The activation maxima ranged

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from 257 to 457  $m\mu$ , the fluorescence maxima ranged from 321 to 506  $m\mu$  (with about two-thirds in the invisible range), and the fluorescence intensities varied over a 450-fold range. The ultraviolet absorptivities of these hydrocarbons above 260  $m\mu$ , however, varied by less than one tenth of the range of the fluorescence intensities.

Although the sensitivity of the Haenni-Hall test is not quite as great as that of the fluorescence test, the ultraviolet absorption parameter is not subject to the vagaries of fluorescence phenomena. It permitted design of the test to limit to a maximum of 5 ppm any of nineteen representative hydrocarbons (tricyclic to pentacyclic); seven of these, including the three potent ones cited above in the fluorescence test, could be limited to a maximum of 1 ppm.

Accordingly, it was our purpose to improve the sensitivity and selectivity of the Haenni-Hall test while retaining its simplicity as far as possible. We consider that such simplicity tends to improve consumer protection, for a simple practical test not only encourages the users of food additives to maintain adequate quality control testing, but it also enables regulatory agencies to give more thorough coverage in enforcing such specifications. To accomplish our purpose we sought a solvent for condensed polynuclear hydrocarbons which might preferentially extract these hydrocarbons from the aliphatic and simpler aromatic constituents of mineral oils. A preliminary study of possible solvents showed dimethyl sulfoxide (5) to be the solvent of choice. Preliminary work also indicated that dilution of the oil before extraction facilitated phase separation and reduced the amount of background material extracted. Dilution with an equal volume of purified hexane was found adequate. Under these conditions it follows from the principle of distribution equilibria of a solute between two immiscible solvents that in the absence of polymerization or like associative changes in the solute:

$$C = \frac{C_o}{2 \left( \frac{1}{K} + \frac{V_o}{V_s} \right)} \quad (1)$$

$C$  = concentration of solute in extraction solvent;

$C_o$  = concentration of solute in oil;  
 $K$  = distribution ratio (concentration in extraction solvent/concentration in sample solution)

$V_o$  = volume of extraction solvent;

$V_s$  = volume of sample solution.

The ultraviolet absorption test that yields the maximum sensitivity with a minimum of operations is one which attains a maximum concentration of the constituents sought in a single extraction of the sample. For a maximum sensitivity,  $V_o$  should be at a minimum.

The minimum practicable volume was considered to be 5 ml. Preliminary work showed that a 25 ml sample of oil should be ample to yield the sensitivity (0.3 ppm) proposed by Drueckery, *et al.* (3). As a general procedure the extract was backwashed with 2 ml of hexane to remove any entrapped oil and to further reduce the extraneous background.

Under these conditions, it is calculated that if  $A_o$  is the absorbance (1 cm path) of the washed extract, then:

$$C_o = kA_o \quad (2)$$

where  $k$  is a constant for a given hydrocarbon which includes its absorptivity and the relevant distribution constants in the extraction process. If the absorptivity is based on 1 mg/L concentration for 1 cm path, then the value of  $C_o$  is a measure in parts per million (mg/L) of that hydrocarbon in the oil for any selected limit value of  $A_o$ . Hence, if we determine  $A_o$  experimentally for a known quantity of polynuclear hydrocarbon added to an oil compared as a reference to the extract from the untreated oil, we can calculate the equivalent hydrocarbon concentration for any selected limit value of  $A_o$ . This equivalent concentration for the limit value of 0.10 for  $A_o$ , adopted in this test, is then the sensitivity of the test for the hydrocarbon involved.

#### Results

The sensitivity of the test at a limit value of  $A_o$  equal to 0.10 has been determined for thirty-six polynuclear hydrocarbons in accordance with the conditions outlined above and by the procedure at the end of this report. Each hydrocarbon was added at a level of 0.3 ppm to a light grade of mineral oil. To demonstrate that the test is applica-

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ble to all relevant grades of oil, it was repeated in the case of seven hydrocarbons with the heavy and extra heavy grades. Table I, Group I, shows the results for all of the hydrocarbons available to us at this time that have been shown conclusively to produce tumors on testing in animals. The table also includes (Group II) values for some hydrocarbons which have been reported to be carcinogenic on the basis of tests considered to be possibly inconclusive for one or more of a number of reasons. No evaluation of the adequacy of the tests indicated as negative (Group III) has been made.

The new test has been applied (Table 2) to twenty-two refined mineral oils, including the eight available samples of thirteen used in development of the Haenni-Hall test. Nearly all of the U.S.P. or N.F. oils were purchased on the retail market, and they represent sixteen different brands.

#### Discussion

At least one of the oils (Sample 6) which failed the new test contained a substantial concentration of BHT as an antioxidant and the others may have contained BHT or other antioxidants at high enough concentration to cause their failure. Tocopherol, the only antioxidant permitted (maximum 10 ppm) in U.S.P. or N.F. oils until the last revisions, does not cause interference in the new test, as it is not extracted from the sample solution by dimethyl sulfoxide. However, the current official drug compendia permit use of unspecified "suitable stabilizers" in mineral oil without reference to a limiting concentration. The new test is intended to control the quality of mineral oil in food additives use. Current petitions for such use do not include requests for use of antioxidants in the oil, so that their potential interference is not relevant to the new proposed criterion at this time.

The full significance of the single minimum-volume extraction procedure devised for our purpose is not obvious. Equation (1) was developed to show clearly that this technique yields a maximum concentration of the polynuclear and hence maximum absorbance, i.e. sensitivity. It is an apparent paradox that this same technique also ex-

tracts the minimum proportion of the polynuclear from the sample. However, because of the relatively enormous concentrations of simpler aromatics that are potentially present in oil, this technique still yields the highest obtainable ratio of polynuclear to simpler aromatic in the extract. Referring to equation (1), it is apparent that  $C$  will be a maximum when  $\left(\frac{1}{K} + \frac{V_s}{V_e}\right)$  is a minimum.

The maximum reasonable limit for  $\frac{V_s}{V_e}$  is 1 and its ultimate limiting value  $\rightarrow 0$ . For low values of  $K$  (simpler aromatics) even at the limit  $\frac{V_s}{V_e} \rightarrow 0$ ,  $C$  cannot exceed a fraction of  $C_o$ , but for higher values of  $K$  (more highly condensed polynuclears),  $C$  can be a multiple of  $C_o$ . For example it may be predicted with confidence that the  $K$  value will not exceed 2 for the alkyl substituted aromatics (monocyclic and bicyclic) and for the hydroaromatics present in a typical refined white oil (boiling point minimum about 300°C) at a level of 600 ppm. From equation (1) it is readily calculated that the concentration of these aromatics in the first dimethyl sulfoxide extract  $\left(\frac{V_s}{V_e} = \frac{5}{50}\right)$  will be not over 500 ppm. If the oil also contained 0.3 parts ppm of dibenz(a,h)anthracene ( $K \sim 13$ ), the first extract will contain a concentration of 0.96 ppm of the carcinogen, a more than 3-fold increase in concentration. Even for 0.3 ppm of 3-methyl cholanthrene with the relatively low  $K$  value of 5.5, although the first extract will contain only about 35% of the total carcinogen, its concentration (0.52 ppm) will be almost double that in the oil and its proportion to the simpler aromatics will be double that in the oil. It would require repetition of the extraction 7 times to recover 95% of the 3-methyl cholanthrene, and its proportion to the simpler aromatics would then be only slightly greater than that in the oil. In addition the total extract would contain over two-thirds of the simpler aromatic content of the oil sample. It would accordingly be necessary to apply other separation techniques, such as chromatography, to achieve the same order of sensitivity provided by the simple new test. It is true that greater specificity could

Table 1. Calculated sensitivities for representative polynuclear hydrocarbons based on new test applied to mineral oils with 0.3 ppm added polynuclear

Source No.	Chemical Abstracts Name	Other Common Name	Wave length at Max. Abs.	Maximum Absorbance*			Calculated Sensitivity in ppm for Absorbance Limit of 0.10		
				Light Grade (M)	Heavy Grade (M)	Extra Heavy Grade (M)	Light Grade (M)	Heavy Grade (M)	Extra Heavy Grade (M)
<b>Group I: Positive Carcinogenic Tests</b>									
702	Cholanthrene		3000	0.164			0.18		
883	3-methyl-1,2-benzanthracene	20-methyl-1,2-benzanthracene	2490	0.133	0.141	0.142	0.22	0.21	0.21
325	7-methyl-1,2-benzanthracene	10-methyl-1,2-benzanthracene	2412	0.288	0.261	0.275	0.10	0.11	0.11
705	7-methyl-1,2-benzanthracene	9-methyl-1,2-benzanthracene	2401	0.265			0.15		
704	12-methyl-1,2-benzanthracene	10-ethyl-1,2-benzanthracene	284	0.249			0.13		
438	7-ethyl-1,2-benzanthracene	5,10-dimethyl-1,2-benzanthracene	285	0.179			0.17		
---	7,12-dimethyl-1,2-benzanthracene	9,10-dimethyl-1,2-benzanthracene	275	0.240			0.13		
---	8,12-dimethyl-1,2-benzanthracene	5,9-dimethyl-1,2-benzanthracene	300	0.117			0.20		
---	Benzo(a)phenanthrene	3,4-benzophenanthrene	285	0.109			0.28		
---	5-methyl-1,2-benzanthracene	2-methyl-1,2-benzanthracene	287	0.108			0.15	0.16	0.15
712	Benzo(a)pyrene	3,4-benzopyrene	300	0.159	0.151	0.147	0.18	0.20	0.20
778	5,6-dimethylchrysene		278	0.311			0.10		
621	1,2,3,4,6,7,8,9-octamethyl-1,2,3,4,6,7,8,9-octamethylanthracene		301	0.357	0.357	0.358	0.08	0.08	0.08
601	1,2,3,4,6,7,8,9-octamethyl-1,2,3,4,6,7,8,9-octamethylanthracene		298	0.280	0.283	0.313	0.14	0.15	0.14
---	1,2,3,4,6,7,8,9-octamethyl-1,2,3,4,6,7,8,9-octamethylanthracene		297	0.657			0.53		
---	1,2,3,4,6,7,8,9-octamethyl-1,2,3,4,6,7,8,9-octamethylanthracene		297	0.101	0.157	0.152	0.10	0.10	0.20
<b>Group II: Questionable Positive Tests</b>									
404	9,10-Dimethylanthracene		291	0.230			0.13		
694	1-Methylbenzo(a)anthracene		282	0.167			0.18		
777	Benzo(f)pyrene		293	0.193			0.10		

(Continued)

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Table I. (Continued)

Nuc. No.	Chemical Abstracts Name	Other Common Name	Wave- length at Max. A, mμ	Maximum Absorbance*		Calculated Sensitivity in ppm for Absorbance Limit of 0.10	
				Light Grade (H)	Extra Heavy Grade (H)	Light Grade (H)	Extra Heavy Grade (H)
(Group II: Questionable Positive Tests (Continued))							
571	Chrysene	---	272	0.452	---	0.07	---
718	6-methyl- fluoranthene	---	279	0.018	---	0.03	---
719	16,17-Dihydro-17-methyl-15H-cyclopenta(a)phenan- threne	3-methylcyclopenta-phenanthrene	274	0.302	---	0.10	---
---	Benzo(b)fluoranthene	2,3-Benzofluoranthene	284	0.013	---	2.31	---
---	---	---	---	0.130	0.128	0.23	0.23
(Group III: Negative Test or Not Tested (N.T.))							
705	Triphenylene	---	260	0.788	---	0.04	---
612	Fluoranthene	---	280	0.125	---	0.24	---
730	Benzo(a)anthracene	1,2-benzanthracene	286	0.112	---	0.27	---
673	7-m-propyl- fluoranthene	10-m-propyl- fluoranthene	287	0.120	---	0.23	---
584	7-m-butyl- fluoranthene	10-m-butyl- fluoranthene	285	0.133	---	0.23	---
524	7-m-amyl- fluoranthene	10-m-amyl- fluoranthene	285	0.312	---	0.12	---
618	Benzo(a)phenanthrene	3,4-benzofluoranthene	286	0.126	---	0.24	---
617	2,3-dimethyl- fluoranthene (N.T.)	2,3'-dimethyl- fluoranthene (N.T.)	286	0.104	---	0.29	---
---	Benzo(a,h)pyrene (N.T.)	2,6-dimethyl- fluoranthene (N.T.)	303	0.105	---	0.18	---
---	Coronene (N.T.)	1,2-benzopyrene	305	0.460	---	0.07	---
---	6-Methyl benzo(e)pyrene (N.T.)	4'-methyl-1,2-benzopyrene	302	0.102	---	0.20	---

\* From Survey of Compounds Which Have Been Tested for Carcinogenic Activity, 2nd Ed. (1951), by J. L. Hartwell, National Institutes of Health.

be so achieved, and we are now extending such techniques to the identification and determination of specific polynuclear hydrocarbons in refined petroleum waxes and in other potential food additive materials of petroleum origin.

The new proposed specification for mineral oil is given at the end of this report. The reasons for stating the limiting absorbance in the specification in terms of a standard reference absorbance have been adequately discussed in the earlier paper (1). The change in wavelength range adopted in the new test (260  $m\mu$  to 350  $m\mu$ ) is made possible by the fact that under the conditions of this test the simpler aromatics in the oil giving rise to strong absorbance between 260 and 290  $m\mu$  have been reduced to very low concentrations in the extract. By extension of the wavelength to as low as 260  $m\mu$ , the major maxima of the chrysenes, anthracenes, and some other compounds can be utilized, so that it is not necessary to extend the range above 350  $m\mu$ , as in the Haenni-Hall test, to attain the desired sensitivity for these substances.

Dr. Philippe Shulak kindly provided us with a preliminary summary of his evaluation of the available data on animal tests of those polycyclic aromatic hydrocarbons reported to induce tumors. We have used this information and other sources in classifying these and the other hydrocarbons included in Table I. We find that they can be classified as the following structural types (including the alkyl substitution products) in order of decreasing number of representatives: benz(a)anthracene (19), cholanthrene (7), benzo(a)pyrene (3), acc-benz(a)anthracene other than cholanthrene (3), benzo(e)-phenanthrene (3), cyclopentenobenz(a)anthracene (3), dibenzopyrene (2), and benzofluoranthene (2), plus the single carcinogens, 5,6-dimethylchrysene, dibenz(a,h)anthracene, benzo(g)chrysene, cyclopenteno-aceanthrene, and 1,2,3,6-dibenzofluorene. Group I, Table I, includes at least one member of all except one (benzofluoranthene) of the above eight classes of more than one number and in addition includes three of the five single types. Group II, Table I, includes a benzofluoranthene. We wish to emphasize here that Dr. Shulak is in

no way committed by our use of his information to the classifications in Table I.

2,7,8,9-Tetrahydro-1H-cyclopent(j)aceanthrylene is the only hydrocarbon in Group I, Table I, for which the sensitivity of the test exceeds 0.3 ppm. Only 16,17-dihydro-17-methyl-15H-cyclopenta(a)phenanthrene significantly exceeds 0.3 ppm. It should also be emphasized that nearly all of the carcinogenic hydrocarbons in Table I represent synthetic compounds which have not been identified in petroleum products. Neither 2,7,8,9-tetrahydro-1H-cyclopent(j)aceanthrylene nor 16,17-dihydro-17-methyl-15H-cyclopenta(a)phenanthrene has been found in petroleum. All of these hydrocarbons are presented solely to illustrate the order of sensitivity of the proposed test for a wide representative range of carcinogenic hydrocarbon structures and related structures. It is not suggested that carcinogenic hydrocarbons have been reported in refined white mineral oil, or are to be expected in such oil or will be tolerated in oil of food additive grade.

The results (Table 2) of the examination of twenty-two refined mineral oils demonstrate the improved selectivity of the new test as compared with the Haenni-Hall test.

The maximum level of mineral oil permitted as a food additive is 1500 ppm. If the oil so used meets the new specification, it is reasonable to conclude that the maximum content of the above hydrocarbons which could get into a food from such oil would be of the order of 1 ppb or less. Although the questionably carcinogenic 16,17-dihydro-17-methyl-15H-cyclopenta(a)phenanthrene, if present alone, could exceed this level, it has not been found in petroleum, and there is only an infinitesimal probability of its presence in the absence of other hydrocarbons for which the test is far more sensitive.

#### Summary and Conclusions

An ultraviolet absorption criterion for mineral oils has certain advantages as compared to a fluorescence criterion.

A new practical test based on the ultraviolet absorption of a single dimethyl sulfoxide extract of mineral oil has been shown to be more sensitive and more selective than the Haenni-Hall test.

The new test limits to a maximum of

Table 2. Comparative results by Haenni-Hall test and new test on representative mineral oils

Sample No.	Haenni-Hall Test Absorbance of Oil				New Test Absorbance of Extract	
	1 mm 275 mμ	10 mm 295-299 mμ	10 mm 300-400 mμ		10 mm 290-350 mμ	
Extra Heavy Oil						
1	0.16	0.14	0.11	Pass	0.01	Pass
2	0.16	0.07	0.04	Pass	0.13	Fail
3	0.09	0.14	0.11	Pass	0.12	Fail
4	0.27	0.19	0.15	Pass	0.00	Pass
5	0.21	0.17	0.14	Pass	0.04	Pass
6	0.77	1.18	0.93	Fail	0.31	Fail
7	0.35	0.62	0.50	Fail	0.03	Pass
Heavy Oil						
8 (11)	0.14	0.22	0.16	Pass	0.01	Pass
9	0.05	0.17	0.12	Pass	0.01	Pass
10	0.31	0.19	0.11	Fail	0.04	Pass
11 (8)	1.38	>3.4	2.3	Fail	0.07	Pass
12	0.57	0.62	0.50	Fail	0.10	Pass
13 (12)	0.23	0.11	0.34	Fail	0.04	Pass
14 (5)	0.76	1.79	1.46	Fail	0.01	Pass
15 (1)	0.55	0.55	0.44	Fail	0.65	Pass
Light Oil						
16	0.24	0.19	0.14	Pass	0.04	Pass
17 (13)	0.12	0.16	0.13	Pass	0.01	Pass
18	0.14	0.13	0.12	Pass	0.01	Pass
19	0.08	0.10	0.08	Pass	0.01	Pass
20 (3)	1.76	>2.4	>2.4	Fail	0.17	Fail
21 (9)	0.70	1.16	0.94	Fail	0.01	Pass
22	0.23	0.25	0.21	Fail	0.03	Pass
Total passing				11		18
Total failing				11		4

Sample numbers in parentheses indicate same samples used in development of Haenni-Hall test (1).

ppm the quantity of any of a wide range of polynuclear hydrocarbons which could be present in a mineral oil meeting the specification. Eighteen of twenty-two refined mineral oils representing sixteen brands tested passed the specification. At least some of those failing the test contained interfering anti-oxidants.

At the indicated sensitivity (0.3 ppm) of

the test on the oil, the corresponding sensitivity on a food product containing the maximum permitted oil additive (1500 ppm) would be of the order of 1 ppb of any of the polynuclears tested. If use of an oil results in contamination of a food product with any carcinogenic hydrocarbon, such use is prohibited under the Food Additives Amendment.

#### Acknowledgment

We deeply appreciate the cooperation of Dr. Philippe Shubik, Division of Oncology, Chicago Medical School, in making available to us the summary of his preliminary evaluation of the published pharmacological data on carcinogens. We are also indebted to his associate, Dr. William Lijinsky, for supplying us with some of the polynuclear hydrocarbons. Most of these, we are glad to acknowledge, were supplied by the Laboratory of Chemistry, National Institute of Arthritis and Metabolic Diseases, and by the Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health, Bethesda, Maryland.

#### SPECIFICATION

##### Spectrophotometric Measurements

All measurements are made in an ultraviolet spectrophotometer in optical cells of 10 mm length and in the wavelength range of 260-350 m $\mu$  under the same instrumental conditions. The standard reference absorbance is the absorbance at 275 m $\mu$  of a standard reference solution of naphthalene (National Bureau of Standards Standard Material No. 577 or equivalent in purity) containing a concentration of 7.0 mg/l. in purified iso-octane, measured against iso-octane of the same spectral purity in 10 mm cells. (This absorbance will be approximately 0.30.)

##### Solvents

(a) *Normal hexane*.—Pure grade, having an ultraviolet light absorbance not exceeding 0.10 down to 220 m $\mu$  and not exceeding 0.02 down to 260 m $\mu$ . The purity shall be such that the "solvent control" as defined under *Procedure* shall have an absorbance curve compared to water showing no extraneous impurity peaks and no absorbance exceeding that of dimethyl sulfoxide compared to water at any wavelength in the range 260-350 m $\mu$  inclusive. If necessary to obtain the prescribed purities the hexane may be passed through activated silica gel.

(b) *Dimethyl sulfoxide*.—Pure grade, clear, water white, 99.9% dimethyl sulfoxide, m.p.

18°, with an absorbance curve compared to water not exceeding 1.0 at 264 m $\mu$  and showing no extraneous impurity peaks in the wavelength range up to 350 m $\mu$ . The reagent should be stored in glass-stoppered bottles, as it is very hygroscopic and will react with some metal containers in the presence of air.

##### Apparatus

Glass-stoppered separatory funnels, 125 ml capacity, equipped with tetrafluoroethylene polymer stopcocks or other suitable stopcocks which will not contaminate the solvents used.

##### Procedure

Transfer 25 ml of the mineral oil and 25 ml hexane to a separatory funnel and mix. Add 5.0 ml dimethyl sulfoxide and shake the mixture vigorously for at least 1 minute. Allow to stand until the lower layer is clear. Completely transfer the lower layer to a separatory funnel, add 2 ml hexane, and shake the mixture vigorously. Allow to stand until the lower layer is clear. Draw off the lower layer, designated as "mineral oil extract." Shake 5 ml dimethyl sulfoxide with 25 ml hexane vigorously for at least 1 minute in a separatory funnel. Allow to stand until the lower layer is clear and draw off this layer, designated "solvent control." Determine the absorbance of the mineral oil extract in a 10 mm cell in the range 260-350 m $\mu$ , inclusive, compared to the solvent control. The absorbance of the mineral oil extract shall not exceed that of the solvent control at any wavelength in the specified range by more than one-third of the standard reference absorbance.

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Appendix 5. Overview of Granuloma Formation with Specific Reference to White Mineral Oils (Shell)

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**TOXICOLOGICAL OVERVIEW OF HYPERPHAGOCYtic GRANULOMA  
ASSOCIATED WITH MEDICINAL WHITE OIL AND RELATED MATERIALS**

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December 20, 1989

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TOXICOLOGICAL OVERVIEW OF HYPERPHAGOCYTTIC GRANULOMA  
ASSOCIATED WITH MEDICINAL WHITE OIL AND RELATED MATERIALS

TECHNICAL SUMMARY

In a study by Shell's Sittingbourne Research Centre in which rats were fed medicinal white oil as part of the diets, inclusion oil droplets and microgranulomatous changes were found in the liver, spleen and mesenteric lymph nodes. These observations prompted the present review of the available literature on microgranulomatous changes especially as related to white mineral oil and related materials.

White mineral oil is a highly refined petroleum derivative consisting of a complex combination of saturated hydrocarbons, having carbon numbers predominantly in the C<sub>15</sub> through C<sub>30</sub> range, obtained from the intensive treatment of a petroleum fraction with sulfuric 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. Mineral oils are of variable composition depending on the distillation range of the petroleum fractions used. Mineral oil is also known as liquid petrolatum. For food purposes, usually liquid petrolatum or liquid paraffin are employed which consist essentially of n-alkanes and some cyclic paraffins. It is important to note that the chemical composition of mineral oils differ substantially from that of vegetable oils which comprise a mixture of saturated and unsaturated fatty acids and glycerides.

Petrolatum is a complex combination of hydrocarbons obtained as a semi-solid from dewaxing paraffinic residual oil. It consists primarily of saturated crystalline and liquid hydrocarbons having carbon numbers predominantly greater than C<sub>25</sub>.

Petroleum wax is a complex combination of hydrocarbons obtained from petroleum fractions by solvent crystallization, solvent deoiling or by the sweating process. It consists predominantly of straight chain hydrocarbons having carbon numbers predominantly greater than C<sub>20</sub>.

White oil and liquid petrolatum are widely used throughout the world for purposes ranging from cosmetic to medicinal. Mineral oil hydrocarbons are absorbed from the gastrointestinal tract; this absorption appears to be molecular size- and structure-dependent. Straight-chain compounds are better absorbed than branched or cyclic structures. Lower molecular weight (MW) compounds are better absorbed from the gastrointestinal tract than higher MW compounds; extremely high MW compounds such as those in petroleum waxes do not appear to be absorbed. The absorbed oil is distributed to the liver, spleen, mesenteric lymph nodes and lungs.

Mineral oil induces a state of hyperphagocytosis by the macrophages of the liver and lungs which can lead to microgranulomatous changes in these tissues. The hepatic granulomas are composed primarily of Kupffer cells and/or macrophages with infiltrating polymorphonuclear and mononuclear leukocytes. Pulmonary granulomas consist of oil-containing macrophages, lymphocytes and fibroblasts, together with a slight amount of collagen fibers.

Species differ greatly in their response to mineral oil; dogs and rats are sensitive to the accumulation of white oil while rabbits, hamsters, mice and gerbils seem more resistant to these changes.

No pathological lesions were found in rats fed several types of waxes for two years.

Case studies of individuals using or misusing mineral oil reveal a pattern of structural and functional cellular changes in the liver, lungs, spleen and mesenteric lymph nodes. Accumulation of mineral oil hydrocarbons in human liver, spleen and lymph nodes under conditions of prolonged and/or excessive exposures, has been well documented although it has not been regarded as harmful.

Hepatic granulomatous reactions have been evoked under a variety of experimental conditions: some involve reactions to metallic and other compounds, others involve occlusion of the hepatic vein and yet others relate to familiar pathogens.

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**TOXICOLOGICAL OVERVIEW OF HYPERPHAGOCYTTIC GRANULOMA  
ASSOCIATED WITH MEDICINAL WHITE OIL AND RELATED MATERIALS**

**SECTION I: THE PROCESS OF GRANULOMAGENESIS**

Granulomagenesis appears to be a commonly encountered biological process. According to Guckian and Perry (1966), up to 10% of liver biopsy specimens in general hospitals reveal granulomatous lesions, and according to Fauci and Wolff (1976), 13-36% of liver granulomas are of unknown etiology.

The term "granuloma" as used in the scientific literature is ambiguous at best. However, the key histologic pattern is one of a focal aggregation of macrophages commonly containing phagocytized particulates. Granulomatous reactions may be classified as hyperphagocytic granulomas and immunogenic granulomas, and the precise histological changes seen are the result of two distinct biological processes (Boros and Warren, 1974 and Adams, 1976).

**Hyperphagocytic granuloma:** Results from a hyperphagocytic response to immunologically inert particulates (eg. plastic beads or bentonite particles). Admixed with the phagocytes in this type of granuloma are usually lymphocytes and less often, plasma cells and giant cells. Fibrosis is generally minimal. According to Boros (1978), the mechanisms involved in this type of granuloma are: 1-Minimal cell recruitment; 2-Slow proliferative activity; 3-High proportion of long-lived macrophages which contain the ingested material. This type of granuloma is the one observed in studies conducted for Shell International Petroleum, in which medicinal white mineral oils were fed as part of the diet to rats, and in which oil droplets and tissue changes described as granulomatous inflammation were found in the liver, spleen and mesenteric lymph nodes.

**Immunogenic granuloma:** Results when the histologic pattern of the hyperphagocytic granuloma is compounded by a parallel T-cell dependent inflammatory response. Admixed with the phagocytes in this type of granuloma are lymphocytes, macrophages, eosinophils and occasionally epithelioid cells. Fibrosis here may be significant. According to Boros (1978), the mechanisms involved in this type of granuloma are: 1-Recruitment of fresh bone marrow supplied, blood-borne cells; 2-Cell proliferation within the granuloma; 3-Longevity of some inflammatory cells.

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The phenomena described as "granulomagenesis" has been have been successfully induced by several agents and treatments. Hyperphagocytic type experimental granulomas have been induced by such mechanisms as hepatic vein ligation and administration of diets containing high levels of edible fats (including vegetable and animal fats) to laboratory animals. Immunogenic type granulomas have been induced by such mechanisms as injection of Streptococcal cell wall fragments, injection of glucan (a component of yeast cell wall), injection of Schistosome eggs or by total parenteral nutrition therapy in animals. No granuloma formation was found in animals fed diets containing petroleum-derived waxes, presumably because the hydrocarbons present in waxes are too large to be absorbed through the gastrointestinal wall.

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## SECTION II: GRANULOMA AND WHITE MINERAL OIL

Stryker (1941) provides a good overview of the history of the use of mineral oil and related materials. According to his review, the first internal use of refined petrolatum probably dates to 1872, when Robert A. Chesebrough of New York was granted a patent for the manufacture of "a new and useful product from petroleum, named vaseline". While various authors (Randolph 1885; Hutchinson 1899; Robinson 1900) published occasional reports advocating the use of liquid petrolatum, the use of mineral oil as a laxative was popularized chiefly through the widely read recommendations of Sir W. Arbuthnot Lane (1913), chief surgeon of Guy's Hospital. In 1914, the Council on Pharmacy and Chemistry of the American Medical Association considered liquid petrolatum and suggested standards for the various types of the oil.

White mineral oil, also known as liquid petrolatum, is a mixture of saturated hydrocarbons of the general formula  $C_nH_{2n+2}$ . Mineral oils vary in composition depending on the boiling point of the petroleum fractions used. For food purposes, usually liquid petrolatum or liquid paraffin are employed, which consist essentially of n-alkanes and some cyclic paraffins. They are chemically inert, especially regarding the straight-chain alkanes.

It is important to note that the chemical composition of mineral oils differ substantially from that of vegetable oils. Rather than simple alkanes and cycloalkanes, vegetable (corn, coconut, olive, peanut) oils and fats are composed mostly of glycerides of the following fatty acids: linoleic, oleic, palmitic and stearic.

### THE SHELL SITTINGBOURNE STUDIES

REPORT SBER.87.010. WHITE OILS: A 90 DAY FEEDING STUDY IN RATS. SHELL RESEARCH, LIMITED, SITTINGBOURNE RESEARCH CENTRE, 1987.

Male and female F-344 rats were administered diets containing 0.5, 1.0 and 2.0% hydrotreated or 0.5, 1.0 and 2.0% oleum-treated white oil for 90 days. Both white oils samples were derived from the same naphthenic crude. The oleum-treated oil, having a viscosity of 26.0 mm<sup>2</sup>/S at 40 ° C was purchased from Buchanan Oils, Renfrew, Scotland. The hydrotreated oil is a proprietary product of Deutsche Shell Aktiengesellschaft, produced in Hamburg, Germany, had a viscosity of 69.2 mm<sup>2</sup>/S at 40 ° C - substantially heavier than the oleum-treated oil tested at Sittingbourne. There were no deaths and no signs of clinical toxicity. Necropsy revealed oil deposits in the liver, spleen and mesenteric lymph nodes (more marked in females than males) and granulomatous inflammation in the liver and mesenteric lymph

nodes. In all cases the oleum-treated oil fed animals were more affected than the hydrotreated animals. No treatment related histopathological changes were found in any other tissues of oleum-treated or hydrotreated oil fed animals.

A hypochromic microcytic anemia was observed in the females, being more pronounced with the oleum-treated oil fed animals. Rats of both sexes fed 2.0% hydrotreated or oleum-treated oil showed an increased white cell count and absolute number of polymorphic neutrophils. The white cell effects were more marked in the females than the males and more marked in the oleum-treated than in the hydrotreated oil. Accelerated hematopoietic activity was recorded in the bone marrow of a few females in the 2.0% oleum-treated groups.

Oil deposits were found in the liver and mesenteric lymph nodes, being more pronounced in the females than in the males (500% difference) and more marked with the oleum-treated than with the hydrotreated oil (50% difference). Liver, spleen and kidney weights were increased by exposure to the oil, the females being more affected than the males and the oleum-treated oil fed animals being more affected than the hydrotreated oil fed animals. Females fed oleum-treated oil were affected at all dose levels, females fed hydrotreated oil were affected at 1.0 and 2.0% levels only.

Both oils gave rise to moderate to severe granulomatous inflammation associated with lipid droplets at all dose levels in the male and female mesenteric lymph nodes and female livers. Splenic lesions were increased in all oleum-treated oil fed groups and in the 0.5% and 2.0% hydrotreated groups.

**REPORT SBER.87.011. WHITE OILS: A REPEAT 90 DAY FEEDING STUDY IN FEMALE RATS. SHELL RESEARCH, LIMITED, SITTINGBOURNE RESEARCH CENTRE, 1987.**

Female F-344 rats were administered diets containing 0.001%, 0.01%, 0.05%, 0.5%, 1.0% or 2.0% hydrotreated white oil or 0.001%, 0.01%, 0.05%, 0.5%, 1.0% or 2.0% oleum-treated oil for 90 days. An additional group of females was fed a diet containing 0.05% and 1.0% of each oil for 25 days. Both oils samples were the same as those used in the previous study. There were no deaths and no clinical signs of toxicity. Liver and spleen weights were increased by exposure to the oil for 90 days, the oleum-treated oil fed animals being more affected than the hydrotreated oil animals. Liver and mesenteric lymph nodes showed granulomatous changes at 1.0%, and 2.0%, and at 0.5%, 1.0%, and 2.0%, respectively. There were no significant histological changes after 25 days feeding with either oil.

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Livers, after 90 days of treatment, showed centrilobular granulomata and Kupffer cell hypertrophy in both the 0.05% groups and sublobular parenchymenecrosis and occasional fibrosis in the 1.0%, or 2.0% oleum-treated oil fed groups.

Mesenteric lymph nodes showed granulomatous macrocytic syncytia (a multinucleated protoplasmic mass found by the secondary union of originally separate cells) in many of the groups fed oleum-treated and hydrotreated oil for 90 days. The effect was dose-related and was more marked in the oleum-treated oil groups than in the hydrotreated oil groups.

On the basis of the hepatic granulomata, the mesenteric nodal granulomatous lesions and the liver and spleen weights, the NOEL for the hydrotreated oil was reported to be 0.05% and 0.001% for the oleum-treated oil as tested at Sittingbourne.

#### ABSORPTION AND TISSUE DISTRIBUTION OF MINERAL OIL

SECTION SUMMARY: Mineral oil is absorbed in small quantities from the intestines. Once absorbed, circulating mineral oil micelles are removed by phagocytic cells, particularly in the liver, spleen, lymph nodes and in severe cases, lung. Higher molecular weight (MW) hydrocarbons, such as those found in petroleum waxes, do not appear to be absorbed from the intestinal tract. Granuloma formation has been found in animals fed diets high in digestible fats (including vegetable and/or animal fats) (Herting and Harris, 1959).

Stryker (1941) provides an excellent summary of the early studies on the absorption of mineral oil following oral ingestion. These studies were of two main types: the first consisted of feeding liquid petrolatum to the subjects and then determining how much of the material could be recovered from the feces or from the lymphatics. The second method involved the examination of various tissues for hydrocarbon content following oral administration of liquid petrolatum. According to Stryker, results from the first method were generally interpreted to indicate that liquid petrolatum was not absorbed from the gastrointestinal tract, and results of the second, that some absorption probably did occur.

According to Stryker, in studies of the second type, rabbits, rats and guinea pigs were fed a diet containing varying amounts of liquid petrolatum for a period of thirteen, nineteen and fifteen months respectively. Oil absorption was demonstrable in the three species tested, but with some interesting differences.

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In the rabbit, there were vacuolated cells in the lamina propria, jejunum and colon; giant cells and intracellular and extracellular vacuoles in the mesenteric lymph nodes. The rabbit liver contained numerous vacuolated cells scattered throughout the lobules, but most abundantly in the periportal areas. In the rat, there were no changes observed in the intestines. The mesenteric lymph nodes showed lymphatic follicles and medullary cords containing large numbers of vacuolated cells; no giant cells were seen. The rat liver triads and adjacent areas contained large numbers of vacuolated cells and extracellular vacuoles. In the rat spleen, scattered collections of vacuolated cells were seen and no extracellular vacuoles were noted. In the guinea pigs, no changes were observed in the intestines and the mesenteric lymph nodes showed an occasional vacuolated cell and extracellular vacuoles in the medullary and peripheral follicles. The guinea pig liver showed a few vacuolated cells near the triads. In the species used by Stryker (rabbit, rat and guinea pig), the ease of demonstration of absorption of mineral oil and the quantity present in the tissues were related to the length of time this material was fed. These data suggest a species difference in the absorption of mineral oil. Stryker used the presence of giant cells in tissues of animals fed mineral oil as his basis for stating that this material caused a "foreign body" reaction.

In a study by Daniels et al., (1953), rats were maintained for 15 months in diets supplemented with 10% liquid paraffin. While the liver contained 0.4% dry weight liquid paraffin, liver function was not affected.

Oil droplets have been seen in the spleens, livers and abdominal lymph nodes of people known or believed to have ingested large quantities of mineral oil (Boinott and Margolis 1966a, 1966b and 1970). Mass spectrometry data suggest that these hydrocarbons are derived from mineral oil. In the spleen, focal collections of oil droplets were found near the periphery of the splenic follicles and adjacent to the trabeculae and blood vessels. Hepatic lesions were largely limited to the portal triads and showed limited evidence of scarring (Yocum et al., 1986; Kulonen and Potila, 1980, Wahl et al., 1986b). In cases showing extensive alterations of the hepatic architecture, similar clusters of vacuoles in macrophages (lipid granulomas) were present within the hepatic parenchyma. There was a clear correlation between the extent of histologic change and the saturated hydrocarbon content of the tissues examined.

Absorption of saturated hydrocarbons is partly dependent on the type of saturated hydrocarbons administered. For example, n-alkanes were apparently more readily absorbed than the complex mixtures of branched and cyclic alkane which constitute mineral oil as cited by Boinott and Margolis, 1970; Savary and Constantin, 1967 and Kolattukudy et al., 1966.

83 Shubik et al. (1962) reported no pathological finding attributable to the feeding of any of five test waxes, at a level of 10% in the diet to male and female Sprague-Dawley rats for two years. No differences between groups fed different waxes were noted. No pathologic findings attributable to the treatment were observed suggesting that the high molecular weight hydrocarbons present in petroleum waxes are not significantly absorbed through the gastrointestinal tract.

It should be noted that the granuloma formation is not a process uniquely associated with petroleum-derived oils. Herting and Harris (1959) have reported granuloma formation in rats fed diets containing 30-50% saturated fatty acids (fed as palmitic acid, stearic acid, ethyl stearate, hydrogenated lard, or as monoglycerides or acetylated monoglycerides made from hydrogenated lard). This effect was not seen in control groups fed triacetin (an acetate formed from glycerol and acetic acid used chiefly as a plasticizer and solvent) during the 48-week test period. Complete reversal of the granuloma with no evidence of permanent damage to adipose tissue, was brought about by replacing the above diets with corn oil.

#### **METABOLISM OF MINERAL OIL**

SECTION SUMMARY: The metabolism of saturated hydrocarbons by mammals has been demonstrated in several species. According to Stetten, (1942), McCarthy, (1964), Kolattukudy and Hankin, (1966), Nickolaides, (1966) and Mitchell and Hübscher, (1967), n-alkanes, including octadecanes ( $C_{18}H_{38}$ ) and hexadecanes ( $C_{16}H_{34}$ ), are rapidly metabolized to fatty acids of the same carbon chain length, suggesting a metabolic pathway via omega oxidation (ie, oxidation of the terminal carbon atom).

McCarthy (1964) provided a window of observation into the process of metabolism of octadecane and hexadecane in the goat, rat and chicken. Apparently the same type of general metabolic reaction occurs in these species leading to the formation of fatty acids of the same carbon chain length as the hydrocarbon administered. This is consistent with the results of Stetten (1942), who described the metabolism of deuterated n-hexadecane to deuterated palmitic acid. Rats and monkeys administered mineral oil with a radioactive n-hexadecane tracer were observed to incorporate the tracer into naturally occurring fatty acids (Bollinger, 1970). Both authors conclude that straight chain hydrocarbons, whether components of mineral oil or other complex mixtures, are absorbed, transported or mobilized from the site of injection and metabolized by a number of animal tissues. No data were

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identified on the metabolic disposition of cycloalkane (naphthenic) hydrocarbons.

Laying White Leghorn chickens were administered [1-<sup>14</sup>C]-n-octadecane orally. Analysis of the oils in eggs demonstrated that, of the radioactive labels isolated in fatty acids, 71% was contained in 18-carbon chain fatty acids (McCarthy, 1964).

[1-<sup>14</sup>C]-n-Octadecane was added to the contents of a goat rumen and perfused via a heart-lung apparatus for 50 minutes. The blood perfusate showed a substantial amount of radioactive material in the form of fatty acids and not in that of the added hydrocarbons. Analysis of the rumen contents showed the free fatty acids present to be non-radioactive, thus ruling out any conversion by rumen microbes. The absence of radioactivity in blood hydrocarbons suggest that the conversion to fatty acids occurred within the rumen tissue during absorption (McCarthy, 1964).

Goats were administered [1-<sup>14</sup>C]-n-octadecane intravenously and blood samples taken 1, 3, and 5 hours later. Over time, (no data given) there was a decrease in the radioactive content of the non-saponifiable fraction of blood lipids accompanied by a corresponding increase in the radioactivity in the fatty acid fraction. The presence of labeled hydrocarbons in the liver demonstrates the uptake of hydrocarbons by liver tissue before conversion to fatty acids. Results from two such analyses are presented in Table I. The preponderance of the label in the 18-carbon chain fatty acids strongly suggest direct conversion of octadecane to fatty acids by the oxidation of the terminal carbon of the hydrocarbon chain. The symmetrical nature of the octadecane molecule eliminates consideration of types of oxidation other than omega oxidation. It was impossible to tell if the radioactive label in the 16-carbon fatty acid resulted from direct conversion of octadecane to palmitic acid or from the metabolism of the 18-carbon fatty acid, however, the latter possibility seems most likely (McCarthy, 1964).

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TABLE I

Distribution of  $^{14}\text{C}$  in Fatty Acids of goat liver phospholipids following intravenous injection of  $[1-^{14}\text{C}]$  Octadecane (50 $\mu\text{C}$ ).

Component Acid*	Percent of $^{14}\text{C}$ activity	
	Trial I	Trial II
Up to $\text{C}_{16}$	2.3	3.5
$\text{C}_{16}$	9.3	10.2
$\text{C}_{16}$ - $\text{C}_{18}$	3.7	3.5
$\text{C}_{18}$	84.6	83.0

\*Recovered by trapping from a phosphoric acid treated adipate gas chromatography column (McCarthy, 1964).

Mature Wistar rats were administered both  $[1-^{14}\text{C}]$ -n-octadecane and  $[1-^{14}\text{C}]$ -n-hexadecane orally, sacrificed 6 hours later and their livers removed and lipids extracted. The high prevalence of fatty acids of both 18- and 16-carbons chains in the liver demonstrate that the rat is capable of converting saturated hydrocarbons to fatty acids and that both 18- and 16-carbon straight-chain hydrocarbons were metabolized. The presence of radioactive non-saponifiable fraction of liver oil droplets is a strong indication that at least a portion of the hydrocarbons were absorbed unaltered from the gut and removed from the blood by the liver. Results of studies with liver homogenates of both the goat and rat indicate that hexadecane is more rapidly metabolized than octadecane, as seen in Table II (McCarthy, 1964).

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TABLE II

Distribution of  $^{14}\text{C}$  in Fatty Acids of rat liver oil droplets following the oral administration of  $^{14}\text{C}$ -labeled aliphatic hydrocarbons.

Component Acid	Percent of $^{14}\text{C}$ Activity	
	[I- $^{14}\text{C}$ ] Hexadecane Administered	[I- $^{14}\text{C}$ ] Octadecane Administered
Up to $\text{C}^{16}$	5.5	0.3
$\text{C}^{16}$	69.1	8.3
$\text{C}^{16}-\text{C}^{18}$	0.6	1.3
$\text{C}^{18}$	24.1	90.1

Rats were administered deuterated n-hexadecane in the diet until 200 grams had been consumed. The animals were then sacrificed. Data obtained from alkaline hydrolysis of the liver, feces and gastrointestinal tract seem to suggest that hexadecane was well absorbed from the gastro intestinal tract of rats. Also, high deuterium concentrations were noted in the fatty acids of the carcass (body less the liver and the gastro intestinal tract), indicating a catabolic degradation via an oxidative process in which hexadecane was converted to palmitic acid. (Stetten, 1942).

Female white rats and female squirrel monkeys were administered 0.1 ml and 0.3 ml respectively of a 1- $^{14}\text{C}$ -n-hexadecane-labeled emulsion made with mineral oil and mannide monooleate by subcutaneous or intramuscular routes. After dosing, the animals were sacrificed on days 1-, 2- or 7 and after 1, 2, 3, and 10 months. Mineral oil was slowly removed from the site of injection. In monkeys, 96-98% of the radioactivity was still present after one week, while in rats, this amount ranged from 85-90% one week post-dosing. Both groups retained 65-75%, 50-60% and 25-30% of the radioactivity at the site of injection, after one, three and ten months respectively. Virtually all (95-99%) of the activity remaining at the site of injection in monkeys after three and ten months was present in the hydrocarbon fraction, while 3-4% of the activity found in the site of injection in the rats had been incorporated into triglycerides with 91-93% still associated with the hydrocarbon fraction. Twenty four hours post-dosing, all organs contained radioactivity,

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the liver having the highest activity. A substantial portion of the radioactivity in the liver (30%), fat (42%), kidney (74%), spleen (81%), and ovary (90%) was un-metabolized. The remaining radioactivity was located in various lipid classes, indicating hexadecane was undergoing metabolism (Bollinger, 1970).

#### EXCRETION OF MINERAL OIL

SECTION SUMMARY: When white mineral oil is administered orally, most passes through the gastrointestinal tract and is recovered in the feces. When it is administered intraperitoneally, gastrointestinal excretion of the oil occurs slowly.

Sprague-Dawley rats were administered non-labeled mineral oil orally at a dose of 0.66 ml/kg for 31 consecutive days, on the thirty-second day of treatment, the animals were administered 0.66 ml/kg of <sup>3</sup>H-mineral oil orally and sacrificed 5, 24, and 48 hours post-dosing. Five hours post-dosing, 80% of the <sup>3</sup>H-mineral oil remained in the gastrointestinal tract, 24 hours post-dosing, 4.5% of the dose of the tritiated oil was present in the gastrointestinal tract, and 48 hours post dosing, only 0.7% of the dose was present in the gastrointestinal tract (Ebert, Schleiffer and Hess, 1966).

Sprague-Dawley rats were administered non-labeled mineral oil intraperitoneally at a dose of 0.66 ml/kg for 31 consecutive days, on the thirty-second day of treatment, the animals were administered 0.66 ml/kg of <sup>3</sup>H-mineral intraperitoneally and sacrificed 24 hours post dosing. Only 11% of the <sup>3</sup>H-mineral oil was recovered in the feces 8 days post dosing. Therefore, the major portion of the dose remained in the animal at this time, by this route (Ebert, Schleiffer and Hess, 1966).

#### TISSUE EFFECT AND SPECIES DIFFERENCE WITH RESPECT TO INHALED MINERAL OIL AEROSOLS

SECTION SUMMARY: The biological response to inhaled mineral oil mists appears to be highly species specific. Clearance of inhaled mineral oil droplets by pulmonary macrophages appear to be more effective in dogs and rats than in rabbits, mice, hamsters and gerbils.

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Six species of animals (dog, rat, rabbit, hamster mice, gerbil) were exposed to mineral oil mists by inhalation for periods ranging from one year to 26 months at concentrations of either 5 or 100 mg/M<sup>3</sup>. Histologic evaluation of tissues of the 100 mg/M<sup>3</sup> exposed dogs and rats presented a significant pulmonary alveolar and hilar lymph node oil deposition and/or granuloma formation after 12 months of dosing. Mice, hamsters, gerbils and rabbits showed essentially no major pathologic response to the oil mist, (Wagner, Wright and Stokinger, 1964 and Stula and Kwon, 1978).

Dogs showed foamy macrophage in the parenchymal air spaces, oil droplets and periluminal foci of varying-sized coalesced oil droplets with adjacent non-nuclear cells. Within hilar lymph nodes, there were scattered coalesced oil droplets at the 5 mg/M<sup>3</sup> dose. At the higher dose, there was similar response but with a much greater evidence of parenchymal granulomas, consisting of lymphocytes and macrophages and containing small and large oil droplets (Wagner, Wright and Stokinger, 1964 and Stula and Kwon, 1978).

Rats revealed a progressive reaction to the inhaled oil as primarily that of increasing numbers of lipid-filled macrophages. Clear vacuoles were quite prominent in the cytoplasm. The number and clustering of these macrophages in the air spaces was observed to increase as the length of exposure to the oil increased. Compared to dogs, the most striking differences in the phagocytic response were the prominent presence of the macrophages and their oil-containing cytoplasm in rats as opposed to the almost complete absence of macrophages in dogs, and the oil droplets lying free in the parenchymal air spaces and hilar lymph node tissue. This phenomenon is believed to be due in part to a species difference in inflammatory cell response. Pulmonary tissue alteration were of significance only in the rats exposed to the 100 mg/M<sup>3</sup> oil concentration. (Wagner, Wright and Stokinger, 1964 and Stula and Kwon, 1978).

In rabbits scattered foamy macrophages containing small clear vacuoles were observed within the pulmonary alveolar spaces (Wagner, Wright and Stokinger, 1964 and Stula and Kwon, 1978).

Hamsters, after 15 months of treatment, showed essentially no major pathologic changes even at 100 mg/M<sup>3</sup> (Wagner, Wright and Stokinger, 1964 and Stula and Kwon, 1978).

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Mice showed essentially no major pathologic response to 12 months of oil mist inhalation at either 5 or 100 mg/M<sup>3</sup> concentration aside from the presence of random scattering of single or small clumps of macrophages. No inflammatory reaction accompanied these cells. Lymphatic tissue adjacent to the bronchi contained some lipid-bearing macrophages (Wagner, Wright and Stokinger, 1964 and Stula and Kwon, 1978).

In gerbils exposed to either 5 or 100 mg/M<sup>3</sup> of oil mist for up to one year, no oil mist lesions were found, except for a few oil-containing macrophages in the bronchial lumen (Stula and Kwon, 1978).

### SECTION III: HUMAN EXPERIENCE

#### HUMAN CASE STUDIES OF MINERAL OIL AND ITS EFFECTS

SECTION SUMMARY: The reviewed literature on human contact with medicinal white oil includes numerous case reports of individuals who ingested this material for unusually long periods of time and/or in amounts that exceed standard medical practice. Under such conditions, high levels of oil can accumulate in the liver, spleen, lymph nodes and may result in a degree of dysfunction in those particular organs. Use of mineral oil as a laxative was not found to be causative, contributory or incidental to gastrointestinal cancer in humans.

Accumulation of mineral oil hydrocarbons in human liver, spleen and lymph nodes under conditions of prolonged and/or excessive exposures, has been well documented (Boinott and Margolis, 1966a, b, 1970; Liber and Rose, 1967) although it has not been regarded as harmful (Boinott and Margolis, 1966b). Blewitt et al., (1977), described hepatic damage associated with mineral oil droplets in a 33-year old male who was instructed to swallow one tablespoon of liquid paraffin as a laxative once a day. It is not clear that he followed the dosing regimen correctly. The patient's liver specimen revealed edema of the connective tissue, scattered groups of cystic spaces and portal triads showing increased fibrous tissue. Changes observed in the lungs included extensive lesions attributable to oil deposition including the typical histiocytic and giant cell granulomatous responses of an active lipid pneumonia.

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Carrillon et al., (1988) cite the case of a 61 year-old woman with chronic pneumonia showing extensive, bilateral consolidation of the mid and lower lung fields upon chest X-ray coinciding with a history of daily use of paraffin oil as a laxative.

Ferguson and Miller (1988) present the case of a 36 year-old female patient showing bilateral alveolar infiltrates predominantly in the upper lobes of the lungs who was ingesting mineral oil while hospitalized for peripheral edema. Histological examination revealed severe lipoid pneumonitis, bronchiolitis and patchy interstitial fibrosis. Transbronchial biopsy specimens showed macrophage vacuolization.

Berg and Burford (1950) mention the case of a 51 year-old white male patient complaining of dyspnea for one year's duration, productive cough for six months and frequent lower respiratory infections for many years; the patient showed no hemoptyses. The patient had used mineral oil at night as a laxative for as long as he could remember. Bronchoscopic findings consisted of diffuse infiltration of in the right main-stem bronchus. The lesion showed huge cysts in the right upper lobe and the posterior basal segment of the right lower lobe and masses with ill-defined, yellowish-gray mottled oily surfaces. Microscopic examination revealed a typical paraffinoma. The regional lymph nodes contained macrophages filled with mineral oil.

Boyd and Doll (1954) found a correlation between the use of mineral oil as a laxative and cancer of the large intestine. Test on animals administered mineral oil have proved negative for carcinogenicity. Authors could not ascertain whether the use of mineral oil for purgative purposes was causative, contributory or incidental to gastrointestinal cancer.

Higginson (1966) reported no differences in dietary patterns and personal habits between gastric cancer patients and controls matched by age, race and sex. In a retrospective study to identify possible etiological factors in gastric carcinoma, Higginson found that although gastric cancer patients showed a dietary pattern indicating a slightly increased use of animal fats, cooked fats, fried foods and a decreased use of dairy products, the differences between the studied group and controls were not significant. There was a more frequent history of constipation and use of laxatives by the cancer patient group, however, the validity of this data is doubtful since many patients took several types of laxatives and were uncertain as to the identity of some laxatives. The results of Boyd and Doll (1954) were not confirmed by Higginson (1966).

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LIQUID MINERAL HYDROCARBONS IN FOOD: REVIEW OF CURRENT  
ISSUES, EXXON CORPORATION'S TOXICOLOGICAL DATA AND  
CONSIDERATION OF POTENTIAL HUMAN HEALTH EFFECTS

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### EXECUTIVE SUMMARY

Liquid mineral hydrocarbons produced from petroleum constitute an important class of direct and indirect (or incidental) food additives. These materials include highly refined distillates (white mineral oils) as well as technical mineral hydrocarbon products produced synthetically or from atmospheric petroleum distillates.

Recently the U.K. Ministry of Agriculture, Fisheries and Food (MAFF) announced its intention to ban the use of mineral hydrocarbons in direct and indirect food uses. MAFF cited apparently insufficient data on the potential carcinogenic, mutagenic, developmental and reproductive effects of mineral hydrocarbons as a basis for the proposed ban. MAFF also cited the toxicity findings in two unpublished 90-day toxicity studies conducted by Shell in which white mineral oils were administered to rats at dietary concentrations from 10 ppm to 20,000 ppm (w/w). Two white mineral oils produced from naphthenic crude oils were studied: a low viscosity, oleum-treated oil and a high viscosity oil produced by hydrogenation. Accumulation of mineral oil was observed with evidence of adverse effects to the liver, spleen, kidneys and lymph nodes. The oleum-treated oil appeared to elicit the more severe effects and included some liver cell necrosis. Based on these studies, it was concluded that the no observable effect level (NOEL) for the oleum-treated and hydrogenated oils were 10 and 500 ppm, or 0.6 and 29 mg oil/kg body weight/day (mg/kg/d), respectively. However, as noted below, a significant amount of additional data (published and unpublished) which was not cited by the Ministry attests to the overall safety of liquid mineral hydrocarbons<sup>1</sup>.

Subchronic dietary and oral gavage 90-day toxicity studies have also been conducted by Exxon on four additional white mineral oils and a technical grade mineral oil. Four of these oils were paraffinic (one oleum-treated oil and three hydrogenated oils) and were evaluated in rats and dogs at dietary concentrations of 300 and 1500 ppm (w/w). No toxicity was observed with any oil, and none of the oils appeared to accumulate in the tissues of either species. Thus, the NOEL exceeded 1500 ppm in feed or consumption rates of approximately 125 mg/kg/day in rats and 52 mg/kg/day in dogs. A fifth oil (medicinal grade) was an oleum-treated naphthenic product which was given to rats by oral gavage at a dose of 4350 mg/kg, five days per week, for 90 days. No toxicity was observed; thus, the NOEL exceeded 4350 mg/kg/day.

White mineral oils and petrolatums have been tested in lifetime dietary feeding studies in rats. These studies also failed to establish any chronic toxicity or carcinogenic effects. The approximate NOELs exceeded 1200-6000 mg/kg/day in these studies.

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<sup>1</sup> No consideration is given here to solid mineral hydrocarbons (i.e., waxes).

Numerous studies indicate that white mineral oils from either paraffinic or naphthenic crude sources are not carcinogenic. These include studies conducted by the dermal and inhalation routes of exposure as well as the dietary feeding studies discussed above. Further studies indicate that white mineral oils are neither mutagenic nor developmental or reproductive toxicants.

The toxicity of technical mineral hydrocarbons has also been characterized. The technical mineral hydrocarbons discussed in this report are made by different processes than the white mineral oils and are typically of lower average molecular weight, lower final boiling point, lower viscosity, and higher volatility. All studies of technical mineral hydrocarbons were by inhalation because this was considered to be the most relevant route of industrial human exposure. The specific studies included subchronic (i.e., 90 day) inhalation, teratology, and dominant lethal studies as well as acute toxicity tests.

None of the three tested technical mineral hydrocarbons produced evidence of acute health hazards. There was no evidence of cumulative toxicity in rats exposed to vapor concentrations of up to 900-1180 ppm, 6 hours/day, 5 days/week for 12 weeks, with the exception of effects on the kidneys. However, this specific renal effect, also known as light hydrocarbon nephropathy (LHN), is a phenomenon which occurs only in male rats and is not considered to be a toxic endpoint which represents a human health concern. Of particular note was the absence of pathologic evidence of mineral hydrocarbon accumulation or specific organ toxicity. Additionally, there was no evidence of developmental toxicity in rats exposed to vapor concentrations of up to 1200 ppm, 6 hours/day from days 6-15 of gestation. Finally, there was no evidence of testicular toxicity or genetic toxicity in dominant lethal studies which utilized the same exposure levels. The lack of effect in the dominant lethal study also indicates that these products are not male reproductive toxicants. Corroborative findings can be found in the published literature.

In humans, prolonged and repeated exposures to white mineral oils has been presumed to result in their accumulation in certain tissues, such as the liver, spleen and mesenteric lymph nodes. However, no toxic responses or disease states appear to result from the presence of this oil. In laboratory animals, it has long been known that white mineral oils absorbed from the gastrointestinal tract can be distributed to the liver, spleen and mesenteric lymph nodes. As with humans, until now there were no indications from animal studies that the occurrence of oil in these tissues caused any toxic effects.

The data which has been available to Exxon has indicated that saturated mineral hydrocarbons, regardless of boiling range, are relatively non-toxic and safe for the permitted use in food applications. The Shell studies are not consistent with this conclusion, at least for white mineral oils. There are no clear explanations for the toxicity differences observed in the two sets of subchronic feeding studies with white mineral oils. One possible explanation may be that these oils contain different hydrocarbon

distributions which resulted in different patterns of absorption, distribution, metabolism and resulting toxicity. However, a wide spectrum of products have been evaluated without observations of toxicity. Alternatively, the Shell oil(s) may have contained undesirable contaminants. Finally, protocol differences may have contributed to the differential toxicity observed in the two sets of data. Elucidation of these potential variables would require further study.

In summary, a large body of evidence indicates that white mineral oils and technical mineral hydrocarbons have a very low order of toxicity and present minimal human health concerns. The data reviewed by MAFF in its decision to ban mineral hydrocarbons from food use were incomplete since a large number of studies on these mineral hydrocarbons were not readily available or in the published literature. The additional data reviewed in this report represent past and current commercial products produced for use as direct and/or indirect (or incidental) food uses. These products included vacuum and atmospheric distillates, naphthenic and paraffinic crude sources, and represented a wide range of processing conditions including oleum-treatment and hydrogenation to form "white mineral hydrocarbons", and technical grade mineral hydrocarbons and solvents. Although there are many unanswered questions raised by differences in the subchronic feeding studies, overall the data indicate a low potential for acute and chronic toxicity of mineral hydrocarbons used in accordance with current regulations.

## I. INTRODUCTION

This document has been prepared as a comprehensive review of experimental toxicological data and human health observations which are associated with ingestion of liquid mineral hydrocarbons. The information included in this paper was initially submitted to the U.K. Ministry's of Agriculture, Fisheries and Food (MAFF) who proposed an amendment to the Mineral Hydrocarbons in Food Regulations 1966 (SI NO 1073) to generally ban the use of mineral hydrocarbons in food. The Minister's decision was based upon advice from the Food Advisory Committee (FAC) and the Committee on the Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) that all mineral hydrocarbons should no longer be considered suitable for use in food.

The liquid mineral hydrocarbons<sup>1</sup> covered by the UK ban are mainly white mineral oils but also include food grade solvents. They are defined in the UK Mineral Hydrocarbons in Food Regulations 1966. They constitute an important class of direct and indirect (or incidental) food additives but are also used in other health related applications such as in cosmetics or in pharmaceuticals. A second class of hydrocarbon products called technical mineral hydrocarbons can be indirectly affected by the proposed UK ban. This class of products, which is defined by relevant regulations such as the US FDA, includes technical solvents and technical white oils. These products are approved for food applications when incidental contact with food is possible or for processing of certain food packaging materials.

Several factors were cited in the MAFF recommendation to ban the use of mineral hydrocarbons in foods. These included insufficient data regarding the long term toxicity, mutagenicity, carcinogenicity, teratogenicity and reproductive toxicity of materials currently used in food applications, particularly for oils refined by hydrogenation. In addition, recent animal studies conducted by Shell Research Limited, London, provided evidence of target organ toxicity following subchronic exposure via dietary feeding of certain white mineral oils. The target organs identified in these animal studies were also sites of accumulation in humans of what is presumed to be mineral hydrocarbons. Finally, MAFF communicated the likelihood that tentative Acceptable Daily Intakes (ADIs) for mineral hydrocarbons, if based on the Shell studies, would be far less than probable daily intakes of mineral oils in the U.K.

A significant amount of toxicologic data, both published and unpublished, is available for liquid mineral hydrocarbons which was not

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<sup>1</sup> See Appendix A for descriptions of refining, processing and product specification. See the Glossary for definitions of terms used in this report. This terminology refers to both technical mineral hydrocarbons and white mineral oils. No consideration is given in this document to solid mineral hydrocarbons (waxes).

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acknowledged in the reviews by FAC, COT and MAFF. These additional data are the primary focus of this critical review. The bulk of the presented data concerns white mineral oils which are the primary liquid mineral hydrocarbons affected by the proposed UK ban. Additional data on technical mineral solvents are also considered because those products are used in applications with indirect or incidental food contact and also because they give complementary information on lower molecular weight hydrocarbon products. When relevant, toxicological information is also provided for solvent extracted or acid treated distillates. On the other hand, no consideration has been given to solid mineral hydrocarbons (i.e., waxes). Some of this additional data may be beneficial to regulatory or scientific bodies in further evaluation of mineral hydrocarbon use in food applications.

This document begins with an overview of some general considerations of the toxicology of mineral hydrocarbons. Results of numerous experimental studies conducted in laboratory animals are then presented. These specifically include studies on the long-term toxicity, carcinogenicity, genetic toxicity, developmental toxicity and reproductive toxicity of mineral hydrocarbons. Limited data on the absorption, distribution and metabolism of mineral hydrocarbons, available from experiments in laboratory animals, are also presented. Following is a review of the available data on the absorption, accumulation and toxicity of mineral hydrocarbons in humans. Finally, the entire set of data is compared and contrasted in an attempt to provide a balanced perspective on its significance to human health. Appendix A contains descriptions of the processing and specifications of the classes of liquid mineral hydrocarbons with food applications. A glossary of terms is also attached.

## II. SOME GENERAL CONSIDERATIONS OF THE TOXICOLOGY OF LIQUID MINERAL HYDROCARBONS

Liquid mineral hydrocarbons can be produced from either naphthenic or paraffinic crude oils. As detailed in Appendix A, liquid mineral hydrocarbons can be produced from crude oil by either atmospheric distillation (i.e., less than about 370°C under normal atmospheric pressure) or by further distillation under reduced pressure (vacuum distillation) of the residuum from the atmospheric pipestill. These raw distillates are then further refined by a variety of processes, including treatment with hydrogen or acid. These processes saturate double bonds and remove impurities such as sulfur, nitrogen and oxygen. Certain technical grade liquid mineral hydrocarbons are synthesized from petroleum gases, but are chemically similar to their distillate-derived counterparts. Specifically, they contain the same types of molecules (i.e., paraffins, isoparaffins and naphthenic products).

Irrespective of crude source, distillation range or refining process, liquid mineral hydrocarbons do not present an acute toxicity hazard. Distillation range has been demonstrated to be an important variable with respect to carcinogenic potential to skin. However, this toxicological activity can be minimized or eliminated by extensive

refining. Raw vacuum distillates (i.e., lubricating oil feedstocks) produced from both naphthenic and paraffinic crude oils contain potentially cancer-causing polycyclic aromatic hydrocarbons (PAH). These molecules occur naturally in crude oils and are found predominantly in those refinery streams produced by vacuum distillation. From these streams the condensed ring aromatic constituents are removed, usually by solvent-extraction, to produce high quality lubricating oils. To produce white mineral oils, the solvent-extracted oils are refined further by hydrogenation or oleum-treatment. These processes (described in Appendix A) remove all unsaturated compounds, aromatic compounds, and other constituents that can influence color, odor, taste, and the acceptability of the product as pharmaceutical or food grade material. Thus, the highly refined lubricating oils (white mineral oils) contain negligible levels of PAH (controlled in the ppb range) which explains their lack of carcinogenic potential. A large number of experiments have conclusively demonstrated that highly refined oils, including white mineral oils and solvent-extracted lubricating oils, do not pose a carcinogenic hazard. These data have been reviewed in two publications (Bingham et al., 1979; IARC, 1984).

As well, relatively few PAH are found in atmospheric distillates. Similar to vacuum distillates, technical mineral hydrocarbons intended for indirect (or incidental) food uses and derived from atmospheric distillates are not acutely toxic. Certain low boiling materials may present an acute aspiration hazard if ingested directly. However, this is not critical in food applications because of low residues. For those technical mineral hydrocarbon products that do contain aromatic species, the concentrations of known toxicologically active species, such as benzene or polycyclic aromatic molecules, are extremely low. The remaining molecules have not been associated with any specific toxicological endpoint with respect to man.

Until recent time, it was believed that all highly refined white mineral oils were not hazardous to humans. However, the recent studies conducted by Shell Research Limited (1987a,b) suggest that long-term exposure to certain white mineral oils can result in toxicity to the liver, spleen, mesenteric lymph nodes and kidneys. Because these Shell data contributed to the MAFF decision to ban mineral hydrocarbons from use in food, they are reviewed first.

### **III. EXPERIMENTAL STUDIES IN LABORATORY ANIMALS**

#### **A. Long-Term Toxicity Of Liquid Mineral Hydrocarbons**

##### **1. Subchronic Feeding Studies In Rodents-Naphthenic White Mineral Oils**

Two 90-day rat feeding studies conducted by Shell Research Limited (1987a,b) were reviewed by MAFF for its current decision. Both studies were conducted to compare the toxicologic properties

of white mineral oils produced by different processes. These oils were a hydrogenated white oil (Shell Ondina Oil 68) and an oleum-treated white oil (Liquid Paraffin WOM 24, supplied by Buchanan Oils). The studies were not intended to be used to assess the overall safety of white mineral oils in food. As summarized in Table I, these oils were derived from naphthenic crude oils. The hydrogenated oil (alternatively described by Shell as triple hydrotreated or hydroprocessed) met British Pharmacopoeia and U.S. FDA (21 CFR 178.3620(A)) standards. Indication as to whether the oleum-treated oil met these standards was not provided in the laboratory reports. The two studies were conducted in sequence, i.e., a comprehensive initial study was followed by an abbreviated repeat study in female rats only.

In the initial study (Shell Research Limited, 1987a), the white oils were administered at dietary concentrations of 0, 5000, 10,000 and 20,000 ppm for 90 days to male and female Fischer 344 rats (10 rats/sex/dose level, 20 rats/sex/control group). Based on food consumption measurements, these dietary levels were calculated to represent average daily intakes of white oil of approximately 0, 340, 688 and 1381 mg oil/kg body weight/day (mg/kg/d) in males, and 0, 386, 784 and 1605 mg/kg/d in females. These dietary concentrations produced no mortality, no effect on body weight or food consumption and no clinical signs of toxicity. At study termination, effects were observed in the mesenteric lymph nodes, liver, kidneys and spleen. In general, the most severely affected animals were female rats fed the oleum-treated oil (Liquid Paraffin WOM 24). These female rats exhibited increased liver, spleen and kidney weights at all dose levels. Similar effects were noted in male rats fed oleum-treated oil only at the two highest dose levels. In male and female rats treated with the hydrogenated oil (Ondina Oil 68), increased weights of these organs were observed only at the two highest dose levels (10,000 and 20,000 ppm). Foci of granulomatous lesions were found in the mesenteric lymph nodes and livers of both sexes. Again, the more severe effects were observed in female rats fed the oleum-treated oil. These foci contained vacuoles which stained positive with Sudan IV and negative with osmium tetroxide. Since Sudan IV is a histochemical stain for saturated lipids and osmium tetroxide is a stain for unsaturated lipids, these results were interpreted to indicate that the vacuoles contained saturated lipids which were presumed to be mineral hydrocarbons.

Analyses were conducted for mineral oil in the liver and mesenteric lymph nodes from rats fed 20,000 ppm of either oil relative to control animals. The method of analysis was developed by Shell and had a detection limit of 0.2 mg of white oil per gram of tissue. No mineral hydrocarbons were detected in control animals, but rats fed 20,000 ppm of either oil contained the hydrocarbons in both tissues. Concentrations in female rats

were approximately 3- to 5-fold greater than corresponding concentrations in male rats. Also, mineral oil concentrations in rats fed oleum-treated oil were approximately 25-55% greater than in rats fed the hydrogenated oil. These findings appear to be consistent with the pattern of severity of pathological findings.

Hematology and clinical chemistry evaluations identified several small but statistically significant effects in female rats fed oleum-treated oil. These included a very mild hypochromic microcytic anemia, white blood cell counts elevated up to 2-times over control values (but not dose related), less than 2-fold increases in serum enzymes which are commonly associated with release from damaged liver cells (aspartate aminotransferase [AST] and alanine aminotransferase [ALT]), and mild effects on triglycerides and serum proteins. Individually, these effects would be considered of limited significance. However, collectively, they might be interpreted as suggestive of low grade liver damage.

Microscopic examinations revealed "foci of moderate to severe sub-acute parenchymal necrosis", diffuse parenchymal hypertrophy and an increased mitotic rate in several female rats fed 10,000 and 20,000 ppm oleum-treated oil. Together with the hematological and clinical chemistry findings, these results are indicative of low grade liver damage with a resultant inflammatory response. Splenic changes were also reported in both sexes after treatment with either oil. Effects were seen at all dose levels of the oleum-treated oil, but only at the 5000 and 20,000 ppm concentrations of hydrogenated oil. In males, these included "patchy capsular adhesions and subcapsular inflammation". Females were found generally with splenic congestion, erythropoiesis and myelopoiesis in the red pulp. Capsular lesions were also found in female rats fed 20,000 ppm oleum-treated oil.

In light of the findings of granulomatous/inflammatory reactions in the initial study, Shell conducted a repeat study in an attempt to determine a no observed effect level (NOEL)(Shell Research Limited, 1987b). This repeat study was limited to female rats, histopathological evaluations of the liver and mesenteric lymph nodes and organ weight measurements of liver and spleen. Thus, the most sensitive indicators of toxicity, as determined in the initial study, were selected for further evaluation.

In the repeat study, the white oils were administered to female Fischer 344 rats (10/dose level and 20/control group) at dietary concentrations of 0, 10, 100, 500, 5000, 10,000 and 20,000 ppm for 90 days. Based on food consumption measurements, these dietary levels were calculated to represent an average daily intake of white oil of approximately 0, 0.6, 5.7, 29, 285, 580 and 1150 mg/kg/d.

Many of the findings of the repeat study confirmed Shell's earlier work. In rats treated with the oleum-treated oil, liver and spleen weights were increased at dietary concentrations greater than or equal to ( $\geq$ ) 5000 ppm. Liver granulomata were observed at  $\geq$  5000 ppm and sublobular parenchymal necrosis of the liver was observed at 10,000 and 20,000 ppm. An increased severity (compared to control) of granulomatous macrophage syncytia were noted in the mesenteric lymph nodes at  $\geq$  100 ppm. Thus, it was concluded that the NOEL for the oleum-treated oil was 10 ppm or 0.6 mg/kg/d.

In rats fed the hydrogenated oil, the NOEL was determined to be 500 ppm or 29 mg/kg/d. Organ weights were increased at  $\geq$  10,000 ppm, liver granulomata occurred at  $\geq$  5000 ppm, and granulomatous macrophage syncytia in the mesenteric lymph nodes were noted only at concentrations of 5000 ppm or more.

No hematological or clinical chemistry evaluations were conducted in the repeat study. The biochemical and hematological effects observed in the initial study were generally of low magnitude and not consistently dose responsive.

## 2. Subchronic Feeding Study In Rodents-Paraffinic White Mineral Oils

Exxon conducted a subchronic (90-day) feeding study in Long-Evans rats on four white oils; one test oil was an oleum-treated oil and the remainder were refined by hydrogenation (Biodynamics, 1977a). This unpublished study was not cited by MAFF in its decision. All four white oils were derived from paraffinic crude oils, as summarized in Table 1. The oleum-treated oil was a low viscosity medicinal grade white oil (MARCOL 72). The comparable low viscosity white oil prepared by hydrogenation was MARCOL 82. Also included in this study were two higher viscosity paraffinic oils prepared by hydrogenation; EZL 550 was a medicinal grade oil whereas the EZL 600 sample was an experimental blend which may not have met all international specifications for medicinal oils, and was considered a technical mineral hydrocarbon product.

The white oils were fed to male and female rats (20/sex/dose level and 40/sex/control group) at dietary levels of 0, 300 and 1500 ppm (w/w) for 90 days (Biodynamics, 1977a). Based on food consumption measurements, these dietary levels were calculated to represent average daily intakes of white oil of 0, 21 and 108 mg/kg/d in males, and 0, 25 and 125 mg/kg/d in females. These dose levels are similar to dose levels which produced evidence of subtle effects in the second Shell study. These values are composite averages for the four white oil test materials. Evaluations for toxicity included hematological, clinical chemistry and pathological parameters. Selected tissues were stained with Oil Red O, another lipid stain, to identify any mineral oil deposition.

In rats, "evaluations of mortality, physical observations, ophthalmology, food consumption, clinical chemistry, urinalysis and organ weights and ratios did not reveal any differences from control [untreated] considered to be of toxicological significance." A significantly increased WBC count was observed in two experimental groups: female rats fed 300 ppm of MARCOL 72 and female rats fed 1500 ppm of the medicinal-grade white oil EZL 550. However, these findings were not judged to be biologically important in the absence of corroborative findings. There also was "no evidence of macroscopic or microscopic tissue changes considered related to administration" of any of the four test oils. Specifically, there were no microscopic anomalies observed in the liver, spleen, kidneys, or mesenteric lymph nodes which were considered of any importance. In addition, no significant lipid deposition in liver, kidneys, spleen, mesenteric lymph nodes, stomach, duodenum, ileum, or colon was detected by Oil Red O staining. Thus, for each of the tested white oils, the NOEL in rats based on this 90 day study would exceed 1500 ppm or 108 to 125 mg/kg/d.

### 3. Subchronic Feeding Study In Nonrodents-Paraffinic White Mineral Oils

The same four paraffinic white oils discussed in the preceding section were also administered to beagle dogs (4/sex/dose level and control group) for 90 days (Biodynamics, 1977b). This unpublished data also does not appear to have been reviewed by MAFF. The dietary concentrations were 0, 300 and 1500 ppm (w/w). Based upon food consumption measurements, these dietary levels were calculated to represent average daily intakes of 0, 10 and 50 mg/kg/d in males and 0, 10 and 52 mg/kg/d for females. Again, these values are composite averages for the four white oil test materials.

Findings in this study included decreased relative testes weights in dogs fed 300 and 1500 ppm of MARCOL 72, 1500 ppm EZL 600 and 1500 ppm MARCOL 82. In addition, relative ovary weights were decreased after feeding with 1500 ppm MARCOL 72, and 300 and 1500 ppm of MARCOL 82; and relative liver weights were increased in dogs fed 1500 ppm MARCOL 82. However, since there were no significant histopathological (or macroscopic) findings in these, or any other tissues, these alterations in relative organ weight were considered biologically unimportant. Hematological, clinical chemistry, food consumption and urinalysis results were unremarkable. The white oils did not appear to interfere with the absorption of either vitamin A or D<sub>3</sub>. Microscopic examinations of liver, spleen, mesenteric lymph nodes, kidney, stomach, duodenum, ileum and colon with Oil Red O stain revealed no accumulations of white oil in any group. An increased incidence or frequency of observations of emesis, soft feces and mucoïd or mucohemorrhagic fecal discharges were not judged to be toxicologically significant. Thus, for each of these white oils, the NOEL in dogs based on this 90-day study would exceed 1500 ppm or 50-52 mg/kg/d.

4. **Subchronic Gavage Studies In Rodents-Naphthenic White Mineral Oil**

Exxon has also conducted two 90-day oral gavage toxicity studies on PRIMOL 185, an oleum-treated naphthenic medicinal white oil (McKee et al., 1987; Exxon Biomedical Sciences, Inc, 1984; 1985a). Neither of these published studies appears to have been reviewed by MAFF. The specifications for this oil are shown in Table 1. Both studies were conducted in Sprague-Dawley rats (18/sex) at a dose volume of 5.0 ml/kg. This is equivalent to a dose of 4350 mg/kg/d. The total oil intake in the Exxon gavage studies was similar to the total oil intake at the high feed levels of the Shell study (Table 2). In contrast to the Shell studies, no indications of any toxicity were observed in these Exxon studies. Specifically, there were no findings indicative of toxicity to the liver, spleen, kidneys or mesenteric lymph nodes. There were no changes in absolute or relative organ weights and no gross nor microscopic abnormalities. Table 3 compares selected hematological, clinical and pathological indices of toxicity for these organ systems to data from the same laboratory for untreated or water-treated control female rats. (These data were selected for presentation due to their sensitivity to the effects of white oils, as reported by Shell.) The data in Table 3 demonstrates that similar values were obtained for white oil or water (or untreated). Thus, there was no evidence of toxicity due to the white mineral oil.

It is concluded that the NOEL for this white oil in rats, based on these 90-day studies, would exceed 4350 mg/kg/d.

Two significant protocol features of the Exxon gavage studies deserve comment. First, it is likely that the absorption of white oil following a bolus dose would differ somewhat from equivalent intake via the feed. However, there are no data to quantify any such difference, i.e., for comparison to the Shell feeding studies. The Exxon oral gavage studies successfully demonstrated that ingestion of large amounts of white oil for 13 weeks does not necessarily lead to adverse effects. Second, following 13 weeks of oral gavage, a two week non-dosing period preceded study termination and necropsy. Thus, it is conceivable that any minor pathological changes that may have occurred during the study resolved prior to necropsy.

5. **Subchronic Inhalation Studies in Rodents-Technical Mineral Hydrocarbons**

Exxon has conducted subchronic inhalation studies on three representative technical mineral hydrocarbon products which

include an isoparaffinic hydrocarbon boiling between 98-106°C, an isoparaffinic hydrocarbon boiling between 157-176°C, and dearomatized white spirit boiling between 153-187°C (Biodynamics 1977c, 1977d, 1977e, 1977f, 1978a). The inhalation route of exposure was selected because these technical mineral hydrocarbons are relatively volatile and, therefore, inhalation was considered to be a more probable route of potential human exposure. Groups of male and female Sprague-Dawley rats were exposed for 6 hours/day, 5 days/week for 12 weeks to 385 or 1180 ppm of isoparaffinic hydrocarbons (boiling point 98-106°C), to 314 or 992 ppm of isoparaffinic hydrocarbon (boiling point 157-176°C), or to 300 or 900 ppm of dearomatized white spirit (boiling point 153-187°C).

All of the animals survived each exposure period. Body weights were either not different from control or any fluctuations were judged to be biologically insignificant. All of the clinical and hematological values fell within the normal biological ranges. Liver weights and liver to body weight ratios were significantly elevated at several interim sacrifices but were not significantly elevated at the final sacrifice. Additionally, there was no microscopic evidence of liver damage. Kidney weights were significantly elevated only in male rats, and microscopic examination indicated multifocal renal tubular injury as discussed below (Phillips and Egan, 1984a, 1984b; Phillips and Cockrell, 1984).

A large body of information has revealed that the kidney toxicity, now referred to as light hydrocarbon nephropathy, is associated with the presence of a low molecular weight protein (alpha-2<sub>s</sub>-globulin) in male rats. The specific pathology (hyaline droplet formation leading to proximal convoluted tubular cell degeneration and necrosis) appears to result from inefficiencies in the catabolism of this molecule in male rat kidney. However, there is no evidence of similar injury in female rats, mice, or other species (Alden, et al., 1984). Thus, it is believed that light hydrocarbon nephropathy is a sex/species-specific response without clinical significance in man (Kloss and Bus, 1985). Other than this specific effect, there was no evidence that any of the three technical mineral hydrocarbons produced any significant cumulative toxicity.

#### 6. Chronic Toxicity/Carcinogenicity Dietary Studies In Rodents-Mineral Hydrocarbons

Three published chronic feeding studies have been conducted on liquid, semi-liquid or solid mineral hydrocarbons. Schmahl and Reiter (1953) fed 30 rats 2% white mineral oil in the diet for 500 days (or apparently until spontaneous death). Assuming that an adult rat consumes 60 grams of food per kilogram of bodyweight per day, this would represent an average daily intake of approximately 1200 mg/kg/d. One rat developed a tumor on the

bifurcation of the uterus after 890 days. This tumor was not considered to have been treatment related. Otherwise, there were no apparent differences between treated and control animals.

The results of a two year feeding study were reported by Shubik et al. (1962). Groups of approximately 50 male and 50 female rats were fed either of five petroleum waxes (which differed in UV absorptivity at 290 nm) at a dietary concentration of 10%. Using the assumption listed above, this would correspond to an average daily consumption of 6000 mg/kg/d. Survival, body weight changes and all pathologic findings were similar in test and control groups. Thus, there were no toxicologic or pathologic findings attributable to treatment.

A more comprehensive 2 year feeding study was reported in 1965 (Oser et al., 1965). Although this was a study of petrolatums, it is relevant to this discussion because food grade petrolatums are composed of >50% white mineral oil. In this study, rats (50/sex/group) were fed diets containing 5% of one of three grades of petrolatum which met either U.S. Pharmacopeia (USP) XVI or National Formulary (NF) XI criteria. This feed concentration corresponds to an approximate average daily intake of 3000 mg/kg/d. Experimental parameters included body weights, hematology, blood glucose, blood urea nitrogen, urinalysis, organ weights and extensive histopathology. No significant differences were reported between treatment and control groups for any of the parameters investigated. Survival and body weight gain were similar in test and control animals. There were no striking differences in hematological or clinical chemistry measurements. There was suggestive evidence of an elevated WBC count in petrolatum-fed female rats. However, the significance of these data are unclear because no statistical analyses (and no fiducial limits) were reported, and the WBC values in the control females exhibited an unexplained decline with age. The autopsy findings were comparable in all groups and the few histologic observations appeared to be related to the geriatric state of the rats rather than to the dietary treatments. Thus, there was no evidence that chronic ingestion of mineral hydrocarbons produced either chronic toxicity or cancer in rats.

#### 7. Summary - Long-Term Toxicity of Liquid Mineral Hydrocarbons

The weight of the evidence indicates that liquid mineral hydrocarbons with the proper refining, regardless of distillation range, are without potential for long term toxicity. Published and unpublished subchronic and chronic toxicity studies of liquid mineral hydrocarbons, conducted by feeding, oral gavage or inhalation routes of exposure, have been mostly without any substantive toxic effect. The only studies available to date which have resulted in findings of concern

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were the two unpublished subchronic feeding studies conducted by Shell. These apparent inconsistencies in the data are not fully understood and point to the possible need for further studies. However, these apparent inconsistencies in the data also indicate that the Shell studies should not form the sole basis for human health assessment or new regulatory action.

## B. Carcinogenic Potential Of Liquid Mineral Hydrocarbons

### 1. Dermal Carcinogenicity Bioassays-White Mineral Oils

The carcinogenicity of crude oil fractions and refined petroleum distillates has been studied for over 60 years. Much of this work was conducted in mice via the dermal route of exposure. Early studies demonstrated that unrefined distillates, which had been associated with skin cancer in man (Leitch, 1924), contained PAH and were capable of inducing skin tumors in mice as well as men (Twort and Fulton, 1929; Twort and Twort, 1931; Twort and Twort, 1933; Twort and Lyth, 1939; Cook, 1958). Studies commissioned by Standard Oil of New Jersey, a predecessor of Exxon, conclusively demonstrated that unrefined vacuum distillates were carcinogenic and that the carcinogenic activity was associated with the aromatic fractions of these distillates. Further, the paraffinic fraction remaining after removal of the aromatics (i.e., the raffinates) were inactive in dermal carcinogenesis bioassays (Smith et al., 1951; Sunderland, 1951).

Studies with medicinal white oils indicate that these materials are not carcinogenic. Within Exxon, a medicinal white oil (brand name PRIMOL 185) has been used routinely as a negative control material and vehicle in many dermal carcinogenicity studies. Since 1975, only one mouse of 1140 mice (less than 0.1%) treated with PRIMOL 185 has developed a tumor, and it was a benign papilloma. All 1140 mice from these studies were examined grossly and microscopically for skin tumor induction (published in part in McKee et al., 1986; McKee and Lewis, 1986; Biles et al., 1988; McKee et al., 1989a; McKee et al., 1989b). This result is consistent with the evidence that spontaneous skin tumors are rare in the C3H mouse (Squire et al., 1978). There was no evidence that the white oil reduced the life span of the mice. Finally, approximately 450 of the white oil treated mice were subjected to extensive histopathological evaluation. The only visceral tumors which were relatively common were hepatocellular carcinomas (published in part in McKee et al., 1986; Biles et al., 1988), a tumor type with high spontaneous incidence in this mouse strain (Squire et al., 1978). Thus these data indicated that repeated dermal treatment with medicinal white oil did not induce cancer of the skin or visceral organs and also did not cause chronic toxicity.

Numerous studies on solvent-extracted lubricant base oils also indicate that white mineral oils (which are derived from

the base oils by further refining) are noncarcinogenic (Doak et al., 1983; Gradiski et al., 1983; Halder et al., 1984; Kane et al., 1984). In 1984, the International Agency for Research on Cancer (IARC, 1984) concluded, "There is no evidence that severely solvent-refined oils [class 3] are carcinogenic to experimental animals". These published data are further supported by other unpublished studies of solvent-extracted lubricant base oils (Exxon Corporation, unpublished data). The tested samples represented a broad range of crude oils, extraction solvents and extraction severities. Some of the samples were also hydrogen treated. More than 2000 (2250) lubricant base oil treated mice have been examined. The data (summarized in Table 4) indicate that solvent-extracted base oils are not dermal carcinogens. The one sample which produced a response considered clearly indicative of carcinogenic potential (i.e., 4/40), was only mildly solvent extracted and not representative of commercial production. Otherwise, the data indicate that high quality lubricating oils derived from a variety of paraffinic and naphthenic crude oils are neither toxic nor carcinogenic to the skin. Exxon also has evidence that dermal treatment with petroleum hydrocarbons, including those materials which are clearly carcinogenic to the skin, does not result in visceral tumors (Freeman et al., 1989).

## 2. Miscellaneous Carcinogenicity Bioassays-White Mineral Oils

Several published studies indicate that mineral oils, including white mineral oils and petrolatum, can elicit injection site neoplasms. Tumors have been observed following injection or implantation by the intraperitoneal, intramuscular or subcutaneous routes of administration (Schmahl and Reiter, 1953; Oser et al., 1965; Potter and Robertson, 1960; Potter and Boyce, 1962; Rask-Nielsen and Ebbesen, 1965; Shubik et al., 1962). However, the significance of these tumors has been controversial since their discovery. Potter and Boyce (1962) drew attention to the fact that these tumors could also be induced by inert materials. Prigal (1967) noted the possibility that tumor formation in these studies might have been secondary to irritation, and also, that mineral oil injection in humans has not been associated with the onset of cancer. IARC (1984; 1987) concluded that "the significance of production of plasma cell tumors is difficult to interpret" and there was inadequate evidence that highly refined oils were carcinogenic to animals.

The effects of chronic inhalation of mineral oil (apparently a purchased white oil meeting National Formulary specifications) was assessed by Wagner and coworkers (1964). The oil was composed of naphthene-base saturated hydrocarbons having a molecular weight of 350-410 (approximately 95% naphthenes and 5% paraffins). Five species of animals (dog, rabbit, rat, hamster, and mouse) were exposed daily for periods of from one year to 26 months to a mist of petroleum base oil. Exposure levels were 5

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mg/m<sup>3</sup> and 100 mg/m<sup>3</sup>. Histologic examination of tissues indicated pulmonary alveolar and hilar lymph node oil deposition. Lipid granuloma formation was noted in the high exposure group in dogs and rats. In addition, the dogs and rats from the high dose group showed significant increases in alkaline phosphatase activity. At the low dose of 5 mg/m<sup>3</sup>, there were no indications of toxicity and no carcinogenic effects reported by the authors.

An additional study of a solvent-extracted paraffinic base oil resulted in no evidence of tumor initiating or tumor promoting potential in a two-stage carcinogenicity bioassay in CD-1 mice (Gerhart et al., 1988).

### 3. Dermal Carcinogenicity Bioassays-Mineral Seal Oil

Dermal carcinogenicity testing has also been conducted on a mineral seal oil meeting US FDA specifications for a technical white mineral oil (McKee and Scala, 1986; Bushy Run Research Center, 1985; data in Biles, et al., 1988). The mineral seal oil was an acid-treated atmospheric distillation product with a boiling range of approximately 254-321°C. This specification of mineral seal oil distinguishes it from the white mineral oils derived from vacuum distillates, e.g., the medicinal white oils. In these studies, mineral seal oil was demonstrated to elicit tumors in the skin of mice. However, it is not mutagenic in the Ames Salmonella test and it contains only very low concentrations of polycyclic aromatic hydrocarbons (approximately 0.2 wt% 3-ring aromatics). Also, neither the whole mineral seal oil nor any chemical fractions, including a 3-rings aromatics fraction, produced evidence of tumor initiating activity in a two stage tumor initiation/tumor promotor study (McKee, et al., 1989). Thus, mineral seal oil did not appear to be a conventional genotoxic carcinogen. Rather, it exhibited weak tumor promoting properties which may have been secondary to significant dermal toxicity (skin irritation) and hyperplasia induced by the chronic skin painting. It is considered that the carcinogenic response of mice to mineral seal oil may have been a threshold phenomenon. That is, unlike genotoxic carcinogens, at low doses (i.e., below the threshold at which toxicity is observed) there would not be a carcinogenic risk. Therefore, the biological properties as well as specifications of mineral seal oil distinguish it from the white oils derived from vacuum distillates, e.g., the medicinal white oils.

## C. Genetic Toxicity Potential of Liquid Mineral Hydrocarbons

### 1. White Mineral Oils

Published genetic toxicity evaluations of highly refined and medicinal grade white oils indicate that these materials are not genotoxic and support the conclusions of that these

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materials are not carcinogenic. Medicinal white oil (Exxon PRIMOL 185) has been tested in vitro for mutagenic potential in Salmonella and mouse lymphoma assays (McKee and Przygoda, 1987). The Salmonella assay was conducted by standard methodology (Ames et al., 1975; OECD, 1981; EEC, 1984). Test concentrations of 10-10,000  $\mu$ g/plate elicited no evidence of increased mutagenic activity. The mouse lymphoma study (conducted according to Clive et al., 1979; OECD, 1981; EEC, 1988) elicited no evidence of mutagenic activity at test concentrations of 50-1000  $\mu$ g/ml. The results of these studies were consistent with the negligible concentrations of PAH in medicinal white oils.

Data for solvent-extracted paraffinic oils indicate that such base oils, and consequently the more highly refined white oils, are not genotoxic. Blackburn and coworkers (Blackburn et al., 1986; Blackburn et al., 1984; Roy et al., 1988) have developed a sensitive method of testing petroleum hydrocarbons for genotoxic activity in Salmonella. These results were then compared with results of dermal carcinogenesis bioassays. For 39 samples, mutagenic activity in the modified Salmonella assay was highly correlated ( $r = 0.85$ ) with dermal carcinogenic activity. It was concluded that for mineral oils with median boiling points above 260°C, the PAH components were largely if not entirely responsible for both the carcinogenic and mutagenic activities (Roy et al., 1988). Thus, it was demonstrated that medicinal white oils<sup>1</sup> and solvent-extracted lubricant base oils are not mutagenic to Salmonella.

Several additional solvent-extracted base oils have been evaluated in a battery of genotoxicity tests including Salmonella, mouse lymphoma, and rat bone marrow cytogenetics (Conaway et al., 1982). Seven samples were tested including 5 paraffinic oils ranging in viscosity, from 64 to 990 Saybolt Universal Seconds (SUS), and 80 and 2000 SUS naphthenic oils. The paraffinic oils were tested in all three assays. The naphthenic oils were tested in the mouse lymphoma and bone marrow cytogenetics assays only. The paraffinic base stocks did not significantly increase the mutation frequencies in any of the five Salmonella strains. The mouse lymphoma data were reported as equivocal; significant increases in mutagenic frequency were found at some concentrations in the presence of metabolic activation. However, none exhibited a clear dose-response relationship. In the rat bone marrow cytogenetics assay, a 331 SUS paraffinic oil elicited a statistically significant response at the highest dose level only (2.0 g/kg orally, daily for five days). All other studies were completely negative. Because of the equivocal nature of the mouse lymphoma studies and the single positive response in the bone marrow assay reported by Conaway et al. (1982), Exxon conducted genotoxicity tests on a series of 5 solvent-extracted paraffinic

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<sup>1</sup> All Esso White Oils sold in the Europe for direct or indirect (incidental) food use have mid-boiling points well in excess of 260°C.

base oils ranging in viscosity from 60 to 600 SUS. None of these oils were genotoxic to five common strains of Salmonella (concentrations of 1,000-50,000 µg/plate after solubilization in DMSO and in the presence of metabolic activation). These samples also were not genotoxic in a mouse micronucleus assay (an in vivo test) following intraperitoneal doses of 1.0-5.0 g/kg (Exxon Biomedical Sciences, Inc., unpublished). Additionally, McKee and Przygoda (1987) reported no evidence of genotoxic potential for two solvent-extracted paraffinic oils (90 SUS and 150 SUS) in Salmonella (strain TA98), mouse lymphoma or in vitro morphologic transformation assay systems. Thus, considered together the evidence indicates that highly refined solvent-extracted oils and consequently white mineral oils (since these are more highly refined than the solvent-extracted oils) are non-genotoxic.

## 2. Technical Mineral Hydrocarbons

The potential for in vivo genetic toxicity of technical mineral hydrocarbons has been assessed by Exxon (unpublished) in vivo using the dominant lethal assay. Male Sprague-Dawley rats were exposed by inhalation 6 hours/day for 5 consecutive days to exposure levels of 400 or 1200 ppm of isoparaffinic hydrocarbons (98-106°C), 300 or 900 ppm of isoparaffinic hydrocarbons (157-176°C), and 300 or 900 ppm of dearomatized white spirit (153-187°C). (Biodynamics 1978c, 1980). Mutagenic potential was evaluated by a sequential mating process which extended over 6 weeks.

There were no significant effects on treated male rats or on implantation or fetal death rates. Additionally, there was no evidence of pathologic damage to the testes of the adult male rats. Thus, these data indicated that these representative technical mineral hydrocarbons were not testicular toxicants or in vivo genotoxicants. This absence of a dominant lethal response indicated that these materials were not male reproductive toxicants.

Consistent with these observations, Gochet and coworkers (1984) have reported that white spirit was inactive in the Salmonella assay, sister chromatid exchange assays in human lymphocytes, and in vivo in a mouse bone marrow assay. These data, along with the dominant lethal data summarized above, indicate that technical mineral hydrocarbons are unlikely to be mutagens or male reproductive toxicants.

## D. Developmental And Reproductive Toxicity Potential

### 1. Developmental Toxicity-White Mineral Oil

Data from published Exxon studies provide evidence that a white mineral oil product, Exxon PRIMOL 185 (CAS # 8042-47-5) is

not a developmental toxicant (McKee et al., 1987a). In this study, the white oil treatment group served as a vehicle control for another test material. Pregnant Sprague-Dawley rats were treated by oral gavage with the white oil at 5.0 ml/kg/day (4350 mg/kg/d) on gestational days 6-19. This dose level exceeds the EEC recommended maximum dose of 1000 mg/kg. Comparison of these data with those from water treated control animals from the same laboratory are presented in Table 5. For all studies, the females were approximately 9-11 weeks of age at the time of mating. The protocol for these studies was the same with one notable exception: the water control animals received four fewer treatments as they were only dosed on gestational days 6-15.

The malformation rate (the number of malformations per litter) observed in the two white mineral oil treated groups was comparable or lower than that observed in the three water control groups. In addition, there was no evidence of fetal toxicity as indicated by a lower incidence of resorptions, no alteration in the fetal sex ratios and no reduction of crown-rump length. The apparent increase in fetal weights was not attributed to treatment and was considered the result of the lower number of both implantations/litter and fetuses/litter that was observed in the mineral oil treated animals. Collectively, these results provide evidence that white mineral oil products are not fetotoxic or teratogenic.

## 2. Developmental Toxicity-Technical Mineral Hydrocarbons

Exxon has conducted developmental toxicity studies (unpublished) on three representative products which include an isoparaffinic hydrocarbon boiling between 98-106°C, an isoparaffinic hydrocarbon boiling between 157-176°C, and a dearomatized white spirit boiling between 153-187°C (Biodynamics, 1978b, 1979).

In the developmental toxicity studies, pregnant Sprague-Dawley rats were exposed by inhalation for 6 hours/day on days 6-15 of gestation to exposure levels of 400 or 1200 ppm of isoparaffinic hydrocarbons (98-106°C); to 300 or 900 ppm of isoparaffinic hydrocarbons (157-176°C), or 300 to 900 ppm of the dearomatized white spirit (153-187°C). On gestational day 21 the animals were sacrificed and the uterine contents were examined.

There was no evidence of maternal or fetal toxicity. There were no significant differences in number of fetuses per litter, mean fetal weight, or mean crown-rump length. Additionally, there was no evidence of visceral or skeletal malformations or variations. Thus, these data indicated that the three representative technical mineral hydrocarbon species were not developmental toxicants.

### 3. Reproductive Toxicity-White Mineral Oil

Published studies by Exxon in which white mineral oil was used as the control vehicle for synthetic coal liquids indicate that white mineral oil does not pose a reproductive risk. Similar reproductive parameters have been observed in a control group (i.e., air exposed) from an inhalation developmental study conducted during the same time period in the same laboratory.

McKee and coworkers (1987b) administered via oral gavage 4350 mg/kg/day (5 ml/kg/day) white mineral oil (Exxon PRIMOL 185) to groups of rats for 5 days/week for 13 weeks. This dose concentration exceeds the EEC recommended maximum of 1000 mg/kg. Each group included 72 females and 36 males. Following the 13th week each male was housed with 2 females. Mated females were maintained through gestation until day 21 of lactation. At lactation day 21 all adult females and pups were examined. A similar protocol was used in the inhalation study used for comparison (Exxon Biomedical Sciences, Inc., 1983).

Comparison of white mineral oil treated groups to the air control group (Table 6) revealed no evidence of reproductive toxicity. There were no significant differences in the number of pups delivered/litter, the number of live births/litter, the number of malformed pups/litter or pup survival at lactation days 4, 14, and 21.

Another study was reported in an editorial to the British Medical Journal in 1948. There, it was reported that "daily consumption by rats of raw or heated liquid paraffin (British Pharmacopoeia), in doses up to 2 ml. per 200 g. body weight daily, had no demonstrable effect on the growth or reproduction of rats over two generations". Unfortunately, no other details were provided.

#### E. Evidence Of Absorption And Metabolism In Experimental Animals

Studies of the absorption and metabolism of white mineral oils have historically been complicated by their complex nature. As a result, most of the experimental studies of the absorption and metabolism of mineral oils have been qualitative studies. The available data has been adequately reviewed by the International Agency for Research on Cancer (1983), McTurk and Eckardt (1960) and Lester (1979). Several studies indicate that normal, branched and cyclic paraffins are absorbed from the mammalian gastrointestinal tract. There are two reports that absorption of n-paraffins is inversely proportional to the carbon chain length with little absorption above C<sub>30</sub>. Boitnott and Margolis (1970) indicated that n-paraffins may be absorbed to a greater extent than iso- or cyclo-paraffins, at least with respect to the carbon chain lengths likely to be present in mineral oil.

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Mineral hydrocarbons absorbed from the gastrointestinal tract appear to be distributed to a number of tissues, including the lymph nodes (particularly the mesenteric nodes), liver and spleen (reviewed in IARC, 1984; McTurk and Eckardt, 1960; Lester, 1979). As has been reported for humans, this distribution can then result in foreign body reactions typified by macrophages and giant cells. Interestingly, until now there has been no association in animal studies between deposition of mineral oil in tissues and toxicity. Although mineral oils are deposited in internal tissues, data indicate that this deposition can be reversible. The metabolism of paraffins via oxidative pathways has been conclusively demonstrated both in vivo and in vitro. Thus, n-paraffins with carbon chain length less than C<sub>20</sub>, and possibly less than C<sub>32</sub>, can be metabolized to some extent to the corresponding alcohols and fatty acids and incorporated into lipid metabolism. Similar products have been identified from the oxidative metabolism of iso- and cyclo-paraffins (at least for carbon chains ≤ C<sub>7</sub>). The work of Tulliez et al. (reviewed in Lester, 1979), although unconfirmed, suggests that iso-paraffins are metabolized to the greatest extent.

F. Effect Of Dietary Mineral Oil Administration On Nutritional Status

The high dose of 1500 ppm in the Exxon dietary studies with paraffinic white mineral oils (Biodynamics, 1977a,b) was selected based on anecdotal information that higher doses could interfere with vitamin A absorption from the gut. The effect of mineral oil on absorption of fat soluble vitamins (A, D, K and E) was extensively reviewed by McTurk and Eckardt (1960). Overall, mineral oil appeared to have the greatest effect on Vitamin A absorption. The greatest reduction in absorption occurred when mineral oil was provided in the diet (rather than separate from the diet), and when the basal diet contained an inadequate supply of the vitamin. The dietary doses of mineral oil used in the Exxon Studies did not appear to alter the absorption of vitamins A or D since levels of these vitamins were similar in control and treated dogs of both sexes (Biodynamics, 1977a,b). However, the effect of higher dietary concentrations of mineral oil on vitamin absorption has not been routinely assessed as a part of subchronic or chronic feeding studies. Potential impact on the nutritional status of animals fed higher dietary concentrations of mineral oil represents an additional confounding variable in interpretation of study results.

IV. EFFECTS ON HUMANS OF LONG TERM EXPOSURE TO MINERAL HYDROCARBONS

Examination of human autopsy tissue samples indicate that chronic exposure to mineral oils may lead to selective tissue accumulation of these oils. Wiland and Smith (1957) examined spleens from 432 autopsy and 133 splenectomy cases and reported that the incidence of "follicular lipidosis" (defined as lipid globules in the lymphoid follicles of the spleen) increased with age until approximately 40, after which the incidence leveled off. The incidence was significantly

higher in males than females. Because the incidence of follicular lipidosis was similar in the autopsy and splenectomy groups, it appears that the lipid deposits were not causally related to death.

Rose and Liber (1966) used thin-layer chromatography and gas chromatography to study the chemical nature of the lipid vacuoles which occur in human tissues. The authors examined the spleens of 12 corpses (seven of these spleens displayed follicular lipidosis). The vacuoles were found to contain primarily  $C_{21}$  to  $C_{23}$  saturated hydrocarbons which were hypothesized to originate from mineral oil. Although mineral oil may contain some shorter carbon chain hydrocarbons, the authors suggested that they might be metabolized more rapidly and accumulate to a lesser degree than those longer hydrocarbon chains which might occur in the oil. This speculation was based on evidence for oxidation of  $C_9$  -  $C_{18}$  alkanes. However, it does not address the lack of accumulation of saturated hydrocarbons of  $>C_{23}$  which may also be present in mineral oil.

Boitnott and Margolis (1966a) also used analytical techniques to identify the oil droplets in autopsy specimens. In lymph nodes from 49 of 61 consecutive autopsies on persons 20 years of age and older, they found large oil droplets in 78% of the specimens. Analysis by thin layer chromatography (and also mass spectrometry in 3 cases) indicated that the oil droplets probably consisted of saturated liquid hydrocarbons. The authors suggested that because there are probably no other likely sources of saturated hydrocarbons in human tissues, the material was probably mineral oil. However, as reviewed by Gerarde and Gerarde (1961), hydrocarbons of a wide range of structures, including saturated hydrocarbons, originate from food sources. In another analysis of spleens from an undefined population, Liber and Rose (1967) stated they found follicular lipidosis in 62 out of 100 cases. Because the authors gave no information about the population from which these cases were selected, nor any information on the age or year of death of these cases, the significance of this finding can not be determined.

Liber and Rose (1967) also examined 199 human spleens collected by the Armed Forces Institute of Pathology from 1862 to 1956. Whereas no cases of follicular lipidosis were identified in 115 spleens dating from 1862 to 1937, 23 cases were found in the 70 spleens dating from 1938 to 1956 (fourteen spleens were not examined because they showed severe autolysis). Dincsoy and coworkers (1982) examined 824 consecutive liver biopsy specimens gathered from 1978 to 1980 and 240 liver biopsies obtained between 1952 and 1953. Whereas 4.6% of the more recent samples had lipogranulomas (and no evidence of alcoholic liver disease), an incidence of only 1.7% was observed in the older specimens. In a more recent study of the occurrence of follicular lipidosis, Cruickshank (1984) examined the change in the incidence of follicular lipidosis over a period of 24 years in both Toronto and Richmond, Virginia. Approximately 20% of the spleens obtained from individuals from Toronto and Richmond who died during 1946 showed follicular lipidosis. Spleens obtained in 1956 showed twice the

incidence of those in 1946. By 1970, the incidence had increased to 80% in Toronto and 68% in Virginia. In addition to the increased incidence in 1970, the amounts of the mineral oil in the spleens also increased. Despite this apparent increase with time of the incidence of follicular lipidosis, there does not appear to have been any adverse effect on human health.

Cruickshank (1984) also examined spleens obtained at autopsy from individuals in 41 countries. His results were similar to those of Wiland and Smith (1957). In specimens from Toronto, Canada, both the incidence and amount of mineral oil increased with age until the age of 50, after which the incidence leveled off. No evidence of follicular lipidosis was found in infants younger than 1 year. In contrast, the overall incidence in subjects over 11 years of age was 75% and males showed a significantly higher incidence than females. Thus, again the incidence appeared to be related to age. Spleens of individuals from undeveloped countries, such as India, Mexico, and Zambia, showed no or low incidence of follicular lipidosis. Spleens from individuals from developed countries, such as Canada, U.S., U.K., and European countries, showed up to a 50% incidence of follicular lipidosis. Within these countries, no racial or ethnic factors appeared to influence the incidence of the lesion. These data are suggestive of an environmental etiology.

The source of the (presumed) mineral hydrocarbons in human tissues has been hypothesized to be food (Boitnott and Margolis, 1966a; Dincsoy et al., 1982; Cruickshank, 1984) as no consistent links could be made to medicinal use of mineral oil. Cruickshank (1984) suggested that the likely source of the mineral oil was from its use in the packaging and display of foods.

Accumulation of mineral oil in the liver, spleen, and lymph nodes has generally been regarded as not harmful (Boitnott & Margolis, 1966b, Lester, 1979). In an analysis of 300 consecutive autopsies, Kelsall & Blackwell could not find any correlation between the presence of lipid clusters and diseases of the liver, pancreas, or gastrointestinal tract. Liber & Rose (1967) also could find no association between age, disease, and the presence of mineral oil in the liver. Dincsoy et al. (1982) and Cruickshank (1984) also concluded that lipogranulomas in human tissues are incidental to human health. In a review, Lester (1979) concluded that chronic oral ingestion of paraffins is characterized by accumulation and possibly some metabolism, rather than by any overt pathological changes.

In contrast, two rather poorly documented case histories of adverse effects on human health have been reported. Blewitt and coworkers (1976) reported a case of a 33-year old male who had liver damage that appeared to be associated with mineral oil deposits. Examination of the individual's liver showed inflammation and scarring. This damage appeared to be associated with deposits of mineral oil in the portal triads. This individual estimated he had ingested one tablespoon of mineral oil per day for two months but admitted he had a

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poor memory in regard to his consumption of medicines. Nochomovitz and coworkers (1975) also reported a case in which mineral oil (defined as liquid paraffin and presumed to be medicinal white oil) ingestion reportedly had a deleterious effect on an individual. Although the precise cause of death was not determined, this individual apparently followed "irrational dietary habits" and ingested large amounts of mineral oil over many years. At death, mineral oil deposits were found in the small intestine, abdominal lymph nodes, liver, spleen, and lungs. Chromatograms (GLC) of a liver extract and liquid paraffin were similar. The authors attributed death to unrestricted ingestion of mineral oil.

## V. DISCUSSION

The data summarized in this document indicate that, for the most part, liquid mineral hydrocarbons, possess a low potential for toxicity. For white mineral oils derived from vacuum distillates, extensive data are indicative of no mutagenic or carcinogenic risk to humans. In addition, the available data indicate that white mineral oils do not pose a developmental or reproductive risk. Regarding the long term toxicity of white mineral oils, evidence of toxic potential has been reported only in two unpublished experimental studies (Shell Research Limited 1987a,b). Other toxicity studies have been conducted with oils derived from both naphthenic and paraffinic crude types, at different doses and in rats as well as dogs, but have not resulted in significant toxicity.

Some possible explanations may be offered for the apparently discordant subchronic experimental results. Several factors related to the physical/chemical characteristics of the white oils could be postulated to have affected study outcome, including crude source (naphthenic versus paraffinic), severity of refining and processing history (oleum versus hydrogenation) and viscosity. If any of these parameters affected the distribution of hydrocarbon components in the tested oils, the absorption, disposition and metabolism of these hydrocarbon components could have varied among these petroleum products. Alternatively the toxicity reported by Shell may have resulted not from the white mineral oil per se, but rather from the presence of undesirable contaminants. Variability in the study protocols could also have contributed to perceived differences in toxicity, for example, due to differences in administered dose or differences in the scope of the investigations.

The unpublished studies conducted by Shell utilized two naphthenic white mineral oils. They differed from each other by refining history as well as product specifications. An oleum-treated oil of low viscosity (26 cSt at 40°C) was compared with a hydrogenated oil of high viscosity (69.2 cSt at 40°C). Because the oleum-treated oil was the more toxic in these studies, it could be surmised that the oleum-treatment influenced its toxicological properties. It is not clear how oleum-treatment could have resulted in a more toxic oil,

except possibly via a residual contaminant. However, the high purity of these products indicates that this is not likely. Indeed, in studies conducted by Exxon, both oleum-treated and hydrogenated paraffinic white mineral oils were similarly non-toxic in feeding studies with both rodent and non-rodent species.

Because the two Shell oils also differed in viscosity, it could be considered that viscosity may be an important toxicological variable for white mineral oils. Viscosity differences are indicative of differences in molecular size. Molecular size could influence absorption and metabolism, i.e., limited data suggest that absorption and metabolism are inversely proportional to molecular size. It could be further speculated that sex differences in absorption/metabolism could explain the sex differences in toxicity observed by Shell. Shell reported that concentrations of the lower viscosity oleum-treated oil in selected rat tissues (at the 2% dietary feeding level) were approximately 25-55% greater than the corresponding concentrations of the higher viscosity hydrogenated oil. Also, the concentrations of oleum-treated oil in female rat tissues were several times greater than in male rat tissues. Thus, the highest concentrations were found in the groups which exhibited the most significant toxicity. However, in the Exxon feeding studies, a range of viscosities (12.3-65.9 cSt) were represented. No evidence of toxicity was observed, even at daily intakes in rats (e.g., up to 125 mg/kg/d) at which the Shell oils resulted in subtle effects. These data suggest that viscosity may not be an important toxicological variable for white mineral oils.

Crude type can also be addressed as a potential toxicological variable. Unlike the feeding studies conducted by Shell with naphthenic oils, dietary administration of the paraffinic oils by Exxon resulted in no evidence of oil deposition in the mesenteric lymph nodes, liver or spleen, as measured by organ weights and histopathological observation using a lipid-specific stain. This is an important observation because oil deposition appears to occur in humans, albeit without adverse effects on health. It is possible that no deposition of paraffinic oil was observed because the doses employed in those studies were insufficient. Alternatively, the absorption and metabolism of the paraffinic oils could differ from the naphthenic oils, possibly due to differences in hydrocarbon distribution. However, Exxon has also conducted (and published) oral gavage studies in rats using high doses of an oleum-treated naphthenic oil. These studies also resulted in no evidence of either toxicity or oil accumulation (McKee, et al., 1987; Exxon Biomedical Sciences, Inc., 1984; 1985a). Although no data are available to determine whether absorption in the Exxon bolus dose studies was similar to that in the Shell feeding studies, these data suggest that any differences in hydrocarbon distribution due to crude type may not be of biological importance. Of course, because in the Exxon gavage studies the animals were not dosed for two weeks prior to necropsy, it is not known whether any small accumulations of oil or minor pathological changes may have been reversible and resolved during that time.

It does not appear likely that protocol differences resulted in the toxicity differences reported in the Shell and Exxon feeding studies. The Exxon feeding studies included measurements of many of the same experimental parameters as the naphthenic oil studies conducted by Shell. These included histopathology, clinical chemistry, hematology, evaluations for alterations in organ weights and attempts to detect evidence of mineral oil accumulation in the animal tissues. Many of these parameters were also measured in the Exxon oral gavage study on PRIMOL 185. Thus, all of these investigations were complete, well conducted and evaluated similar parameters.

The results of the Exxon-sponsored subchronic toxicity studies of isoparaffinic and dearomatized white spirits also indicated a low order of toxicity. Repeated exposure did produce kidney damage in male rats; however, this effect appears to be sex/species-specific and without clinical significance to man as explained earlier. Data similar to the Exxon subchronic toxicity data have been obtained in studies of less highly refined materials of similar boiling range. Carpenter et al. (1975, 1976), reported that repeated exposure to vapors of Stoddard solvent or kerosene also produced effects in kidneys of male rats, but produced no other evidence of toxicity. The Exxon samples were not in vivo genotoxins or developmental toxins. Similarly, Stoddard solvent and kerosene were inactive in developmental toxicity studies (American Petroleum Institute 1977, 1978) and were also negative in a battery of genetic toxicity tests (Conaway et al., 1982). Thus, based on the absence of toxicity in animal studies, and considering the probable low exposure risks related to the permitted food use of those products, it is evident that technical mineral hydrocarbons in general present minimal toxic hazards to humans. Further, considered together with the data for white mineral oils, these data indicate that there is a low order of toxicity and hence, minimal risk, associated with the entire boiling range of liquid mineral hydrocarbons intended for use in food contact applications.

In summary, experience in humans suggests that exposure to mineral hydrocarbons in the food does not cause adverse health effects. Experimental data from animal studies support the conclusion that white mineral oils present no concerns for chronic toxicity endpoints such as carcinogenicity, mutagenicity, reproductive toxicity or teratogenicity. However, the available animal data for long-term toxicity are not altogether consistent. The occurrence of target organ toxicity in the Shell feeding studies represents, to date, the only indication that repeated exposure to liquid mineral hydrocarbons may entail some risk. At this time, it is not clear whether these effects were the result of a particular hydrocarbon distribution, the presence of contamination or the use of extremely high feed concentrations. It is unlikely that the basis for these differences can be entirely resolved by speculation of similarities and differences between the various study protocols and test materials. However, it is clear that significantly more data exists with regard to liquid mineral hydrocarbon toxicity than originally reviewed by MAFF. Thus, the entire weight of evidence needs to be considered to provide an adequate and balanced assessment of the

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potential health implications associated with the use of liquid mineral hydrocarbons in food applications. Resolution of the outstanding questions may require further study.

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TABLE 3

SELECTED INDICES OF POTENTIAL TOXICITY FOR FEMALE SPRAGUE-DAWLEY RATS FROM EXXON 90-DAY ORAL GAVAGE STUDIES

Test Material	WBC <sup>1</sup> (x10 <sup>3</sup> )	RBC (x10 <sup>6</sup> )	HGB (g/dl)	HCT (%)	ALT (IU/L)	AST (IU/L)	Liv/BW (%)	Kid/BW (%)
PRINOL 185 <sup>2</sup> 5 ml/kg/d (4350 mg/kg/d)	5.5 <sup>3</sup> 0.9 17	7.49 0.46 17	14.3 0.6 17	42.4 2.0 17	67 14 18	44 10 18	3.2 0.2 18	0.66 0.03 18
PRINOL 185 <sup>3</sup> 5 ml/kg/d (4350 mg/kg/d)	5.1 1.4 18	7.68 0.41 18	15.4 0.4 18	44.2 1.5 18	65 10 18	36 8 18	3.3 0.2 18	0.65 0.04 18
untreated <sup>4</sup>	7.4 2.4 20	7.25 0.23 20	16.9 0.6 20	44.8 1.8 20	76 15 20	21 6 20	2.6 0.3 20	0.742 0.06 20
water <sup>5</sup> 10ml/kg/d	6.1 2.0 19	7.00 0.32 19	14.8 0.6 19	43.6 1.7 19	86 38 19	30 26 19	2.6 0.2 19	0.69 0.06 19
water <sup>6</sup> 1 ml/kg/d	6.3 1.5 15	7.25 0.35 15	15.4 0.8 15	43.1 2.0 15	76 19 15	24 10 15	2.8 0.2 15	0.62 0.04 15
water <sup>7</sup> 1 ml/kg/d	7.0 1.7 20	7.08 0.29 20	15.9 0.6 20	44.7 1.6 20	75 18 20	42 14 20	3.4 0.3 20	0.66 0.06 20

\* All values are mean, S.D., and number of animals.

1. Abbreviations: WBC, white blood count; RBC, red blood count; HGB, hemoglobin; HCT, hematocrit; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Liv/BW, liver/body weight ratio; Kid/BW, kidneys/body weight ratio, IU/L, International Units per liter
- 2-7. Exxon Biomedical Sciences, Inc. Study Nos. 301970 (published as McKee et al., 1987), 305770, 252370, 254370, 252170 and 230370 (published as Daughtrey et al., 1989). All studies were conducted from 1983-1985.

TABLE 1

SPECIFICATIONS OF SHELL AND EXXON MEDICINAL WHITE OILS TESTED FOR SUBCHRONIC TOXICITY

Tested Oil	Supplier	Crude <sup>1</sup> Type	Refining <sup>2</sup> Process	Viscosity (cSt @ 40°C)	Specific Gravity (g/ml @ 15°C)
Liquid Paraffin WOH 24	Shell/Buchanan	N	oleum	25.6	.874
Ondina Oil 68	Shell	N	hydrogenation	69.2	.878
MARCOL 72	Exxon	P	oleum	12.3	.838
MARCOL 82	Exxon	P	hydrogenation	13.8	.842
EZL 550	Exxon	P	hydrogenation	65.9	.854
EZL 600	Exxon	P	hydrogenation	31.6	.870
PRINOL 185	Exxon	N	oleum	35.7	.870

1. Crude Type N: naphthenic  
P: paraffinic

2. Refinery Process: oleum-treatment: treatment of solvent extracted lubricating oil basestocks with oleum.  
hydrogenation: treatment of solvent extracted lubricating oil basestocks with hydrogen under high pressure.

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TABLE 4

SUMMARY OF DERMAL CARCINOGENICITY STUDIES OF SOLVENT-EXTRACTED LUBRICANT BASE OILS (CONTINUED)

<u>SAMPLE NUMBER</u>	<u>PROCESS<sup>1</sup> HISTORY</u>	<u>CRUDE<sup>2</sup> SOURCE</u>	<u>VISCOSITY<sup>3</sup> GRADE</u>	<u>ISCOSITY<sup>4</sup> INDEX</u>	<u>TUMOR<sup>5</sup> RESPONSE</u>
1294	SE/H	S. LOUIS	150	89	0/50
1307	SE/H	W. T. SOUR	150	89	0/50
1309	SE/H	B. S. MIX	150	97	0/50
961	SE/H	TIJUANA	80	NA	0/40
999	SE/H	COASTAL	80	NA	1/40

1. SE = Solvent extraction; H = Hydrogen treatment;
2. ARAB LT. = Arabian light crude; ARAB HVY = Arabian heavy crude; W. CAN. = Western Canadian; S. LOUIS. = South Louisiana crude; W. T. SOUR = West Texas Sour crude; B. S. MIX = Brent Sea mixed crude; TIJUANA/COASTAL = naphthenic crudes (remainder were paraffinic);
3. Saybolt universal seconds (SUS) at 100°F
4. Empirical, unitless number indicating the effect of temperature change on the kinematic viscosity of an oil
5. # tumor bearing animals (papillomas and carcinomas) per # mice originally placed on test.
6. NA = not available

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TABLE 4

SUMMARY OF DERMAL CARCINOGENICITY STUDIES OF SOLVENT-EXTRACTED LUBRICANT BASE OILS

<u>SAMPLE NUMBER</u>	<u>PROCESS<sup>1</sup> HISTORY</u>	<u>CRUDE<sup>2</sup> SOURCE</u>	<u>VISCOSITY<sup>3</sup> GRADE</u>	<u>VISCOSITY<sup>4</sup> INDEX</u>	<u>TUMOR<sup>5</sup> RESPONSE</u>
963	SE	ARAB LT.	150	NA <sup>3</sup>	0/40
985	SE	ARAB LT.	150	102	0/40
898	SE	ARAB LT.	150	101	0/40
1008	SE	ARAB LT.	150	105	0/40
1009	SE	ARAB LT.	150	85	4/40
1141	SE	ARAB LT.	150	105	0/50
1142	SE	ARAB LT.	150	95	0/50
1143	SE	ARAB LT.	150	110	0/50
1265	SE	ARAB LT.	150	100	0/50
987	SE	ARAB LT.	600	87	0/40
991	SE	ARAB LT.	600	88	0/40
1261	SE	ARAB LT.	600	94	0/50
1266	SE	ARAB LT.	600	89	0/50
1296	SE	ARAB HVY.	175	93	1/50
1298	SE	ARAB HVY.	175	98	0/50
1301	SE	ARAB HVY.	600	82	0/50
1302	SE	ARAB HVY.	600	88	0/50
1263	SE	W. CAN.	150	88	0/50
1300	SE	S. LOUIS	150	79	0/50
1306	SE	W. T. SOUR	150	90	0/50
1308	SE	B. S. MIX	150	96	0/50
1177	SE/H	ARAB LT.	60	97	1/50
1016	SE/H	ARAB LT.	75	NA	0/40
1255	SE/H	ARAB LT.	75	NA	0/40
992	SE/H	ARAB LT.	90	103	0/40
994	SE/H	ARAB LT.	150	103	0/40
1007	SE/H	ARAB LT.	150	101	2/40
1140	SE/H	ARAB LT.	150	NA	0/50
1144	SE/H	ARAB LT.	150	106	0/50
1147	SE/H	ARAB LT.	150	NA	0/50
1270	SE/H	ARAB LT.	150	103	0/50
995	SE/H	ARAB LT.	600	96	0/40
1262	SE/H	ARAB LT.	600	97	0/50
1271	SE/H	ARAB LT.	600	90	0/50
1297	SE/H	ARAB HVY.	175	96	0/50
1299	SE/H	ARAB HVY.	175	101	0/50
1303	SE/H	ARAB HVY.	600	93	1/50
1304	SE/H	ARAB HVY.	600	84	0/50
1305	SE/H	ARAB HVY.	600	87	0/50
993	SE/H	W. CAN.	90	89	0/40
1017	SE/H	W. CAN.	150	NA	0/40
1264	SE/H	W. CAN.	150	90	0/50
1293	SE/H	S. LOUIS.	150	79	0/50

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TABLE 6

LACK OF REPRODUCTIVE TOXICITY OF WHITE MINERAL OIL

Test Material	# Pups Delivered	# Live Births	Day 4	% Survival	Day 21	# Malformations
PRIMOL 165 <sup>1</sup> 4350 mg/kg/d	11.7 ± 2.6 <sup>2</sup>	11.2 ± 2.9	94	91.1	90.2	1
PRIMOL 165 <sup>1</sup> 4350 mg/kg/d	11.1 ± 2.7	10.7 ± 2.8	90	86.9	86.9	2
Air <sup>3</sup>	10.63 ± 3.1	9.5 ± 3.5	94	90.5	89.5	.1

1. Published in McKee, et al (1987).

2. Mean ± S.D.

3. Exxon Biomedical Sciences, Inc. (1983).

TABLE 5

## LACK OF DEVELOPMENTAL TOXICITY OF WHITE MINERAL OIL

Test Material	# Litters	# Malformations	Malformation Rate	# Resorptions/ litter	Crown-rump length (mm) M	Fetal Weight (g) M	Male/Female ratio
RINOL 185 <sup>3</sup> 4350 mg/kg/d	49	3 (1 head)	0.06	0.47 <sup>4</sup> ± 0.68	3.60 ± 0.16	4.23 ± 0.32	1.06
RINOL 185 <sup>3</sup> 4350 mg/kg/d	25	3	0.12	0.06 ± 1.00	3.66 ± 0.14	4.26 ± 0.33	0.92
later <sup>5</sup> 2500 mg/kg/d	20	4	0.20	1.15 ± 0.88	3.55 ± 0.12	3.44 ± 0.26	1.04
later <sup>6</sup> 1000 mg/kg/d	20	2	0.10	0.65 ± 0.6	3.59 ± 0.14	3.51 ± 0.28	1.27
later <sup>7</sup> 800 mg/kg/d	38	4	0.11	0.89 ± 0.98	3.57 ± 0.14	3.49 ± 0.33	0.98

1. Skeletal malformations unless otherwise indicated.

2. Malformations/litter.

3. McKee, et al. (1987c).

4. Mean ± S.D.

5. Exxon Biomedical Sciences, Inc. (1985). Project #352134 (unpublished).

6. Exxon Biomedical Sciences, Inc. (1985). Project #230334 (unpublished).

7. Exxon Biomedical Sciences, Inc. (1986). Project #261634 (unpublished).

### Medicinal White Oil Production

The chemical composition of a white oil is related to both its purity specification and its refining. These products are typically derived from the vacuum distillation process.

By definition, medicinal white oils are composed of saturated hydrocarbons. They are free of aromatics, of unsaturated compounds, of sulphur, nitrogen or chloride compounds and of impurities. They are therefore exclusively composed of a mixture of saturated hydrocarbons which can be either iso-alkanes (paraffins) or cyclo-alkanes (naphthenes).

The average molecular weight of the molecules as well as the ratio between the paraffins and the naphthenes are a function of the refining conditions. The average molecular weight of a medicinal white oil is defined by the distillation conditions, and can vary from below 300 for the lighter grades to above 500 for the heavier grades. The ratio between naphthenes and paraffins is affected by various parameters but the origin of crude oil is the most significant. White oils produced from naphthenic crudes generally have a higher content of naphthenes; this results in a white oil which has a higher specific gravity and lower volatility relative to similar grade white oils produced from paraffinic crudes.

Specifications and regulations have been established in the majority of developed countries to control the quality and usage of medicinal white oils. Medicinal white oils are registered under different names in those regulations.

Some examples of these differences include the following:

- "Liquid Paraffins", according to the national Pharmacopoeias,
- "White Mineral Oils", according to the U.S. Food and Drug Administration,
- "Liquid Mineral Hydrocarbons" in the U.K. "Mineral Hydrocarbons in Food, Regulations 1966", and
- "Mineral Oils" according to the U.N. Food and Agriculture Organization (FAO).

They can also be "Pharmaceutical White Oils" or "Food Grade White Oils" according to their final application. The specifications used to define medicinal white oils can change from one legislation to another. The changes are often minor and concern mainly the viscosity/molecular weight definition of the products or the method description of the purity tests.

Medicinal white oils are produced by appropriate refining of naphthenic or paraffinic crude oils. The overall refining process can be separated into two main steps.

The first step includes conventional refining processes used for the production of conventional mineral oil. It is usually composed of the following stages.

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## APPENDIX A

### Additional Technical Information on Production and Composition of Food Grade Mineral Hydrocarbons

A number of excellent references are available which describe petroleum refining technology and processes in relation to physical, chemical and biological properties (Bingham et al., 1980; IARC, 1984). The purpose of this Appendix is to highlight some of the petroleum refining technology that is relevant to those products used in direct and indirect or incidental food applications. The emphasis will be on medicinal white oils and technical mineral hydrocarbons.

Three basic processes used in petroleum refining include distillation, cracking and finishing operations. Distillation procedures are used to separate components of petroleum (or mineral) hydrocarbons according to boiling range. Cracking procedures are used to split molecules into smaller units or to rearrange molecules into different or larger molecules. Refineries use a combination of distillation and cracking procedures to meet the demand for various products from the available crude oils. Finishing procedures are used to modify and improve the properties of crude products to make them acceptable for their intended use.

All crude oils are complex mixtures of straight- and branched-chain paraffinic, naphthenic (cyclo-paraffin) and aromatic hydrocarbons. Crude oils are generally classified as naphthenic or paraffinic depending on the preponderance of these molecular species in the crude. The chemical composition of "finished" refinery products are affected by the original crude type and the refining procedures used. After severe refining, variations in chemistry due to crude are less apparent. Likewise, with simple refining techniques, the composition of the finished product more closely reflects that of the original crude oil.

Petroleum crude oils are first distilled at atmospheric pressure to produce "straight run" distillate fractions of various boiling ranges, up to  $-370^{\circ}\text{C}$ . The hydrocarbon molecules in these distillation streams may contain as many as approximately 25 carbons. The residue from atmospheric distillation (reduced crude) may then be further fractionated by distillation under reduced pressure to produce fractions with boiling ranges from approximately  $200^{\circ}$  to  $600^{\circ}\text{C}$  and carbon chain sizes of up to approximately 50 carbons. The higher the carbon number and the molecular weight, the more viscous are the oils. At this point, paraffinic crude oils are characterized by high wax content, high natural viscosity index (low rate of change in viscosity with temperature) and relatively low aromatic hydrocarbon content. Naphthenic crudes are typically characterized by low wax content and are relatively high in cyclo-paraffins and aromatic hydrocarbons.

Subsequent finishing operations such as solvent extraction, dewaxing, hydrotreating and other specialized refining procedures result in better definition of the final product and are discussed below in relation to specific mineral hydrocarbons which have been approved for direct and/or indirect (or incidental) food applications.

absorbance measurement of a DMSO extract of the oil. The content of six major PAH has been found at levels lower than 1 micro g/kg in 10 samples representative of the medicinal white oil market (CONCAWE 1984).

- The Readily Carbonizable Substances Test is a measure of both the low aromatics content and the lack of impurities in the white oil. This test is a very sensitive measure for impurities or degradation of the oil which could occur during handling.

The purity and medicinal quality of a white oil can also be assessed by other tests such as the acidity test, the sulphur compounds test or by the lack of odor. To reach the specified level of quality, severe refining is used to produce on-specifications white oil. Special procedures are then used during handling and storage to preserve the high purity of the oil until its final use.

### Exxon White Oils

The current production of Esso white oils is representative of the paraffinic white oil production by the modern hydrogenation process. It is illustrated in Figure A1.

The paraffinic crude is first conventionally refined to obtain a white oil feedstock, which has most of the physico-chemical characteristics of the final white oil. It is then fed into the two stage hydrogenation process. The first stage reduces the content of most of the aromatic compounds and removes sulphur. The desulfurized product is then adjusted to the desired viscosity and volatility before being hydrogenated in the second stage to complete the saturation of residual aromatic compounds. Because of the high sensitivity of the product to contamination, special procedures have also been devised to remove (filtrate) any solid particles, to control the white oil quality and to handle the finished products.

Technical grade white oils also can be produced by the hydrogenation process. Technical white oils are less refined than medicinal white oils, but as they have been severely hydrotreated, are low in aromatics content and are suitable for certain applications with incidental or indirect food contact.

Exxon white oils have been produced in the same plant, located in Port Jerome, France, using the same process for more than 15 years. The unique method of production and the consistent manufacturing process contribute to the consistently high quality of Exxon's white oils that are supplied throughout the world.

A VACUUM DISTILLATION stage, fractionates the crude oil in vacuum distillates and determines the final boiling range, average molecular weight and viscosity of the final white oil.

A SOLVENT EXTRACTION stage, with an optional HYDROGEN TREATMENT, selectively removes undesirable polar compounds and significantly reduces the content of aromatic and polycyclic aromatic hydrocarbons. This stage also facilitates obtainment of the medicinal purity in the final purification stage.

A SOLVENT DEWAXING stage, removes crystallizable compounds (all n-paraffins and few iso-paraffins) and imparts low temperature flow properties to the oil. This stage, which is mandatory with paraffinic oils, defines the final pour point (temperature at which the oil can flow) of the oil.

The second step of refining is a purification stage, which is specific to white oil products. It is intended to totally eliminate any aromatic compounds present in the white oil feedstock in order to meet the medicinal quality specifications. Two processes for medicinal white oil production can be considered.

The ACID PROCESS, is the historical process in which the aromatic compounds are physically separated from the saturated compounds. The white oil feedstocks are repeatedly treated with strong sulfuric acid (or oleum or SO<sub>2</sub> gas) to separate the aromatic compounds (A. Cluer 1970). Further neutralization and clay treatment result in the final medicinal white oils products.

Alternatively, the HYDROGENATION PROCESS, chemically transforms aromatic compounds into saturated compounds by catalytic hydrogenation under very severe conditions. This modern process was first implemented in early 1970 (Lecomte et al., 1977, Himmel et al., 1986). This process is now widely used and represents more than 80% of the 1989 European production of medicinal white oils.

The purification stage used to meet the medicinal white oil quality is extremely severe and along with the associated quality specifications offers a good degree of control over the end product quality. It has been demonstrated (CONCAWE, 1984) that, independently of crude source or purification process, the chemical composition of medicinal white oil is controlled within tight ranges. The white oils consist predominantly of saturated hydrocarbons. As evidenced by mass spectroscopy, the ratio between iso-paraffins and naphthenes can vary, to a limited extent, between white oils. The presence of nitrogen and sulphur compounds has been assessed by means of total N and total S content and has been found at concentrations lower than the milligram/kg level. The content of the six individual PAH, specified by WHO for drinking water, are in the ppb range which is at the detection limits of the most modern analytical methods.

A common feature to all the refining processes is to control the concentrations of impurities and toxicologically important compounds in the white oil to extremely low levels. Compliance with these standards is best assessed by two specific tests:

- the Polycyclic Aromatic Hydrocarbons (PAH) test, which measures the content of toxicologically important PAH compounds (identified by WHO) by a UV

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### Technical Mineral Hydrocarbon Production

Technical Mineral Hydrocarbons are hydrocarbon fluids used in direct and indirect or incidental food contact applications. While their physical characteristics (e.g., boiling range) may vary to meet the needs of a particular application and/or specification, they are all manufactured to meet the high quality standards associated with the various regulations enacted by the governmental bodies responsible for this area (FDA, BGA, Warensnet, etc.). The technical mineral hydrocarbons discussed in this report are obtained by processing hydrocarbon streams that may be obtained via atmospheric distillation of petroleum crude oil, from cracked streams (or molecules made smaller) from the vacuum distillation stage of petroleum refining, or synthesized from petroleum gases. Technical mineral hydrocarbons contain the same type of molecules (paraffins, iso paraffins, and naphthenes) as white mineral oils, although they are lower in molecular weight and carbon number. They are predominantly C<sub>5</sub> to C<sub>20</sub> hydrocarbons boiling in the range of 30°C to 320°C. They are defined by their physical properties, regulatory requirements and performance characteristics rather than by structural formulae. Like white mineral oils, technical mineral hydrocarbons are considered chemically inert and do not react with various components of products in which they are used. In addition, since they are somewhat volatile, any residue which remains on food from application situations is considered extremely low. Due to the low final boiling point, and confirmed by UV absorbance, these technical mineral hydrocarbon materials are virtually free from polynuclear aromatic hydrocarbons (PAH). As well, due to either chemical synthesis or further refinement, these products are considered to be free from other potential contaminants, such as nitrogen, sulfur, or other molecules.

In general, Technical Mineral Hydrocarbons fall into three different types.

- Type 1: Hydrodesulfurized/Hydrogenated or extracted special boiling-range petroleum hydrocarbons in which the aromatics present in the original feedstocks have been converted to cycloaliphatic (naphthenic) hydrocarbons, e.g., EXXSOL D40, EXXSOL D80, and NAPPAR 10.
- Type 2: Synthetic isoparaffinic petroleum hydrocarbons which are produced from low molecular weight olefinic hydrocarbons via oligomerization or alkylation followed by hydrogenated, e.g., ISOPAR G, ISOPAR M.
- Type 3: Normal paraffinic petroleum hydrocarbons separated via molecular sieves from hydrodesulfurized petroleum feedstocks, e.g., NORPAR 12, NORPAR 13. These products are also dearomatized by treating with acid or a solid adsorbent.

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The current 1989 physico-chemical characteristics of Exxon's medicinal white oils are detailed below.

Product:	MARCOL 52	MARCOL 82	MARCOL 172	PRIMOL 352
Crude Source:	Paraffinic Hydrogen	Paraffinic Hydrogen	Paraffinic Hydrogen	Paraffinic Hydrogen
Refining Process:				
Viscosity at 20°C (cSt)	14	34	85	225
Viscosity at 40°C (cSt):	7	15	32	70
Density at 15°C (kg/m <sup>3</sup> ):	835	848	860	870
Refractive Index at 20° C:	1.458	1.466	1.471	1.475
Pour Point (°C)	-12	- 9	- 6	- 18
Average Molecular Weight:	280	330	390	470
Average Carbon Chain Length	16-24	19-28	24-33	28-40
Sulfur Content (ppm)	<1	<1	<1	<1
Polycyclic Aromatic Content (ppm)	<1	<1	<1	<1
Purity Specification:				
- carbonizable substance	pass	pass	pass	pass
- polycyclic aromatics	pass	pass	pass	pass
- acidity/alkalinity	pass	pass	pass	pass
- sulphur compounds	pass	pass	pass	pass
- solid compounds	pass	pass	pass	pass
- color and odor	pass	pass	pass	pass

The samples MARCOL 82, EZL 550 and EZL 600 tested in the Exxon toxicological studies (see Table 1) were produced in the Port-Jerome refinery using paraffinic crudes and the same processes as the current production.

- The tested MARCOL 82 was very similar to the current MARCOL 82 product.
- The tested EZL 550 was the precursor of the current PRIMOL 352 products. They differ only by the severity of the dewaxing stage during the feedstock refining. EZL 550 had a higher pour point which resulted in lower density than PRIMOL 352.
- It should also be noted that the products MARCOL 82 and EZL 550, which were tested in the Exxon toxicological studies and which are representative of Exxon white mineral oils marketed throughout the world, were also considered in the CONCAWE'S report submitted to MAFF (CONCAWE, 1984). This CONCAWE report assessed and compared the composition of white oils produced by hydrogenation versus acid treatment. In this report, MARCOL 82 was identified under the reference number 6 and EZL 550 under the reference number 7 and 8.
- The tested EZL 600 was a technical grade white oil. It was produced in the first stage of the Port-Jerome white oil plant from a heavy paraffinic feedstock.

MARCOL 72 and PRIMOL 185, the remaining Exxon white oils which were tested toxicologically, were manufactured in the USA. Neither product is now manufactured there. Specifications for these test materials are included in Table 1 of the main report.

• Type 2: Synthetic Isoparaffinic

Figure A3 shows a simplified flow scheme for production of Synthetic Isoparaffinic or Type 2 Technical Mineral Hydrocarbons. The gas oil fraction from crude oil is desulfurized and cracked to produce light olefins. The light olefins are converted to heavier olefins by either oligomerization or alkylation. The heavier olefin fractions (dry point greater than 150°C) are then hydrogenated and fractionated to give narrow boiling range Synthetic Isoparaffins.

The ISOPAR solvent product line consists of a series of narrow boiling range isoparaffinic molecules. The aromatic levels, for example, are less than 0.01 wt % with less than 1 ppm PAH. The product line spans the boiling range of 85-310°C. The two products chosen as representative of the product class, ISOPAR C and ISOPAR G boil between 98-105 and 159-175°C respectively. ISOPAR C contains primarily C<sub>7</sub>-C<sub>9</sub> isoparaffins and ISOPAR G contains C<sub>11</sub>-C<sub>13</sub> isoparaffins.

• Type 3: Normal Paraffinic

Figure A4 represents a simplified flow scheme for the production of Normal Paraffinic or Type 3 Technical Mineral Hydrocarbons. A kerosene cut is hydrofined and then contacted with a molecular sieve adsorbent to separate the normal paraffinic components. The individual products are separated by fractionation and dearomatized by treating with either acid or a solid adsorbent.

Hydrodesulfurization is defined as treatment with hydrogen in the presence of a catalyst to remove sulphur. Hydrogenation is a defined as treatment with hydrogen, in the presence of a different catalyst, which results in the conversion of aromatic hydrocarbons to cycloaliphatic hydrocarbons and the conversion of olefins to paraffins. Typical ranges of pressure and temperature for hydrogenation of these products are 10-100 bars and 100-400°C temperature.

The main impurities and components of toxicological significance in food type uses are sulfur, benzene and polynuclear aromatics. The table below gives the estimated upper limits for these components.

	<u>Sulfur</u>	<u>Benzene</u>	<u>PNA</u>
Type 1	<10 ppm	<0.002 wt %	<5 ppm
Type 2	<10 ppm	<0.002 wt %	<1 ppm
Type 3	<10 ppm	<0.002 wt %	<1 ppm

Further details on the production of Type 1, 2 and 3 technical mineral hydrocarbons, and those evaluated in toxicological studies, are provided below.

#### Production Process

- Type 1 Hydrodesulfurized/Hydrogenated or Extracted

Figure A2 shows a simplified flow scheme for the production of Type 1 Technical Mineral Hydrocarbons. A naphtha or kerosene fraction from crude petroleum is first subjected to hydrodesulfurization (treatment with hydrogen in the presence of a catalyst in order to remove sulfur) followed by hydrogenation (treatment with hydrogen over a different catalyst). This hydrogenation step converts the aromatic hydrocarbons into cycloaliphatic hydrocarbons (total aromatics less than 1.0 wt %, and benzene less than 0.010 wt %). Alternatively, aromatics can be removed by solvent extraction. After aromatic conversion (or extraction), the solvent stream undergoes fractional distillation into different narrow or wide boiling ranges.

EXXSOL D40 is representative of a range of dearomatized white spirits. The EXXSOL solvents are narrow cut atmospheric distillates of crude petroleum oil which span a boiling range of 136-315°C, contain less than 1.0 wt% aromatics and less than 3 ppm PAH and very low levels of other contaminants such as sulfur and nitrogen. Thus these products are comprised of paraffinic and naphthenic constituents which are similar across the entire product line although the molecular weights and carbon number of the individual species increase with boiling range. EXXSOL D40 specifically boils between 153°C and 187°C and contains 0.43 wt % aromatics as determined by gas chromatography.

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Figure A2. Special Boiling-Range Petroleum Hydrocarbons

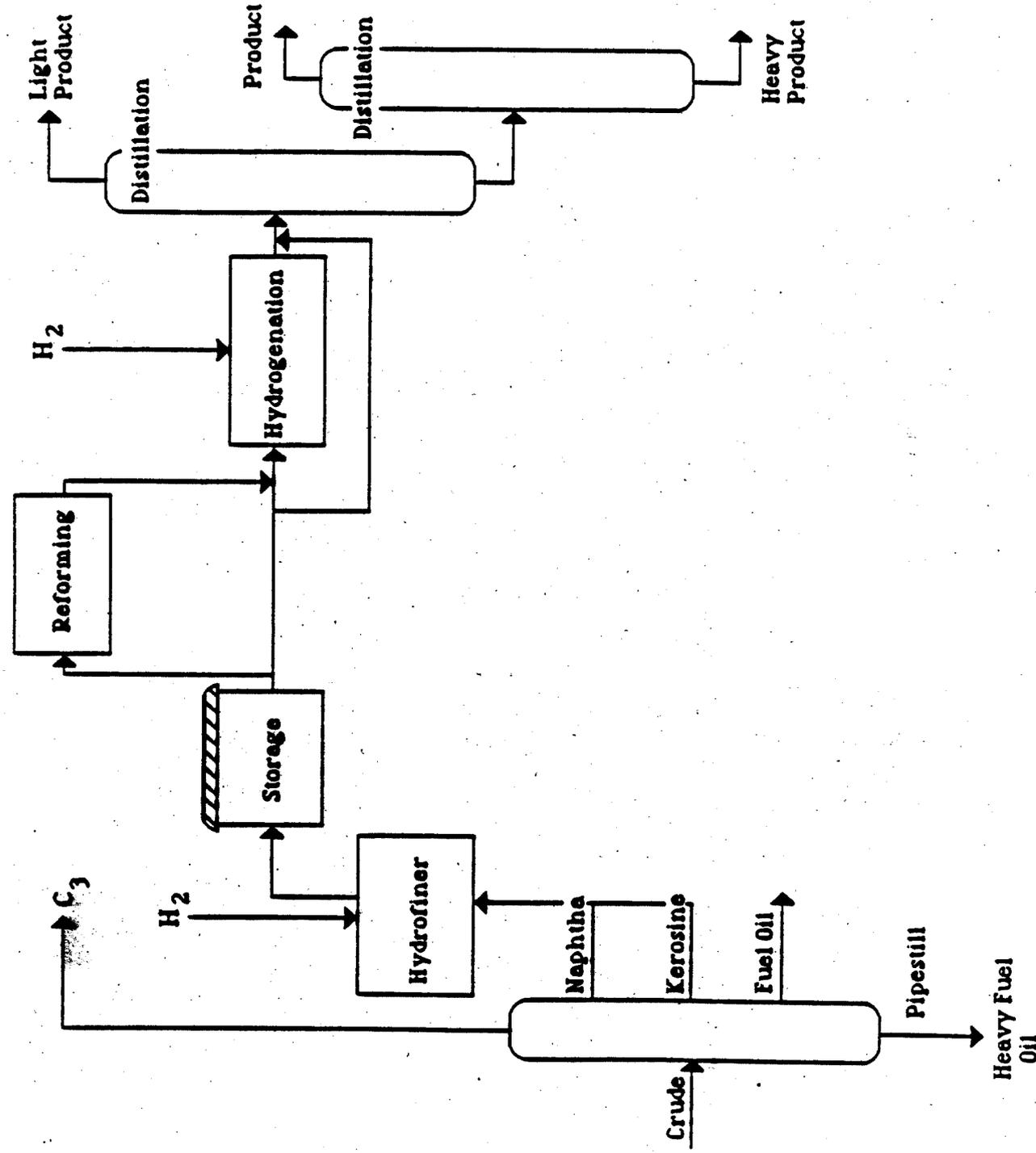
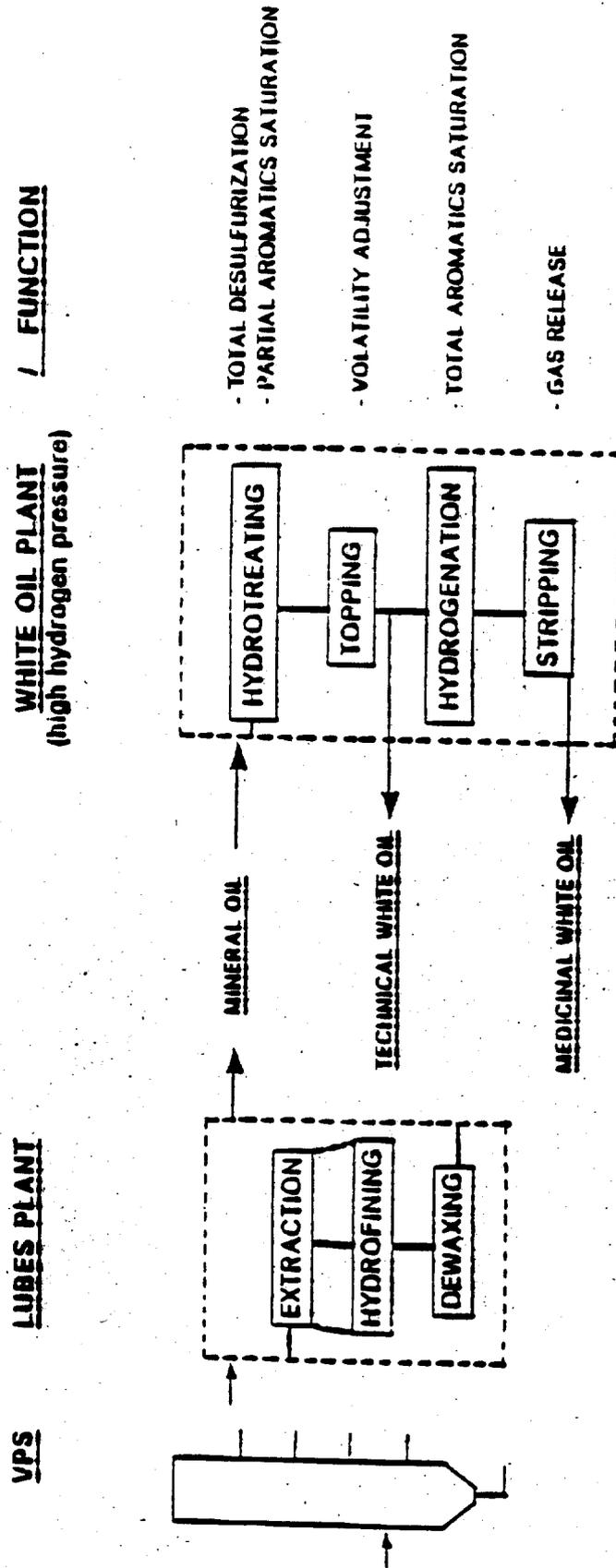


Figure A1

# MANUFACTURING OF ESSO WHITE OILS EXXON PROPRIETARY MANUFACTURING PROCESS



15-2

Figure A4

**NORMAL PARAFFINIC HYDROCARBONS**

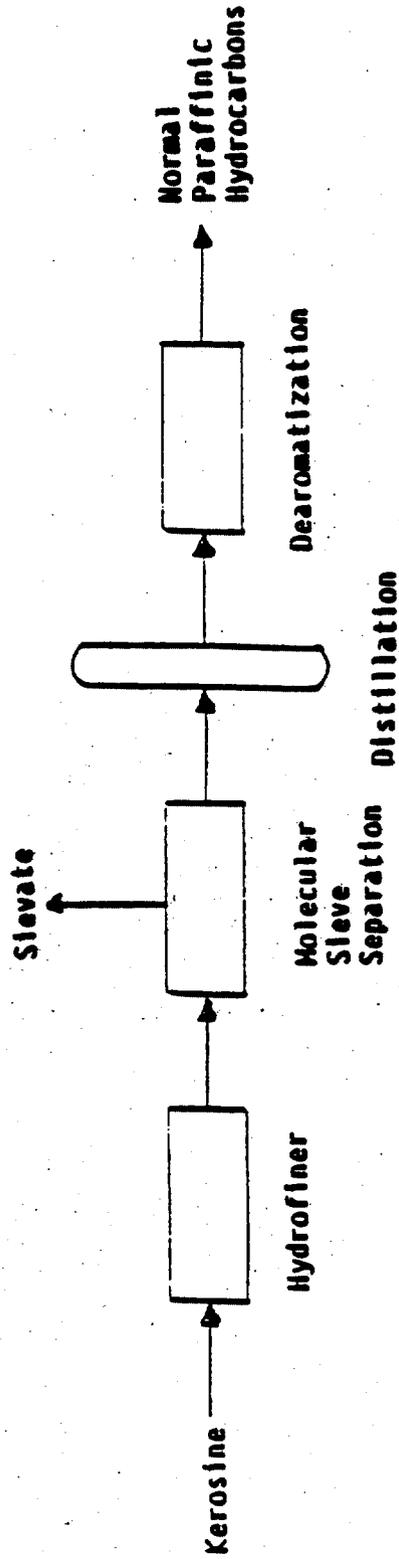
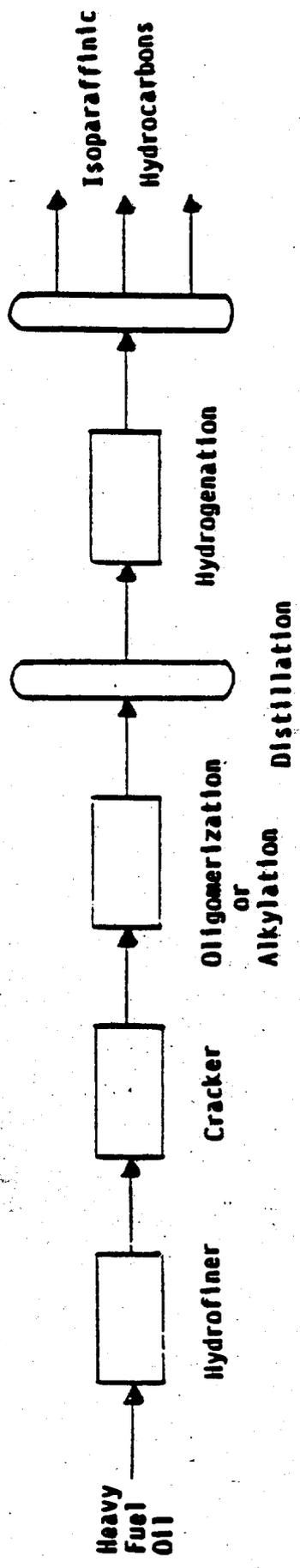


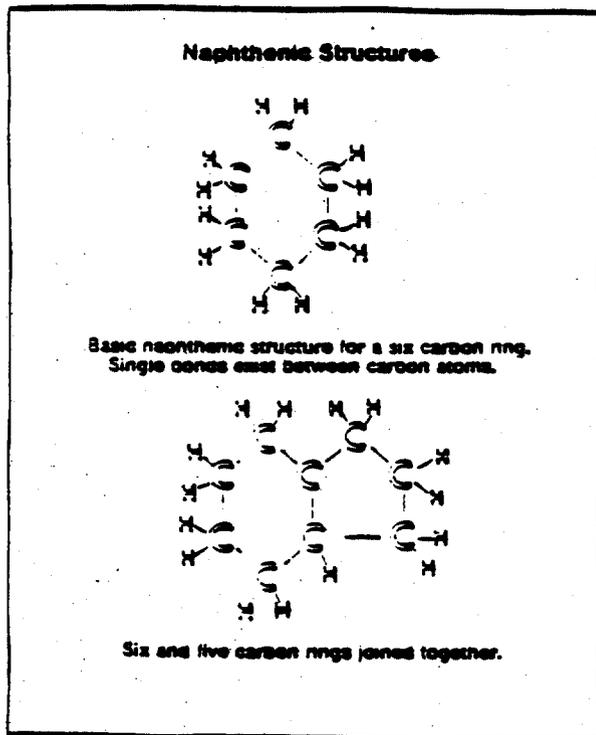
Figure A3

**SYNTHETIC ISOPARAFFINIC HYDROCARBONS**



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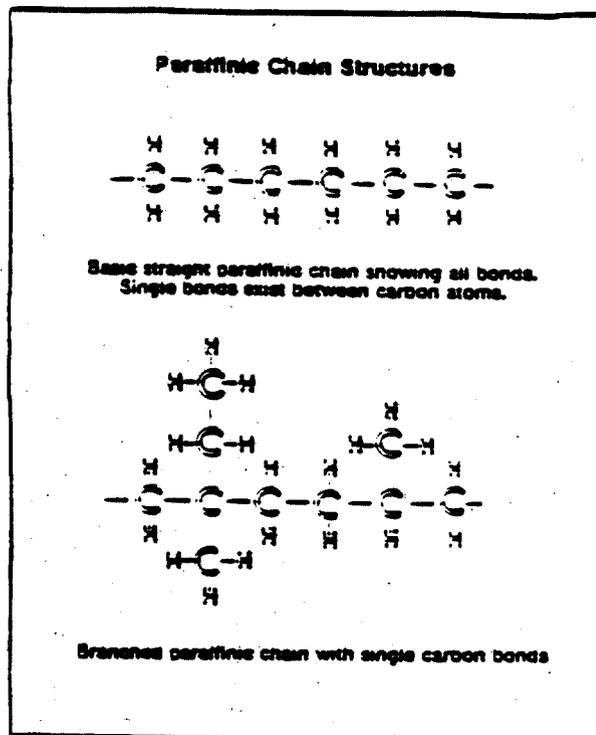
naphthene — hydrocarbon characterized by saturated carbon atoms in a ring structure, and having the general formula  $C_nH_{2n}$ ; also called cycloparaffin or cycloalkane. Naphthenic lubricating oils have low pour points, owing to their very low wax content, and good solvency properties. See hydrocarbon, saturated hydrocarbon.



**NAPPAR** - an Exxon brand name for a class of narrow boiling range naphthenic solvents. These products are produced from atmospheric petroleum distillates and are hydrogen treated to saturate the aromatic constituents. Typically these products contain less than 1.0% aromatic constituents. Examples of these products are NAPPAR 10 (166-188°C) and NAPPAR 11 (182-200°C).

**NORPAR** - An Exxon brand name for a class of narrow boiling range solvents with a very high normal paraffin content (98 +%). These products are produced via molecular sieves from hydrogenated petroleum feedstocks and typically contain less than 1.0% aromatic constituents. As a class, these products span a boiling range of 188-252°C.

paraffin — hydrocarbon identified by saturated straight (normal) or branched (iso) carbon chains. The generalized paraffinic molecule can be symbolized by the formula  $C_nH_{2n+2}$ . Paraffins are relatively non-reactive and have excellent oxidation stability. In contrast to naphthenic (see naphthene) oils, paraffinic lube oils have relatively high wax content and pour point, and generally have a high viscosity index (V.I.). Paraffinic solvents are generally lower in solvency than naphthenic or aromatic solvents. See hydrocarbon, normal paraffin, isoparaffin, saturated hydrocarbon. See illustration on facing page.)



paraffin wax — petroleum-derived wax usually consisting of high-molecular-weight normal paraffins; distinct from other natural waxes, such as beeswax and carnauba wax (palm tree), which are composed of high-molecular-weight esters, in combination with high-molecular-weight acids, alcohols, and hydrocarbons. See wax (petroleum).

petroleum — semi-solid, noncrystalline hydrocarbon, pale to yellow in color, composed primarily of high-molecular-weight waxes; used in lubricants, rust preventives, and medicinal ointments. See wax (petroleum).

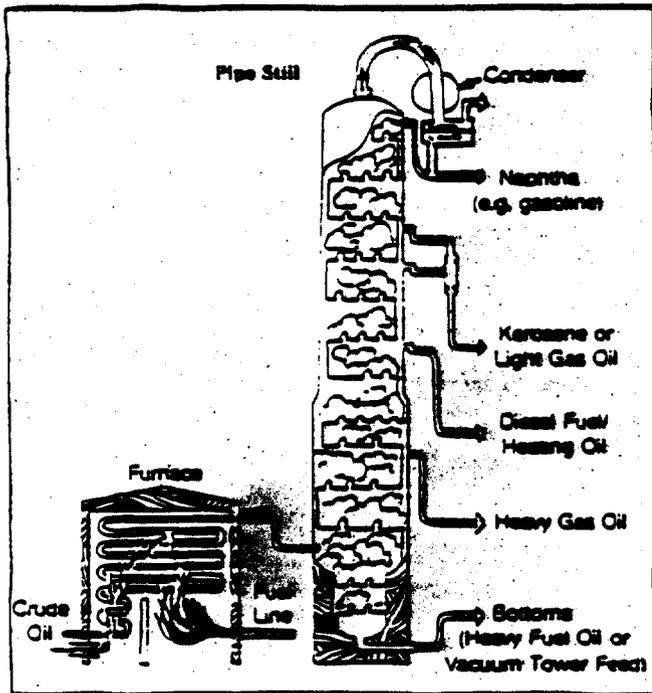
solvent extraction — refining process used to separate reactive components (unsaturated hydrocarbons) from lube distillates in order to improve the oil's oxidation stability, viscosity index (V.I.), and response to additives. Commonly used extraction media (solvents) are: phenol, N-methylpyrrolidone (NMP), furfural, liquid sulfur dioxide, and nitrobenzene. The oil and solvent are mixed in an extraction tower, resulting in the formation of two liquid phases: a heavy phase consisting of the undesirable unsaturates dissolved in the solvent, and a light phase consisting of high quality oil with some solvent dissolved in it. The phases are separated and the solvent recovered from each by distillation. The unsaturates portion, or extract, while undesirable in lubricating oils, is useful in other applications, such as rubber extender oils (see rubber oil) and plasticizer oils.

Stoddard Solvent - a broad cut atmospheric petroleum distillate with an approximate boiling range of 150-200°C.

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## GLOSSARY

distillation (fractionation) — the primary refining step, in which crude is separated into fractions, or components, in a distillation tower, or pipe still. Heat, usually applied at the bottom of the tower, causes the oil vapors to rise through progressively cooler levels of the tower, where they condense onto plates and are drawn off in order of their respective condensation temperatures, or boiling points — the lighter-weight, lower-boiling-point fractions, existing higher in the tower. The primary fractions, from low to high boiling point, are: hydrocarbon gases (e.g., ethane, propane); naphtha (e.g., gasoline); kerosene, diesel fuel (heating oil); and heavy gas oil for cracking. Heavy materials remaining at the bottom are called the bottoms, or residuum, and include such components as heavy fuel oil (see fuel oil) and asphaltic substances (see asphalt). Those fractions taken in liquid form from any level other than the very top or bottom are called sidestream products; a product, such as propane, removed in vapor form from the top of the distillation tower is called overhead product. Distillation may take place in two stages: first, the lighter fractions — gases, naphtha, and kerosene — are recovered at essentially atmospheric pressure; next, the remaining crude is distilled at reduced pressure in a vacuum tower, causing the heavy lube fractions to distill at much lower temperatures than possible at atmospheric pressure, thus permitting more lube oil to be distilled without the molecular cracking that can occur at excessively high temperatures.



**EXXSOL** - An Exxon brand name for a class of narrow boiling range desaturated solvents. These products are produced from atmospheric petroleum distillates and are hydrogen treated to saturate the aromatic constituents. Typically these products contain less than 1.0 wt% aromatic constituents. The representative selected for toxicity testing is EXXSOL D40 which boils between 153-187°C.

**Hydrofining<sup>5</sup>** — form of hydrogen treating in which refinery distillate, lube, and wax streams are treated with hydrogen at elevated temperatures and moderate pressures in the presence of a catalyst, to improve color and stability, and reduce sulfur content. The patented process was developed by Exxon in 1951.

**hydrogenation** — in refining, the chemical addition of hydrogen to a hydrocarbon in the presence of a catalyst; a severe form of hydrogen treating. Hydrogenation may be either destructive or non-destructive. In the former case, hydrocarbon chains are ruptured (cracked) and hydrogen is added where the breaks have occurred. In the latter, hydrogen is added to a molecule that is unsaturated (see unsaturated hydrocarbon) with respect to hydrogen. In either case, the resulting molecules are highly stable. Temperature and pressures in the hydrogenation process are usually greater than in Hydrofining<sup>5</sup>.

**ISOPAR** - An Exxon brand name for a class of narrow boiling range isoparaffinic solvents produced from olefins. As a class, these products span a boiling range of 85-310°C and are extremely low in contaminants including aromatic hydrocarbons. The representatives selected for toxicity testing are ISOPAR C (98-105°C and ISOPAR G (159-175°C).

**Kerosene** - a broad cut atmospheric petroleum distillate with an approximate boiling range of 160-300°C. Most kerosene conforms to ASTM-D-396-66T.

**mineral oil** — any petroleum oil, as contrasted to animal or vegetable oils. Also, a highly refined petroleum distillate, or white oil, used medicinally as a laxative.

**mineral seal oil** — distillation fraction between kerosene and gas oil, widely used as a solvent oil in gas absorption processes (see absorber oil), as a lubricant for the rolling of metal foil, and as a base oil in many specialty formulations. Mineral seal oil takes its name — not from any sealing function — but from the fact that it originally replaced oil derived from seal blubber for use as an illuminant for signal lamps and lighthouses.

Technical mineral hydrocarbons - a generic term for materials produced by processing of petroleum distillates or synthetic hydrocarbon streams which are used for direct and indirect or incidental food contact. Technical mineral hydrocarbons can include both technical solvents and technical white oils. EXXSOL D40, a dearomatized atmospheric distillate, and ISOPAR C & G, synthetically produced isoparaffinic solvents, are examples of technical mineral hydrocarbons which are produced by Exxon.

USP (United States Pharmacopeia) — compendium of drugs, drug formulas, quality standards and tests published by the United States Pharmacopeial Convention, Inc., which also publishes the *NF* (National Formulary). The purpose of the USP is to ensure drug uniformity and to maintain and upgrade standards of drug quality and purity, as well as establish packaging, labeling, and storage requirements. The USP includes standards for *white oils* under two classifications: "Mineral Oil" for heavy grades, and "Mineral Oil Light" for lighter grades.

wax (petroleum) — any of a range of relatively high-molecular-weight hydrocarbons (approximately C<sub>16</sub> to C<sub>30</sub>), solid at room temperature, derived from the higher-boiling petroleum fractions. There are three basic categories of petroleum-derived wax: paraffin (crystalline), microcrystalline and petrolatum. • Paraffin waxes are produced from the lighter lube oil distillates, generally by chilling the oil and filtering the crystallized wax; they have a distinctive crystalline structure, are pale yellow to white (or colorless), and have a melting point range between 48°C (118°F) and 71°C (160°F). Fully refined paraffin waxes are dry, hard, and capable of imparting good gloss. • Microcrystalline waxes are produced from heavier lube distillates and residua (see bottoms) usually by a combination of solvent dilution and chilling. They differ from paraffin waxes in having poorly defined crystalline structure, darker color, higher viscosity, and higher melting points — ranging from 63°C (145°F) to 93°C (200°F). The microcrystalline grades also vary much more widely than paraffins in their physical characteristics: some are ductile and others are brittle or crumble easily. Both paraffin and microcrystalline waxes have wide uses in food packaging, paper coating, textile moisture proofing, candle-making, and cosmetics. • Petrolatum is derived from heavy residual lube stock by propane dilution and filtering or centrifuging. It is microcrystalline in character and semi-solid at room temperature. The best known type of petrolatum is the "petroleum jelly" used in ointments. There are also heavier grades for industrial applications, such as corrosion preventives, carbon paper, and butcher's wrap. Traditionally, the terms *slack wax*, *scale wax*, and *refined wax* were used to indicate limitations on oil content. Today, these classifications are less exact in their meanings, especially in the distinction between *slack wax* and *scale wax*. For further information relating to wax, see *blocking point*, *gloss*, *laminating strength*, *melting point of wax*, *oil content of petroleum wax*, *paraffin wax*, *petrolatum*, *refined wax*, *scale wax*, *stuff resistance*, *sealing strength*, *slack wax*, *strike-through*.

white oil — highly refined straight mineral oil, essentially colorless, odorless, and tasteless. White oils have a high degree of chemical stability. The highest purity white oils are free of unsaturated components (see *unsaturated hydrocarbon*) and meet the standards of the United States Pharmacopeia (*USP*) for food, medicinal, and cosmetic applications. White oils not intended for medicinal use are known as technical white oils and have many industrial applications — including textile, chemical, and plastics manufacture — where their good color, non-staining properties, and chemical inertness are highly desirable.

Appendix 7. Report of ARCO-Sponsored 90-Day White Oil Study

Products Division  
Quality Administration

January 27, 1976

Miss M. S. Butler  
The British Industrial Biological  
Research Association  
Woodmansterne Road, Carshalton  
Surrey, England, United Kingdom

Dear Miss Butler:

Reference is made to past correspondence concerning additional data on our product Tufflo 6056 relative to its safety-in-use, particularly with regard to increasing the maximum 4% use now provided in the BIBRA/BPF Code of Practice.

The additional data that has been developed can be summarized in four categories, as follows:

90-Day Subacute Oral Toxicity Study with Tufflo 6056

A 90-day subacute oral toxicity study has been conducted on Tufflo 6056 using albino rats as test animals, at a dietary feeding level of 10,000 ppm. This test supplements a previous study in which a 50/50 mixture of Tufflo 6016 and Tufflo 6056 was fed at 10,000 ppm.

No untoward behavioral reactions were noted during the course of the study, and all deaths that occurred among test and control animals during the course of the test were as a result of blood collection.

No significant differences between test and control animals were noted in the various parameters studied. The results from hematologic, clinical chemistry and urinalyses testing were within the limits of normal, and pathologic studies revealed no findings different from those in the control animals or attributable to the test material.

The complete detailed report of this investigation is attached.

Acute Oral Toxicity Study with Tufflo 6056

- > An acute oral toxicity study has been conducted with Tufflo 6056 using Sprague-Dawley albino rats. A dose level of 5,000 mg./kg. was administered directly into the stomach. The animals were observed directly for 14 days and then sacrificed. All animals appeared normal during the observation period, and necropsy examination did not reveal any gross pathologic reactions. The acute oral LD50 is calculated to be greater than 5,000 mg./kg.

The detailed report on this study is attached.

Investigation of Tufflo 6056 for Polynuclear Aromatic Hydrocarbons

The sample of Tufflo 6056 used in this investigation was specifically selected as one showing a strong color reaction in the hot acid, or carbonizable substances, test. That is, the sample contained a relatively high proportion of materials that react with conc. sulfuric acid to form color bodies. Also, the sample had an ultraviolet absorbance value on the high side of the maximum permitted by FDA 121.1146, as follows:

Maximum UV absorbance, 260-350 nm      0.071 @ 309 nm

Carbonizable Substances      > 5

A rating of 5 in the hot acid test is equivalent to 200% of ASTM D 565 colorimetric reference standard solution. A rating of 3 is the maximum "passing" limit.

The Tufflo 6056 sample was treated by liquid-liquid and chromatographic procedures to obtain an enriched polynuclear aromatic fraction, and analyzed by gas chromatography against an internal standard of benzo-(b)-chrysene. For control, various polynuclear aromatics were added to the original Tufflo 6056 sample.

Results show that no polynuclear aromatics are present down to the detection limit of this test, which is 0.01 ppm, or  $10^{-8}$  g/g.

The complete original report of this investigation is attached.

Extraction Studies on Polystyrenes Made with Tufflo 6056

Extraction studies have been conducted on approximately 1 mm films of both standard and high impact polystyrene, made with 5.5% Tufflo 6056. The solvents used were distilled water; 3% acetic acid; 10% ethyl alcohol; and a fat simulant which is a  $^{14}\text{C}$ -labelled triglyceride mixture. Test conditions included 10 days at 40°C. and 65% relative humidity; and two hours at 70°C.

Results of these tests show that the total migrated material for both polystyrenes under all conditions in the aqueous solvents was less than 0.1 mg./dm<sup>2</sup>; and in the fat simulant less than 3.3 mg./dm<sup>2</sup>.

The complete original report on this study is attached.

Some of these studies were conducted in Germany in connection with our BGA approval, and in those cases we have included the original report so that you would have the exact description rather than a translation.

I trust that you will find the results of these additional studies on Tufflo 6056 of interest from a technical standpoint, and also persuasive as to its safety for use in plastics for food contact applications at greater than 4% levels.

As in the case of related information previously sent to you, I would appreciate a letter from you acknowledging receipt of this data and the confidentiality of the information supplied.

With kind personal regards.

Yours very truly,

ATLANTIC RICHFIELD COMPANY



H. J. Matson, Manager  
Product Specifications

HJM:jp  
Att.

cc: Mr. R. W. Sublett - Los Angeles (w/attach.)

cc: Mr. T. J. Clough - Harvey (w/attach.)  
Mr. Derek Hughes - Rio de Janeiro (w/attach.)  
Dr. B. W. Turnquest - Los Angeles (no attach.)

✓  
*Industrial* BIO-TEST *Laboratories, Inc.*

1810 FRONTAGE ROAD  
NORTHBROOK, ILLINOIS 60062

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REPORT TO

ATLANTIC RICHFIELD COMPANY

90-DAY SUBACUTE ORAL TOXICITY STUDY WITH  
CODE 7552, SAMPLE 6025-F-51205 (WHITE OIL)  
IN ALBINO RATS

ACCOUNT NO. 8136-5960-A3465

FEBRUARY 6, 1975

IBT NO. 621-05634

*Industrial BIO-TEST Laboratories, Inc.*

1810 FRONTAGE ROAD  
NORTHBROOK, ILLINOIS 60062

February 6, 1975

Mr. H. J. Matson, Manager  
Product Specifications  
Atlantic Richfield Company  
Harvey Technical Center  
400 East Sibley Boulevard  
Harvey, Illinois 60426

Dear Mr. Matson:

Re: IBT No. 621-05634 - 90-Day Subacute Oral Toxicity Study  
--- With Code 7552, Sample 6025-F-51205 (White Oil) in  
Albino Rats - Account No. 8136-5960-A3465

We are submitting herewith our laboratory report prepared  
in connection with the above study.

Very truly yours,

*J. C. Calandra*

J. C. Calandra  
President

JCC:mcb

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REPORT TO

ATLANTIC RICHFIELD COMPANY

90-DAY SUBACUTE ORAL TOXICITY STUDY WITH  
CODE 7552, SAMPLE 6025-F-51205 (WHITE OIL)  
IN ALBINO RATS

ACCOUNT NO. 8136-5960-A3465

FEBRUARY 6, 1975

IBT NO. 621-05634

I. Introduction

A sample identified as Code 7552, Sample 6025-F-51205 (White Oil), was received from the Atlantic Richfield Company for the purpose of conducting a 90-day subacute oral toxicity study using albino rats as test animals. This report presents the results of the investigation.

## II. Summary

Ninety days of feeding White Oil to a group of albino rats at a dietary level of 10,000 ppm revealed the following:

### A. Body Weights and Total Weight Changes

Statistical comparison of total body weight changes revealed no significant differences between test and control group values.

### B. Food Consumption

Differences between the amounts of food consumed by test and control group animals were not significant.

### C. Mortality and Reactions

All deaths were the result of trauma during blood collection and were not related to treatment with the test material.

No untoward behavioral reactions were noted among any of the animals employed in the investigation.

### D. Hematologic Studies

Mean values for leukocyte and erythrocyte counts, hemoglobin concentration and hematocrit were within the limits of normal.

### E. Clinical Chemistry Studies

Mean values for serum glucose, blood urea nitrogen (BUN) concentration, serum alkaline phosphatase (SAP) activity, serum glutamic-pyruvic transaminase (SGPT) activity, cholesterol, triglycerides, phospholipids, total lipids and total esterified fatty acids were within the limits of normal after 42 and 84 days of treatment.

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F. Urinalyses

Mean values for urinary glucose, protein, pH, specific gravity and microscopic elements were within the limits of normal for all rats examined at 42 and 84 days.

G. Pathologic Studies

1. Gross Findings

Gross necropsy findings among test animals were not significantly different from those noted in control animals.

2. Organ Weights and Ratio Data

No effects attributable to the test material were noted.

3. Histopathologic Findings

Tissue changes observed in treated rats were similar to those seen in control rats and all were considered manifestations of intercurrent disease.

Respectfully submitted,

INDUSTRIAL BIO-TEST LABORATORIES, INC.

Report prepared by:

Les Morrow

Les Morrow, B.S.

Assistant Toxicologist  
Toxicology

Report approved by:

Ken McCollum

Ken McCollum

Senior Group Leader  
Toxicology

John W. Goode

John W. Goode, Ph.D.

Manager  
Decatur Research Laboratories

M. L. Keplinger

M. L. Keplinger, Ph.D.

Manager, Toxicology

III. Procedure

A. Experimental Animals

The animals employed in the study were Charles River strain\* albino rats. Sixty rats (30 males and 30 females) were selected for the experiment and housed individually in standard wire-bottomed steel rat cages. Each cage bore a color-coded card identifying the animal with respect to project number, dietary level assignment, individual animal number and sex.

B. Organization of Groups

A structural outline of the experiment is shown in Table I.

TABLE I

TEST MATERIAL: White Oil

90-Day Subacute Oral Toxicity Study - Albino Rats

Outline of Experiment

Group	Number of Animals		Dietary Level (ppm)
	Males	Females	
Control	15	15	None
T-I	15	15	10,000

\* Charles River Breeding Laboratories, Wilmington, Massachusetts.

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C. Body Weights and Total Weight Changes

Each animal used in the study was weighed on the first day of the test and at weekly intervals thereafter. The weights were recorded and served as an index to growth. Weight changes were computed at the conclusion of the 90-day test period and the data subjected to statistical analyses.

D. Food Consumption and Diet Preparation

Food consumption data were collected individually for ten rats of each sex in each group weekly during the study and the data recorded.

The diet for any given group was prepared by blending the appropriate amount of White Oil with standard rat ration\* in a Hobart Mixer.

Fresh diets were prepared each week. Each rat was offered an amount of diet sufficient for one week's ad libitum feeding. However, checks were made daily to ensure that the food jars were not empty.

E. Mortality and Reactions

Abnormal reactions and deaths were recorded daily during the investigation.

F. Hematologic, Clinical Blood Chemistry Studies and Urinalyses

Blood and urine samples collected individually from ten rats of each sex from both the control and T-I (10,000 ppm) groups after 42 and 84 days of feeding were analyzed for the following:

\* Wayne LAB-MEAL for Rats, Allied Mills, Inc., Chicago, Illinois.

1. Hematologic Studies

- a. Hematocrit Value
- b. Erythrocyte Count
- c. Hemoglobin Concentration
- d. Total Leukocyte Count
- e. Differential Leukocyte Count

2. Clinical Chemistry Studies

- a. Blood Urea Nitrogen (BUN) Concentration
- b. Serum Alkaline Phosphatase (SAP) Activity
- c. Serum Glutamic-Pyruvic Transaminase (SGPT) Activity
- d. Fasted Blood Glucose Concentration
- e. Cholesterol
- f. Triglycerides
- g. Total Lipids
- h. Phospholipids
- i. Total Esterified Fatty Acids

3. Urinalyses

- a. Glucose Concentration
- b. Protein Concentration
- c. Microscopic Elements Examination
- d. pH
- e. Specific Gravity

G. Pathologic Studies

Following 90 days of feeding, all surviving animals were rendered unconscious by exposure to carbon dioxide in a closed chamber and immediately exsanguinated. Animals which succumbed during the study were examined grossly unless examination was precluded by postmortem autolysis. At the time of necropsy, representative specimens of all organs were preserved in ten percent neutral buffered formalin. Fixed tissues were processed, embedded in paraffin, sectioned at six microns and stained for microscopic examination. Also at necropsy, the weights of the liver, kidneys, spleen, gonads, heart and brain of each rat were determined and recorded.

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Microscopic examination of tissues taken from ten rats of each

sex from the control and test group was conducted. Tissues were stained with hematoxylin and eosin. In addition, specimens of liver were stained with Osmium tetroxide and specimens of stomach were stained with Alcian Blue PAS. The following tissues were included: esophagus, stomach (cardia, fundus and pylorus), small intestine (duodenum, jejunum and ileum), caecum, colon, liver, kidneys, spleen, sternum, pancreas, urinary bladder, pituitary gland, adrenal gland, testes, ovary, thyroid gland, parathyroid gland, salivary gland (submaxillary), prostate gland, heart, aorta, lung, lymph node (cervical and mesenteric), skeletal muscle, peripheral nerve, spinal cord, uterus, trachea, eye, optic nerve and brain (cerebrum, cerebellum and pons).

#### IV. Results

##### A. Body Weights and Total Weight Changes

Body weight data collected weekly during the 90-day test period are summarized in Table II. Also included in the table are 90-day total weight changes.

Mean male and female body weight data are graphically presented in Figures 1 and 2, respectively.

Statistical comparisons of total body weight changes revealed no significant differences between test and control group values.

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TABLE II

TEST MATERIAL: White Oil

90-Day Subacute Oral Toxicity Study - Albino Rats

Body Weight and Total Weight Change Data

Summary of Mean Values

Dietary Level (ppm)	Sex	0	1	2	3	4	5	6	7	8	9	10	11	12	13	90-Day Total Weight Change (grams/rat)
None	Males	114	178	242	299	327	364	387	397	421	437	453	465	470	489	374
10,000	Males	116	173	231	287	316	355	369	381	404	419	432	446	447	463	348
None	Females	112	155	184	213	221	241	243	248	254	262	268	271	274	284	176
10,000	Females	112	153	183	207	220	239	246	252	261	269	277	282	286	298	187

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TEST MATERIAL: White Oil

90-Day Subacute Oral Toxicity Study - Albino Rats

Mean Male Body Weight Data

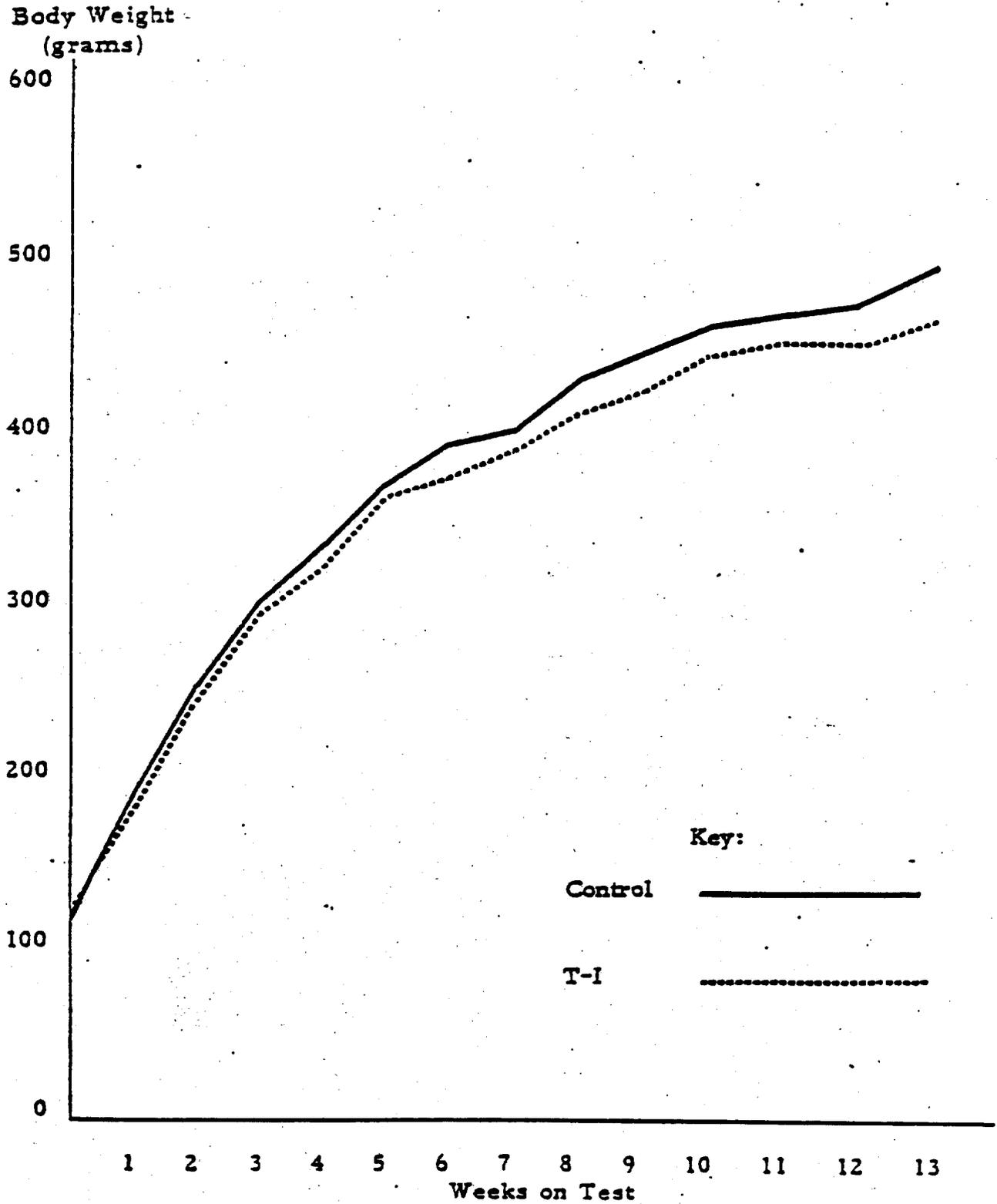


FIGURE 2

TEST MATERIAL: White Oil

90-Day Subacute Oral Toxicity Study - Albino Rats

Mean Female Body Weight Data

Body Weight  
(grams)

400

300

200

100

0

1

2

3

4

5

6

7

8

9

10

11

12

13

Weeks on Test

Key:

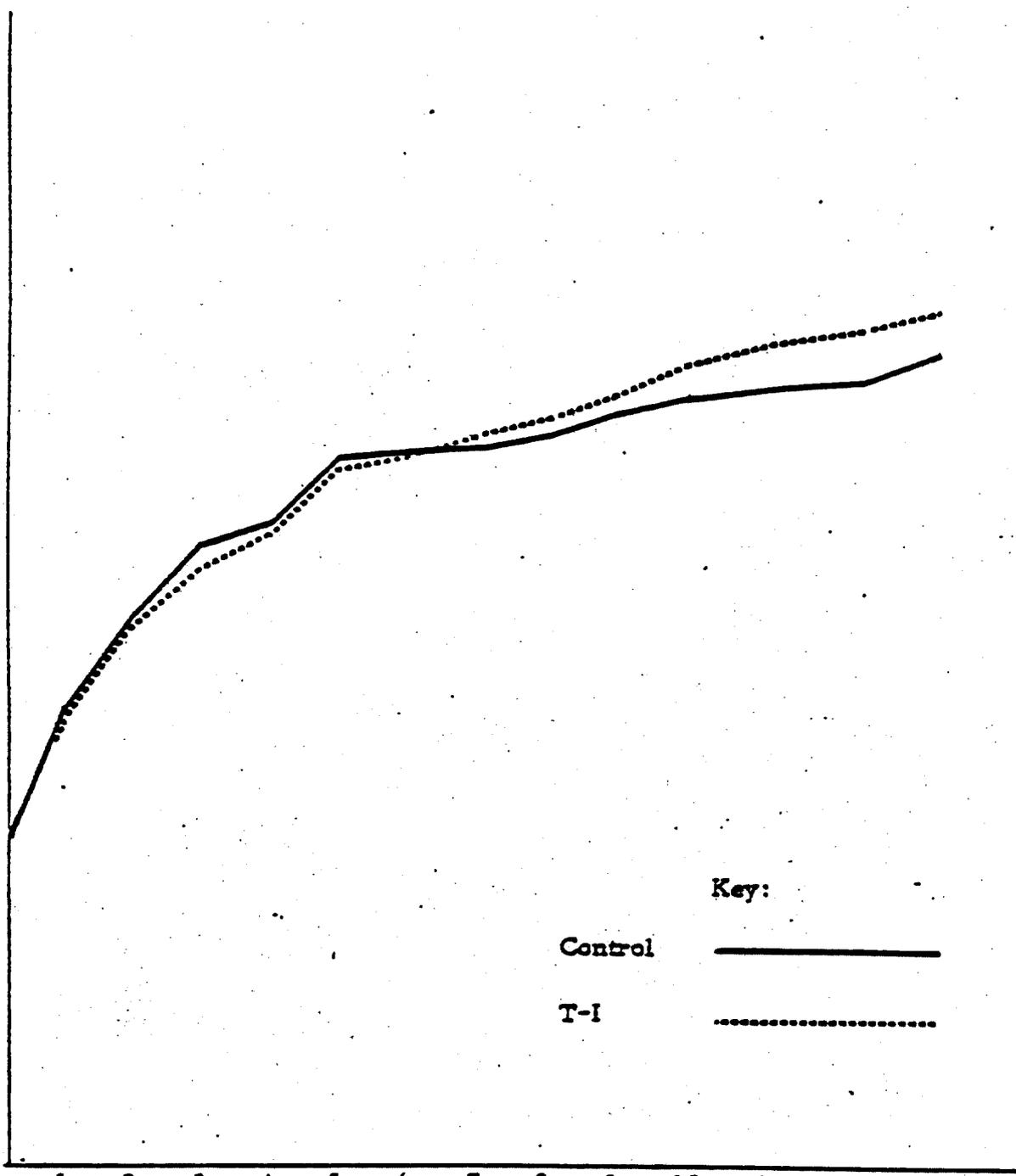
Control

—————

T-I

.....

171



400

300

200

100

0

1

2

3

4

5

6

7

8

9

10

11

12

13

Weeks on Test

Key:

Control

—————

T-I

.....

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B. Food Consumption

Food consumption data collected during the investigation are summarized in Table III.

Differences between amounts of food consumed by test and control group animals were not significant.

TABLE III

TEST MATERIAL: White Oil  
 90-Day Subacute Oral Toxicity Study - Albino Rats

Food Consumption Data

Summary of Mean Values

Dietary Level (ppm)	Sex	Food Consumption (grams/rat/seven days)													90-Day Total Food Consumption (grams/rat)
		1	2	3	4	5	6	7	8	9	10	11	12	13	
None	Males	141	170	180	180	178	167	183	184	192	181	182	174	179	2,291
	Females	133	158	174	191	185	169	175	195	190	179	185	170	194	2,298
10,000	Males	124	134	129	141	136	123	132	140	136	135	140	113	142	1,725
	Females	119	133	124	147	136	130	140	151	148	137	148	121	151	1,785

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C. Mortality and Reactions

A frequency distribution of deaths which occurred during the investigation are presented in Table IV.

No untoward behavioral reactions were noted among any of the animals employed in the investigation.

TABLE IV

TEST MATERIAL: White Oil

90-Day Subacute Oral Toxicity Study - Albino Rats

Mortality Data

Frequency and Distribution of Deaths

Dietary Level (ppm)	Sex	Frequency and Distribution of Deaths													Total Dead Number Tested	
		Week:														
		1	2	3	4	5	6	7	8	9	10	11	12	13		
None	Males	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0/15
10,000	Males	0	0	0	0	0	1*	0	0	0	0	0	0	0	0	1/15
None	Females	0	0	0	0	0	4*	0	0	0	0	0	1*	0	0	5/15
10,000	Females	0	0	0	0	0	2*	0	0	0	0	0	0	0	0	2/15

\* Deaths were a result of blood collection.

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D. Hematology Studies

The results of hematology studies done on male and female rats in the control group and in treatment group T-I (10,000 ppm) are summarized in Tables V and VI.

Mean values for total leukocyte and erythrocyte counts, differential leukocyte counts, hemoglobin concentration and hematocrit were within the limits of normal in rats in all examined groups at 42 and 84 days of treatment.

TABLE V

TEST MATERIAL: White Oil  
 90-Day Subacute Oral Toxicity Study - Albino Rats

Hematologic Data

Summary of Mean Values

Dietary Level (ppm)	Sex	Leukocyte (thousands/mm <sup>3</sup> )		Erythrocyte (millions/mm <sup>3</sup> )		Hemoglobin (g/100 ml)		Hematocrit (%)	
		Test Day: 42	Test Day: 84	Test Day: 42	Test Day: 84	Test Day: 42	Test Day: 84	Test Day: 42	Test Day: 84
None	Males	10.8	9.5	8.02	9.12	16.7	16.3	50	52
10,000	Males	14.5	10.2	8.16	9.15	16.8	16.2	48	51
None	Females	7.5	8.9	7.60	8.81	16.1	16.5	48	51
10,000	Females	9.1	6.8	8.09	8.47	16.8	15.8	46	50

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TABLE VI

TEST MATERIAL: White Oil

90-Day Subacute Oral Toxicity Study - Albino Rats

Hematologic Data

Summary of Mean Values

Dietary Level (ppm)	Sex	Differential Leukocyte Count (Number of Cells per Hundred)											
		Neutrophils		Lymphocytes		Monocytes		Eosinophils		Basophils		Test Day:	
		42	84	42	84	42	84	42	84	42	84	42	84
None	Males	11.9	12.5	86.1	85.0	0.9	1.5	1.1	1.0	0	0	0	0
10,000	Males	14.2	13.6	84.5	84.6	0.8	0.7	0.5	1.0	0.1	0	0	0
None	Females	9.9	12.5	88.8	85.5	0.8	1.2	0.5	0.8	0	0	0	0
10,000	Females	12.9	11.8	85.5	86.1	0.8	0.9	0.8	1.2	0	0	0	0

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E. Clinical Chemistry Studies

The results of clinical chemistry studies done on male and female rats in the control group and in treatment group T-I (10,000 ppm) are summarized in Tables VII through IX.

Mean values for serum glucose, BUN, SAP, SGPT, cholesterol, triglycerides and total lipids were within the limits of normal after 42 and 84 days of treatment\*. Values for phospholipids and for total esterified fatty acids also were normal, when the values of treated animals were compared to those of control animals after 42 and 84 days of treatment.

\* Melby and Altman: Handbook of Laboratory Animal Science, Volume II, CRC Press, Cleveland, Ohio, 1974.

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TABLE VII

TEST MATERIAL: White Oil

90-Day Subacute Oral Toxicity Study - Albino Rats

Clinical Chemistry Data

Summary of Mean Values

Dietary Level (ppm)	Sex	Glucose (mg/100 ml)		BUN (mg/100 ml)		SAP (Bessey-Lowry-Brock Units) (International Units)		SGPT (International Units)	
		Test Day: 42	Test Day: 84	Test Day: 42	Test Day: 84	Test Day: 42	Test Day: 84	Test Day: 42	Test Day: 84
None	Males	125	106	14	13	6.7	5.0	44	44
10,000	Males	128	109	15	12	6.4	4.7	44	49
None	Females	118	107	16	12	4.2	4.0	40	43
10,000	Females	117	99	14	11	4.5	3.6	32	39

TABLE VIII

TEST MATERIAL: White Oil

90-Day Subacute Oral Toxicity Study - Albino Rats

Clinical Chemistry Data

Summary of Mean Values

Dietary Level (ppm)	Sex	Cholesterol (mg/dl)		Triglycerides (mg/dl)	
		Test Day: 42	Test Day: 84	Test Day: 42	Test Day: 84
None	Males	74	70	133	93
10,000	Males	71	64	116	53
None	Females	84	71	74	53
10,000	Females	81	71	74	54

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TABLE IX

TEST MATERIAL: White Oil

90-Day Subacute Oral Toxicity Study - Albino Rats

Clinical Chemistry Data

Summary of Mean Values

Dietary Level (ppm)	Sex	Total Lipids (mg/dl)		Phospholipids (mg/dl)		Total Esterified Fatty Acids (mg %)	
		Test Day: 42	Test Day: 84	Test Day: 42	Test Day: 84	Test Day: 42	Test Day: 84
None	Males	262	250	170	134	363	292
10,000	Males	249	257	148	143	323	273
None	Females	261	219	171	159	323	273
10,000	Females	226	231	145	154	315	300

F. Urinalyses

The results of examination of urine specimens collected from male and female rats in the control group and in treatment group T-I (10,000 ppm) are summarized in Tables X and XI.

Mean values for urinary glucose, protein, pH and specific gravity were within the limits of normal in rats in all groups examined at 42 and 84 days of treatment. Mean values for microscopic elements were also within the limits of normal at these times.

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TABLE X  
TEST MATERIAL: White Oil

90-Day Subacute Oral Toxicity Study - Albino Rats

Urinalyses Data

Summary of Mean Values

Dietary Level (ppm)	Sex	Glucose		Protein		pH		Specific Gravity	
		Test Day: 42	Test Day: 84	Test Day: 42	Test Day: 84	Test Day: 42	Test Day: 84	Test Day: 42	Test Day: 84
None	Males	N	N	+	T	6.8	6.7	1.017	1.013
10,000	Males	N	N	+	T	8.5	6.6	1.022	1.017
None	Females	N	N	N	T	6.8	6.6	1.011	1.013
10,000	Females	N	N	N	T	7.6	6.4	1.014	1.010

Key:

- N = negative
- P = positive
- NL = normal
- T = trace amounts
- + = slight amounts
- ++ = moderate amounts
- +++ = large amounts
- ++++ = extreme amounts

**TABLE XI**

**TEST MATERIAL: White Oil**

**90-Day Subacute Oral Toxicity Study - Albino Rats**

**Urinalyses Data**

**Summary of Mean Values**

Dietary Level (ppm)	Sex	Leukocytes		Erythrocytes		Crystals	
		Test Day: 42	Test Day: 84	Test Day: 42	Test Day: 84	Test Day: 42	Test Day: 84
None	Males	0	0	0	0	+	+
10,000	Males	0	0	0	T	+	T
None	Females	0	T	0	T	NL	T
10,000	Females	0	0	0	0	NL	+

**Key:**

- N = negative
- P = positive
- NL = normal
- T = trace amounts
- + = slight amounts
- ++ = moderate amounts
- +++ = large amounts
- ++++ = extreme amounts

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G. Pathologic Studies

1. Gross Findings

Gross necropsy findings among test animals were not significantly different from those noted in control animals.

2. Organ Weights and Ratio Data

Organ weight and ratio data are presented in Tables XII through XVII.

Significant differences between the test and control groups are designated by asterisks following the test group value.

Due to lack of any deleterious histopathologic findings, the differences noted were considered normal for a random population of rats.

TABLE XII

TEST MATERIAL: White Oil

90-Day Subacute Oral Toxicity Study - Albino Rats

Organ Weight and Ratio Data

Summary of Mean Values

Organ: Brain

Dietary Level (ppm)	Absolute Organ Weight (g)		Organ/Body Weight Ratio (g/100 g)		Organ/Brain Weight Ratio (g/g)	
	Males	Females	Males	Females	Males	Females
None	2.176	1.950	0.4478	0.6896	1.0000	1.0000
10,000	2.196	1.941	0.4787	0.6575	1.0000	1.0000

No statistically significant treatment effects found.

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TABLE XIII

TEST MATERIAL: White Oil

90-Day Subacute Oral Toxicity Study - Albino Rats

Organ Weight and Ratio Data

Summary of Mean Values

Organ: Gonads

Dietary Level (ppm)	Absolute Organ Weight (g)		Organ/Body Weight Ratio (g/100 g)		Organ/Brain Weight Ratio (g/g)	
	Males	Females	Males	Females	Males	Females
None	3.175	0.078	0.6541	0.0274	1.4645	0.0410
10,000	3.319	0.084	0.7276	0.0286	1.5175	0.0448

No statistically significant treatment effects found.

TABLE XIV

TEST MATERIAL: White Oil

90-Day Subacute Oral Toxicity Study - Albino Rats

Organ Weight and Ratio Data

Summary of Mean Values

Organ: Heart

Dietary Level (ppm)	Absolute Organ Weight (g)		Organ/Body Weight Ratio (g/100 g)		Organ/Brain Weight Ratio (g/g)	
	Males	Females	Males	Females	Males	Females
None	1.493	0.963	0.3066	0.3394	0.6869	0.5082
10,000	1.384*	0.962	0.3004	0.3237	0.6306*	0.5103

\* Statistically significant difference at the 95% confidence level

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TABLE XV

TEST MATERIAL: White Oil

90-Day Subacute Oral Toxicity Study - Albino Rats

Organ Weight and Ratio Data

Summary of Mean Values

Organ: Kidneys

Dietary Level (ppm)	Absolute Organ Weight (g)		Organ/Body Weight Ratio (g/100 g)		Organ/Brain Weight Ratio (g/g)	
	Males	Females	Males	Females	Males	Females
None	3.200	1.873	0.6574	0.6586	1.4716	0.9835
10,000	2.963	1.945	0.6438	0.6555	1.3510*	1.0353

\* Statistically significant difference at the 95% confidence level

TABLE XVI

TEST MATERIAL: White Oil

90-Day Subacute Oral Toxicity Study - Albino Rats

Organ Weight and Ratio Data

Summary of Mean Values

Organ: Liver

Dietary Level (ppm)	Absolute Organ Weight (g)		Organ/Body Weight Ratio (g/100 g)		Organ/Brain Weight Ratio (g/g)	
	Males	Females	Males	Females	Males	Females
None	11.717	6.757	2.3095	2.3781	5.3744	3.5607
10,000	10.434*	7.092	2.2525*	2.3902	4.7638*	3.7514

\* Statistically significant difference at the 95% confidence level

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TABLE XVII

TEST MATERIAL: White Oil

90-Day Subacute Oral Toxicity Study - Albino Rats

Organ Weight and Ratio Data

Summary of Mean Values

Organ: Spleen

Dietary Level (ppm)	Absolute Organ Weight (g)		Organ/Body Weight Ratio (g/100 g)		Organ/Brain Weight Ratio (g/g)	
	Males	Females	Males	Females	Males	Females
None	0.714	0.593	0.1465	0.2072	0.3283	0.3094
10,000	0.724	0.494	0.1570*	0.1664	0.3303	0.2636

\* Statistically significant difference at the 95% confidence level

3. Histopathologic Findings

The results of histopathologic examination of male and female rats used in experiment IBT No. 621-05634 are presented in Tables XVIII and XIX.

No histopathologic alterations attributable to treatment with the test material for 90 days were observed. Tissue changes observed in treated rats were similar to those seen in control rats and all were considered manifestations of intercurrent disease. Sections of stomach from male and female rats in the control group and in treatment group T-I (10,000 ppm) were stained with Alcian Blue PAS, and sections of liver from the same rats were treated with Osmium Tetroxide.

Examination of Alcian Blue PAS-stained sections of stomach revealed intense staining of superficial portions of the mucosa by Alcian Blue with faint PAS positivity occurring in the immediately subjacent zone. The intensity of Alcian Blue staining and the total thickness of the zones of reaction to Alcian Blue and to PAS were greater in control rats than in treated rats. No sex differences were observed in Alcian Blue PAS staining reactions.

Examination of liver specimens treated with Osmium Tetroxide revealed osmiophilic globules of varying number and size in hepatocytes usually in portal areas. No difference was observed in number, size or distribution of osmiophilic globules in the livers of control and treated rats.

  
D. J. Sullivan, D.V.M.  
Diplomate, American College of  
Veterinary Pathologists



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TABLE XVIII continued  
 TEST MATERIAL: White Oil

90-Day Subacute Oral Toxicity Study - Albino Rats  
 Histopathologic Changes

Final Sacrifice  
 Sex: Male

Organ	Findings	Group and Dietary Level:		T-1	
		Control (None)	10	(10,000 ppm)	10
		Incidence	Average Grade	Incidence	Average Grade
Urinary bladder	Proteinaceous plug in lumen	5	P	1	P
Tesitis	Focal atrophy with mineralization	1	2.0	0	-
Pituitary gland	Rathke's pouch cyst	0	-	1	P
Adrenal gland	Hematocysts, unilateral	0	-	1	1.0
Brain	Focal meningitis	0	-	1	1.0
Eye	Posterior synechia	0	-	1	1.0
	Iridocyclitis	0	-	1	1.0
	Ilyphema	0	-	1	1.0

**TABLE XIX**  
**TEST MATERIAL: White Oil**  
**90-Day Subacute Oral Toxicity Study - Albino Rats**

**Histopathologic Changes**

**Final Sacrifice**

**Sex: Female**

<b>Organ</b>	<b>Findings</b>	<b>Group and Dietary Level:</b>		<b>T-1</b>	
		<b>Control (None) 10</b>	<b>Average Grade</b>	<b>Incidence</b>	<b>Average Grade</b>
		<b>Number Examined:</b>		<b>(10,000 ppm)</b>	
				<b>10</b>	
<b>Trachea</b>	Chronic tracheitis	3	1.7	1	2.0
<b>Lung</b>	Chronic murine pneumonia	8	1.1	8	1.1
	Terminally inhaled blood	1	1.0	1	3.0
<b>Liver</b>	Focal lymphocytic infiltrates, random distribution	0	-	5	1.0
<b>Colon</b>	Parasite in lumen (nematodiasis)	2	P	0	-
<b>Kidney</b>	Microconcretions in tubules, unilateral	4	1.0	1	1.0
	Microconcretions in tubules, bilateral	2	1.5	5	1.6
	Acute pyelonephritis, unilateral	1	1.0	0	-
	Chronic interstitial nephritis, unilateral	1	2.0	0	-
	Infarction, unilateral	1	2.0	0	-
<b>Uterus</b>	Hydrometra, unilateral	1	1.0	0	-
	Hydrometra, bilateral	4	1.5	2	2.5

**Grading System**

- 1 = minimal or trace in severity
- 2 = mild in severity
- 3 = moderate in severity
- 4 = marked in severity
- 5 = extreme in severity
- P = Present, no grade

*Industrial* BIO-TEST *Laboratories, Inc.*

1810 FRONTAGE ROAD

NORTHBROOK, ILLINOIS 60062

REPORT TO

ATLANTIC RICHFIELD COMPANY

ACUTE ORAL TOXICITY STUDY WITH  
7552 SAMPLE 6025-F-51205  
IN ALBINO RATS

ACCOUNT #8136-5960-A3465

OCTOBER 16, 1974

IBT NO. 601-05633

Industrial BIO-TEST Laboratories, Inc.

1810 FRONTAGE ROAD  
NORTHBROOK, ILLINOIS 60062

Mr. H. J. Matson, Manager  
Product Specifications  
Atlantic Richfield Company  
Harvey Technical Center  
400 East Sibley Boulevard  
Harvey, Illinois 60426

Dear Mr. Matson:

Re: IBT No. 601-05633 - Acute Oral Toxicity  
Study with 7552 Sample 6025-F-51205 in  
Albino Rats - Account #8136-5960-A3465

We are submitting herewith our laboratory report prepared  
in connection with the above study.

Very truly yours,



J. C. Calandra  
President

JCC:slg

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REPORT TO  
ATLANTIC RICHFIELD COMPANY  
ACUTE ORAL TOXICITY STUDY WITH  
7552 SAMPLE 6025-F-51205  
IN ALBINO RATS

ACCOUNT #8136-5960-A3465

OCTOBER 16, 1974

IBT NO. 601-05633

I. Introduction

At the request of Atlantic Richfield Company, an acute oral toxicity study with albino rats was conducted with a sample identified as 7552 Sample 6025-F-51205.

II. Summary

An acute oral toxicity study with albino rats was conducted with 7552 Sample 6025-F-51205. The acute oral median lethal dose (LD<sub>50</sub>) was calculated to be greater than 5,000 mg/kg.

Respectfully submitted,

INDUSTRIAL BIO-TEST LABORATORIES, INC.

Report prepared by: Wendy A. Harrison  
Wendy A. Harrison, B.S.  
Technician.  
Acute Toxicity

Report approved by: C. W. Mastri  
C. W. Mastri, B.S.  
Section Head, Acute Toxicity

M. L. Keplinger  
M. L. Keplinger, Ph.D.  
Manager, Toxicology

slg

2002

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III. Results

A. Mortality and Body Weights

Individual mortality and body weight data are presented in Table I.

---

TABLE I

Acute Oral Toxicity Study - Albino Rats

Mortality and Body Weight Data

Test Material: 7552 Sample 6025-F-51205

Form Administered: Undiluted

Acute Oral LD<sub>50</sub> > 5,000 mg/kg

Strain: Charles River

IBT No.: 601-05633

Classification: Practical

Non-Toxic

Dose Level (mg/kg)	Animal Number and Sex	Individual Body Weights (grams)		Number Dead Number Tested	Percent Dead
		Test Day Number: 0	Test Day Number: 14		
5,000	1-M	238	376	0/10	0
	2-M	238	370		
	3-M	230	361		
	4-M	230	360		
	5-M	224	343		
	6-F	210	262		
	7-F	197	253		
	8-F	178	231		
	9-F	190	250		
	10-F	202	265		

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B. Reactions

The pharmacotoxic symptoms displayed by the rats post-oral administration of the test material included hypoactivity and ruffed fur after one hour. Slightly oily fur at the urinary region was noted within five hours. Within two days, all animals appeared normal.

Necropsy examination of all animals sacrificed at the end of the 14-day observation period did not reveal any gross pathologic alterations.

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IV. Appendix

The detailed investigational procedure employed in this study is presented in the following pages:

ACUTE ORAL TOXICITY STUDY - ALBINO RATS

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Young albino rats derived from Sprague-Dawley stock were used as test animals. All animals were kept under observation for five days prior to experimental use, during which period they were checked for general health and suitability as test animals. The animals were housed in stock cages and were permitted a standard laboratory diet plus water ad libitum, except during the 16-hour period immediately prior to oral intubation when food was withheld.

Initial screening was conducted in order to determine the general level of toxicity of the test material. Selected groups of albino rats were administered the test material at several dose levels. All doses were administered directly into the stomach of the rats using a hypodermic syringe equipped with a ball-tipped intubating needle.

After oral administration of the test material, the rats were housed individually in suspended, wire-mesh cages and observed for the following 14 days. Initial and final body weights, mortalities, and reactions were recorded. A necropsy examination was conducted on all animals.

At the end of the observation period, the acute oral median lethal dose (LD<sub>50</sub>) of the test material was calculated, if possible, using the techniques of Litchfield and Wilcoxon\*. The test material was then assigned a classification in accordance with Harold C. Hodge\*\*. The classification system is presented in the following Table.

\* Litchfield, J. T. Jr., and Wilcoxon, F., "A Simplified Method of Evaluating Dose-Effect Experiments," J. Pharm. & Exp. Ther. 96, 99 (1949).

\*\* Hodge, Harold C., "The LD<sub>50</sub> and its value", American Perfumer and Cosmetics 80, 57 (1965).

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TABLE

Acute Oral Toxicity Study - Albino Rats .

Classification of Test Materials  
Based on Acute Oral LD<sub>50</sub>

Acute Oral LD <sub>50</sub> (Range of Values)	Classification	Probable lethal dose for a 70 kg man in commonly used measures
Less than 5 mg/kg	Extremely toxic	a taste (less than 7 drops)
5 - 50 mg/kg	Highly toxic	between 7 drops and 1 teaspoonful
50 - 500 mg/kg	Moderately toxic	between 1 teaspoonful and 1 ounce
500 - 5,000 mg/kg	Slightly toxic	between 1 ounce and 1 pint or, 1 pound
5,000 - 15,000 mg/kg	Practically non-toxic	between 1 pint and 1 quart
Greater than 15,000 mg/kg	Relatively harmless	more than 1 quart

31. August 1973

2 HAMBURG 39  
BESELALLEE 30 A  
(0 41 11) 61 61 66

Untersuchung von TUFFLO auf seinen Gehalt an  
polycyclischen carcinogenen Kohlenwasserstoffen

Untersuchte Probe

TUFFLO 6056 (Duotreat P-500), sample no 6025-F-51205,  
date 7/5/1973, ATLANTIC RICHFIELD COMPANY, Los Angeles.

Methode

Die einzelnen Anreicherungs-schritte (a - d) wurden mit  
folgenden carcinogenen Originalsubstanzen getestet :  
Benzo(a)anthracen, Chrysen, Benzo(b)fluoranthen, Benzo  
(j)fluoranthen, Benzo(a)pyren, Dibenz(a,h)anthracen,  
Dibenz(a,j)anthracen und Indenopyren.

(a) Flüssig-flüssig-Verteilung : Dimethylformamid-Wasser-  
Cyclohexan (Dtsch. Lebensm.-Rdsch 65 (1969) 229)

(b) Chromatographie an Silicakel mit Cyclohexan (JAOAC 55  
(1972) 631)

(c) Verteilungschromatographie an Sephadex LH 20, statio-  
näre Phase : DMF-Wasser (85-15), mobile Phase : Hexan.

(d) Chromatographie an Sephadex LH 20 mit Isopropanol  
(JAOAC 55 (1972) 631).

Die Auftrennung des Gemisches der so angereicherten  
Fraktion der polycyclischen aromatischen Kohlenwasser-  
stoffe wurde gaschromatographisch durchgeführt (Hoch-  
leistungssäulen aus Glas 10 m x 2 mm, GasChrom Q sila-  
nisiert 100 - 120 mesh, Silicone OV 101, Säulentemp 250°C.  
(Erdöl u. Kohle 25 531 (1972)).

Die quantitative Auswertung erfolgte durch den Vergleich  
der Fläche des inneren Standards (Benzo(b)chrysen) mit  
dem FID-Detektorsignal der entsprechenden Einzelkomponente.

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Die Nachweisgrenze liegt bei  $10^{-8}$  g/g (= 0,01 ppm).

### ERGEBNIS

Das untersuchte Produkt TUFFLO enthält keine nachweisbaren Mengen der eingangs aufgeführten carcinogenen polycyclischen Kohlenwasserstoffe oder Methylderivate dieser Kohlenwasserstoffe. Bei der verwendeten gaschromatographischen Untersuchungsmethode werden alle polycyclischen aromatischen Kohlenwasserstoffe mit 4 bis 7 Ringen erfaßt. Im Gegensatz zu den bisher verwendeten spektrometrischen Bestimmungsmethoden werden sowohl bekannte als auch unbekannte Aromaten erfaßt, da jede kohlenstoffhaltige Verbindung durch den Flammen-Ionisations-Detektor mengenproportional angezeigt wird.

Zur Kontrolle der verwendeten Methode wurde dem Originalmuster TUFFLO (100 g) außer dem inneren Standard Benzo(b)chrysen (42,75 µg) noch folgende polycyclischen Kohlenwasserstoffe zugesetzt :

Chrysen (5,0 µg)

Benzo(b)fluoranthren (5,5 µg)

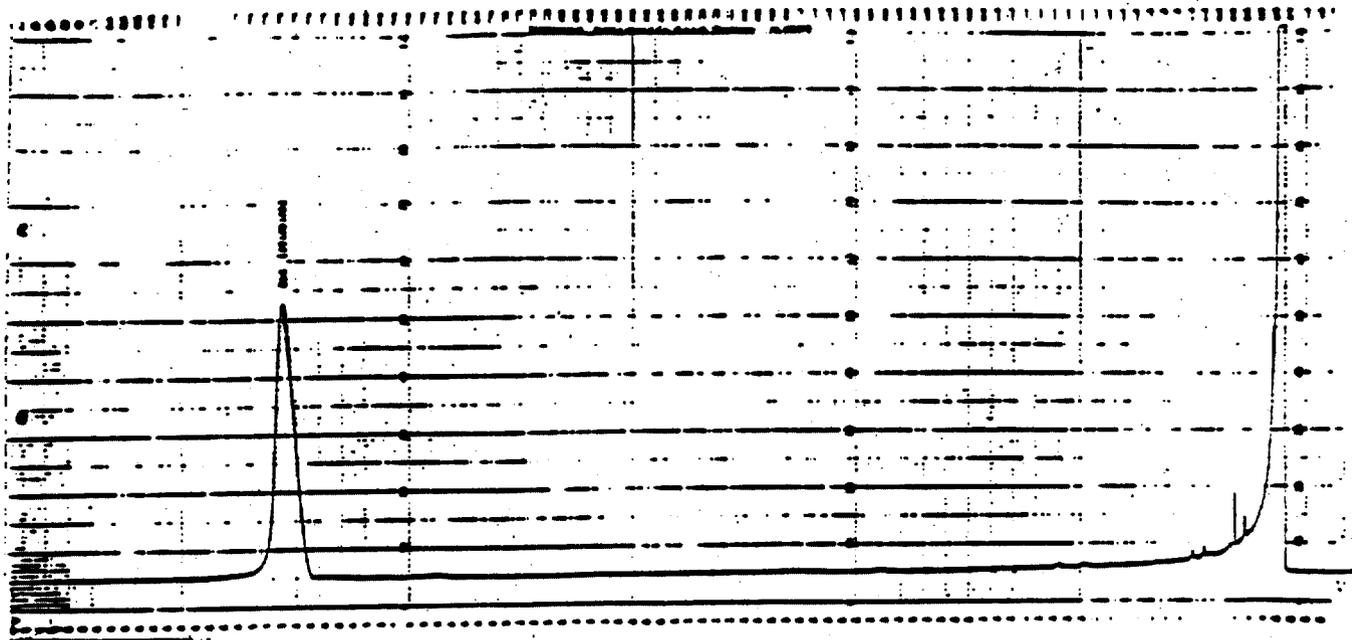
Benzo(a)pyren (4,5 µg)

Dibenz(a,j)anthracen (5,0 µg)

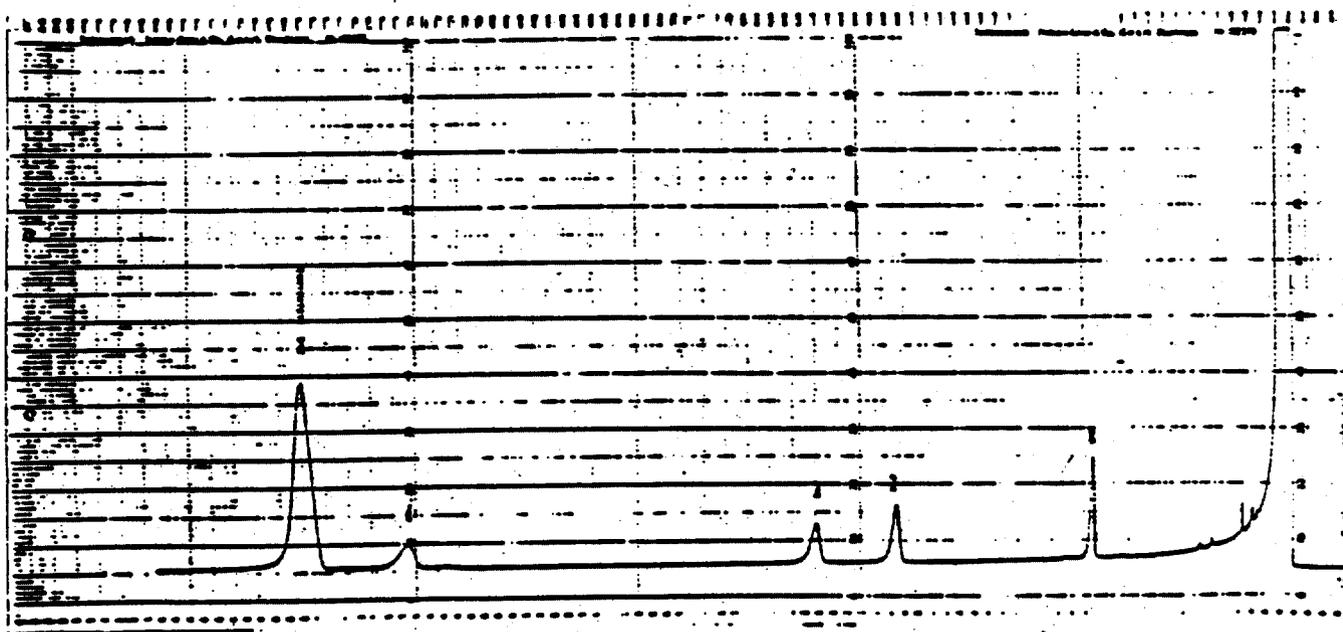
Diese dotierte Probe wurde in der gleichen Weise wie die Originalprobe TUFFLO aufgearbeitet und gaschromatographisch untersucht.

Ein Vergleich beider Proben, der Originalprobe und der mit Kohlenwasserstoffen dotierten Probe, ist in den Bildern 1 und 2 wiedergegeben.

Während die Originalprobe nur den zugefügten inneren Standard erkennen läßt, sind in der zweiten Probe neben dem Standard alle 4 zugesetzten Kohlenwasserstoffe mit einer Ausbeute von 95 - 99 % (bezogen auf den inneren Standard) als Signale nachweisbar.



**Bild 1 :** Registrierstreifen des Gaschromatogramms von TUFFLO (100 g), Originalprobe mit inneren Standard BbC (42,75 µg)  
 Gaschromatographische Bedingungen : Glassäule 2 mm x 10  
 Silicone OV 101 , 5 % aus GasChrom Q, isotherm 250°



**Bild 2 :** Registrierstreifen des Gaschromatogramms von TUFFLO (100 g), das vor der Aufarbeitung mit dem inneren Standard BbC (42,75 µg) und CHRYSEN (5,0 µg), BENZO(b) FLUORANTHEN (5,5 µg), BENZO(a)PYREN (4,5 µg) und DIBENZ(a,j)ANTHRACEN (5,0 µg) versetzt worden war.  
 Gaschromatographische Bedingungen wie oben

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### ZUSAMMENFASSUNG

In dem untersuchten Produkt TUFFLO sind keine polycyclischen aromatischen carcinogenen Kohlenwasserstoffe nachweisbar (Nachweisgrenze  $10^{-3}$  g/g = 0,01 ppm).

Dem Produkt zugesetzte Mengen an Chrysen, Benzo(b)fluoranthren, Benzo(a)pyren und Dibenz(a,j)anthracen in der Größenordnung von 0,05 ppm werden mit hohen Ausbeuten wiedergefunden.

  
Prof. Dr. G. Grimmer

92 JUN 19 AM 8:57

CECATS TRIAGE TRACKING DBASE ENTRY FORM

CECATS DATA: FY-OTS-0592-0849 SEQ. A  
 Submission # ~~0849~~

INFORMATION REQUESTED: FLWP DATE:  
 0501 NO INFO REQUESTED  
 0502 INFO REQUESTED (TECH)  
 0503 INFO REQUESTED (VOL ACTIONS)  
 0504 INFO REQUESTED (REPORTING RATIONALE)  
 DISPOSITION:  
 0639 REFER TO CHEMICAL SCREENING  
 0678 CAP NOTICE

VOLUNTARY ACTIONS:  
 0401 NO ACTION REPORTED  
 0402 STUDIES PLANNED/UNDERWAY  
 0403 NOTIFICATION OF WORKER/OTHERS  
 0404 LABEL/MSDS CHANGES  
 0405 PROCESS/HANDLING CHANGES  
 0406 APP./USE DISCONTINUED  
 0407 PRODUCTION DISCONTINUED  
 0408 CONFIDENTIAL

TYPE: (INT) SUPP FLWP  
 SUBMITTER NAME: American Petroleum Institute

SUB. DATE: 5/19/92 OTS DATE: 5/19/92 CSB DATE: 7/10/92

CHEMICAL NAME: Oil (mineral), white  
White mineral oil (petroleum)  
 CAS# 8042-47-5

INFORMATION TYPE:	P F C	INFORMATION TYPE:	P F C	INFORMATION TYPE:	P F C
0201 ONCO (HUMAN)	01 02 04	0216 EPI/CLIN	01 02 04	0241 IMMUNO (ANIMAL)	01 02 04
0202 ONCO (ANIMAL)	01 02 04	0217 HUMAN EXPOS (PROD CONTAM)	01 02 04	0242 IMMUNO (HUMAN)	01 02 04
0203 CELL TRANS (IN VITRO)	01 02 04	0218 HUMAN EXPOS (ACCIDENTAL)	01 02 04	0243 CHEM/PHYS PROP	01 02 04
0204 MUTA (IN VITRO)	01 02 04	0219 HUMAN EXPOS (MONITORING)	01 02 04	0244 CLASTO (IN VITRO)	01 02 04
0205 MUTA (IN VIVO)	01 02 04	0220 ECO/AQUA TOX	01 02 04	0245 CLASTO (ANIMAL)	01 02 04
0206 REPRO/TERATO (HUMAN)	01 02 04	0221 ENV. OCCUR/REL/FATE	01 02 04	0246 CLASTO (HUMAN)	01 02 04
0207 REPRO/TERATO (ANIMAL)	01 02 04	0222 EMER INCI OF ENV CONTAM	01 02 04	0247 DNA DAM/REPAIR	01 02 04
0208 NEURO (HUMAN)	01 02 04	0223 RESPONSE REQUEST DELAY	01 02 04	0248 PROD/USE/PROC	01 02 04
0209 NEURO (ANIMAL)	01 02 04	0224 PROD/COMP/CHEM ID	01 02 04	0251 MSDS	01 02 04
0210 ACUTE TOX. (HUMAN)	01 02 04	0225 REPORTING RATIONALE	01 02 04	0299 OTHER	01 02 04
0211 CHR. TOX. (HUMAN)	01 02 04	0226 CONFIDENTIAL	01 02 04		
0212 ACUTE TOX. (ANIMAL)	01 02 04	0227 ALLERG (HUMAN)	01 02 04		
0213 SUB ACUTE TOX (ANIMAL)	01 02 04	0228 ALLERG (ANIMAL)	01 02 04		
0214 SUB CHRONIC TOX (ANIMAL)	01 02 04	0239 METAB/PHARMACO (ANIMAL)	01 02 04		
0215 CHRONIC TOX (ANIMAL)	01 02 04	0240 METAB/PHARMACO (HUMAN)	01 02 04		

TRIAJE DATA: NON-CBI INVENTORY YES (CONTINUE) NO (DROP) DETERMINE  
 YES (DROP/REFER) NO (CONTINUE)  
 REFER: Internal (FCAS)  
Review of  
Submittable pump  
 TOXICOLOGICAL CONCERN: LOW MED HIGH  
 USE: PRODUCTION:

COMMENTS:



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

AUG 10 1992

Robert T. Drew, Ph.D.  
American Petroleum Institute  
1220 L Street, N.W.  
Washington, D.C. 20005

OFFICE OF  
PESTICIDES AND TOXIC  
SUBSTANCES

Dear Sir:

This letter acknowledges EPA's receipt of information submitted on a voluntary basis and designated by the Office of Pollution Prevention and Toxics as FYI (For Your Information). For your reference, a copy of the first page of your submission is enclosed and displays the assigned FYI Document Control Number (e.g., FYI 0000-0000) assigned by EPA to your submission. Please refer to this number when submitting follow-up or supplemental information.

All submitted correspondence is screened to determine the need for further evaluation. Submissions are then placed in the Agency's public files unless confidentiality is claimed. Such claims must be substantiated, as described in the enclosed "Support Information for Confidentiality Claims". In all future communications with the Agency regarding this submission, please refer to the assigned EPA Document Control Number and address submission to:

OPPT Document Processing Center (TS-790)  
Attn: (FYI Coordinator)  
Office of Pollution Prevention and Toxics  
U.S. Environmental Protection Agency  
401 M Street, S.W.  
Washington, D.C. 20460

The Agency looks forward to continued cooperation with your organization in sharing information that may assist in evaluating & minimizing potential risks posed by chemicals to health and the environment.

Sincerely,

*JF*  
James F. Darr, Section Chief  
Chemical Risk Identification  
Section/CSB/ECAD/OPPT

Attachment

CONCURRENCES							
SYMBOL							
SURNAME							
DATE							



# Triage of FYI Submissions

Date sent to triage: \_\_\_\_\_

Submission number: 0849A

Study type (circle appropriate):

		Acute	
Epi	Repro	Acute w/neuro	<u>Subchronic</u>
Exp	Mutagenicity/Genotox	Subacute	Chronic/onco
Ecotox	Neuro	Sensitization	

Other \_\_\_\_\_

Notes:

For Contractor Use Only	
<u>entire document</u>	pages <u>—</u> pages <u>*, 48, 49, 50, 51</u>
Notes: use black page numbers on upper right * = first page w/ no number	
Contractor reviewer: <u>JW</u>	Date: <u>8-24-92</u>

CECATS/VIRIAGE TRACKING DBASE ENTRY FORM

CECATS DATA: FYI-OTS-0592-0849 SEQ. A  
 Submission # 95H9

TYPE: (NT) SUPP FLWP  
 SUBMITTER NAME: American Petroleum Institute

INFORMATION REQUESTED: FLWP DATE:  
 0501 NO INFO REQUESTED  
 0502 INFO REQUESTED (TECH)  
 0503 INFO REQUESTED (VOL ACTIONS)  
 0504 INFO REQUESTED (REPORTING RATIONALE)  
 DISPOSITION:  
0539 REFER TO CHEMICAL SCREENING  
 0678 CAP NOTICE

VOLUNTARY ACTIONS:  
0403 NO ACTION REPORTED  
 0402 STUDIES PLANNED/UNDERWAY  
 0403 NOTIFICATION OF WORKER/OTHERS  
 0404 LABEL/MSDS CHANGES  
 0405 PROCESS/HANDLING CHANGES  
 0406 APP./USE DISCONTINUED  
 0407 PRODUCTION DISCONTINUED  
 0408 CONFIDENTIAL

SUB. DATE: 5/19/92 OTS DATE: 5/19/92 CSB DATE: 7/10/92

CHEMICAL NAME:  
Oil (mineral), white  
White mineral oil (petroleum)  
 CAS# 8043-47-5

INFORMATION TYPE:	P F C	INFORMATION TYPE:	P F C	INFORMATION TYPE:	P F C
0201 ONCO (HUMAN)	01 02 04	0216 EP/CLIN	01 02 04	0241 IMMUNO (ANIMAL)	01 02 04
0202 ONCO (ANIMAL)	01 02 04	0217 HUMAN EXPOS (PROD CONTAM)	01 02 04	0242 IMMUNO (HUMAN)	01 02 04
0203 CELL TRANS (IN VITRO)	01 02 04	0218 HUMAN EXPOS (ACCIDENTAL)	01 02 04	<u>0243</u> CHEM/PHYS PROP	01 02 04
0204 MUTA (IN VITRO)	01 02 04	0219 HUMAN EXPOS (MONITORING)	01 02 04	0244 CLASTO (IN VITRO)	01 02 04
0205 MUTA (IN VIVO)	01 02 04	0220 ECO/AQUA TOX	01 02 04	0245 CLASTO (ANIMAL)	01 02 04
0206 REPRO/TERATO (HUMAN)	01 02 04	0221 ENV. OCC/REL/FATE	01 02 04	0246 CLASTO (HUMAN)	01 02 04
0207 REPRO/TERATO (ANIMAL)	01 02 04	0222 EMER. INCI OF ENV CONTAM	01 02 04	DNA DAM/REPAIR	01 02 04
0208 NEURO (HUMAN)	01 02 04	0223 RESPONSE REQUEST DELAY	01 02 04	<u>0248</u> PROD/USE/PROC	01 02 04
0209 NEURO (ANIMAL)	01 02 04	<u>0224</u> PROD/COMP/CHEM ID	01 02 04	MSDS	01 02 04
0210 ACUTE TOX. (HUMAN)	01 02 04	0225 REPORTING RATIONALE	01 02 04	0299 OTHER	01 02 04
0211 CHR. TOX. (HUMAN)	01 02 04	CONFIDENTIAL	01 02 04		
<u>0212</u> ACUTE TOX. (ANIMAL)	01 02 04	ALLERG (HUMAN)	01 02 04		
0213 SUB ACUTE TOX (ANIMAL)	01 02 04	ALLERG (ANIMAL)	01 02 04		
<u>0214</u> SUB CHRONIC TOX (ANIMAL)	01 02 04	METAB/PHARMACO (ANIMAL)	01 02 04		
<u>0215</u> CHRONIC TOX (ANIMAL)	01 02 04	METAB/PHARMACO (HUMAN)	01 02 04		

TRACE DATA: NON-CBI INVENTORY YES (CONTINUE) NO (DROP) DETERMINE

ONGOING REVIEW YES (DROP/REFER) NO (CONTINUE) REFER: Internal (FCAD)

SPECIES TOXICOLOGICAL CONCERN: LOW MED HIGH

USE: PRODUCTION:

COMMENTS: Review of Submittal pump



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY  
WASHINGTON, D.C. 20460

OFFICE OF  
PESTICIDES AND TOXIC  
SUBSTANCES

August 13, 1992

MEMORANDUM

SUBJECT: ECCG Meeting- August 27, 1992  
FROM: Oscar Hernandez *O. Hernández*  
TO: ECCG Participants

Attached are draft summaries for two cases- Oil-based Metalworking Fluids and Methyl ethyl ketone/Methyl isobutyl ketone- scheduled for discussion at the next ECCG meeting on Thursday, August 27, 1992 at 11:00 AM in room E352.

The first case, Oil-based Metalworking Fluids, stems from a letter sent to OTS in 1990 by the UAW expressing their concerns about metalworking fluids and a belief that test rules were needed to evaluate the hazard of these chemical mixtures. A copy of this letter is also enclosed for your information. Thus, the central issue to address in this case is the feasibility of conducting toxicity testing on the title chemicals.

The second case, Methyl ethyl ketone (MEK) and Methyl isobutyl ketone (MIBK), consists of two section 4 chemicals. These chemicals are the subject of various ongoing risk reduction and testing activities. The purpose of this activity is to formally dispose of section 4 test data with an expectation that a conclusive assessment will be conducted when the additional testing is finalized.

a3:metalworking fluids.eccg/oh/08/13/92

T. O'BRYAN  
ECAD/TS-778  
E421B ECCG

# **METAL WORKING FLUIDS**

SANDRA STRASSMAN-SUNDY  
RISK ANALYSIS BRANCH  
EXISTING CHEMICAL ASSESSMENT DIVISION  
**DRAFT**  
RM1 MEETING: Sept. 9, 1992

## **OIL-BASED METALWORKING FLUIDS**

### **SUMMARY**

Oil-based metalworking fluids (cutting oils) are the subject of a possible Toxic Substances Control Act (TSCA) § 21 petition by the International Union, United Automobile, Aerospace and Agricultural Implement Workers of America (UAW) for testing under TSCA §4. Their request is for carcinogenicity testing of cutting oil components and formulations.

A review of the available data on oil-based metalworking fluids indicates that there are insufficient data to define the agent(s) of concern. Testing, therefore, is not feasible. Since this group of chemicals is being reviewed by the Economics and Technology Division (ETD) as a use cluster, the question of risk to workers will be specifically addressed. Our recommendation is that this chemical group be referred to ETD for continued work as a use cluster.

### **BACKGROUND**

On July 5, 1990, the Office of Pollution Prevention and Toxics received a letter from the UAW indicating their intent to submit a petition under TSCA §21 requesting TSCA §4 testing of metalworking fluids. The UAW believes that there is evidence "that these materials pose a cancer and respiratory hazard" and "a hazard to the skin." The test rules are intended "to evaluate the hazards of individual constituents of cutting fluids as well as the effects of combined exposure." The UAW also feels that "[a]dditional rules to control exposures are needed as well" (Mirer 1990).

On September 20, 1990 the Agency received a submission under TSCA § 8(e) regarding a semi-synthetic cutting oil HOLCUT 797-G. This risk notification cited upper respiratory irritation during high speed machine operations (Charm 1990).

These two incidents triggered the need to address the plausibility of a toxicity review of cutting oils components and mixtures.

### **CHEMICAL/PHYSICAL/ECONOMIC INFORMATION SUMMARY**

Metalworking fluids are used to lubricate and cool during machining operations. There are over 400 commercial products belonging to one of four major types: straight, soluble, semi-synthetic, and synthetic. All but synthetic contain mineral oil. There are no standard formulations between and/or among commercial

products.

	----- METALWORKING FLUIDS -----			
	<u>Soluble</u>	<u>Semi-Synthetic</u>	<u>Synthetic</u>	<u>Straight</u>
<u>Composition*</u>				
Mineral Oil	70 - 90%	5 - 30%	none	80 - 100%
Emulsifiers	5 - 20%	5 - 30%	?	ND
Consumption	719 M Ibs	163 M Ibs	none	826 M lbs
UAW Interest	yes	(inferential)	yes	yes
SAT Info	yes	yes	none	none
8E Submission		HOLCUT-797G		

\*Other constituents of cutting oils may include corrosion inhibitors, lubricating additives, extreme pressure additives, couplers (surfactants), biocides, and water. With the exception of the water content in synthetic oils, most additives are present in quantities <10% (Kenon Smith undated).

#### SECTION 4 ISSUES

Do we have sufficient information for rule making? If so, should we?

#### REGULATION/CONCESSION STANDARDS

OSHA has established a TWA/PEL of 5mg/m<sup>3</sup> for oil mist. In addition to a TWA/TLV of 5mg/m<sup>3</sup>, ACGIH has recommended a STEL of 10mg/m<sup>3</sup>.

#### FINDINGS

##### EXPOSURE

There are limited exposure data. The UAW letter cites five epidemiologic reports of worker exposure to cutting fluids. Use to cool many machine operations is presumed to be widespread based on economic consumption figures (Smith 1990). One cross-sectional epidemiologic study that showed decreased pulmonary function included several breathing zone measurements of mineral oil mist that were below the PEL/TLV (Stroup 1990; Silverstein 1988).

##### Hazard

The OPPT Structure Activity Team (SAT) rated the toxicity of many of the known chemical components of metalworking fluids. They noted some chemicals of high and medium concern, but few individual chemical components common to all metalworking fluids. While many of the remaining chemicals are not thought to be intrinsically toxic, the inhalation of fine mists of cutting oils containing not only a mixture of chemicals, but also particles of the material

being cut cannot be excluded. This may produce a toxicity that cannot be linked to any particular chemical (Wagner 1990; Murphy 1990).

HUMAN STUDIES

Data available from epidemiologic studies are summarized below. These findings are discussed below.

-----METALWORKING FLUIDS-----

	<u>Soluble</u>	<u>Semi-Synthetic</u>	<u>Synthetic</u>	<u>Straight</u>
Pulmonary Function	decreased	ND	decreased	no
GI Cancer	yes	yes	yes	no
Brain Cancer	<-----many cutting oils plus other chemicals----->			

RISK CHARACTERIZATION/DISCUSSION

Although there are commonalities between and among the >400 commercially available metalworking fluids, there are no standard compositions. Therefore the UAW request for testing to evaluate the individual constituents and combined exposures from cutting oils is problematic.

The difficulty in defining agents of concern can be exemplified in the case of HOLCUT-797G, the subject of TSCA § 8(e) submission 8EHQ-0890-1078. Workers were reportedly experiencing adverse upper respiratory effects during high speed machining, though not at low speed. Since adverse effects from mineral oil exposure generally target the lung, the causative agent(s) is speculative--and include the material being machined (Murphy 1990).

Moreover, the SAT Health Hazard Review adds little clarity. Although metalworking fluids contain chemicals of high, medium, and low health concern, the inhalation of fine particles of the material being cut must be considered in evaluating total chemical exposure. These particles, coupled with mineral oil mist and other product constituents, may produce a toxicity that cannot be linked to any particular chemical (Wagner 1990; Murphy 1990). Even further obfuscation is evident when looking at HOLCUT-797G relative to the SAT: the only chemicals common both to the SAT list and HOLCUT-797G were glycol ethers.

Information gleaned from available epidemiologic studies similarly falls to elucidate a specific chemical or mixture. Two proportional mortality ratio (PMR) studies show a strong association between exposure to metalworking fluids and gastrointestinal (GI) cancer. And although decreased pulmonary function (FE<sub>1</sub>) occurred at levels below the mineral oil TWA/PEL in one cross-section study, and a significant excess of brain cancer was workplace related in another, neither study could isolate chemical exposure to individual chemical components or mixtures (Stroup 1990).

The available data are inadequate to define specific agents in metalworking fluids for toxicity testing at this time. However, ETD currently has several use clusters that include cutting oils. They are in the process of reviewing commercial formulations of metalworking

fluids and itemizing their constituents (Strassman-Sundy 1992). The resultant product should provide a comprehensive list of pertinent chemicals that might serve as a more precise guide in determining which, if any, chemical constituents and/or mixtures might be tested under TSCA § 4. It must be kept in mind, however, that the available human studies cannot delineate any specific agent(s).

## CONCLUSION

There are insufficient data to define the agent(s) of concern, and therefore testing of oil-based cutting fluids for carcinogenicity is not feasible. The metalworking fluids category could be referred to ETD for further definition as a use cluster.

## REFERENCES CITED/REVIEWED

- Charm J. 1990. Letter from Joel B Charm, Allied Signal to the TSCA 8 (e) Coordinator, Office of Pollution Prevention and Toxics (spell out). 8EHQ-00990-1078 (Initial) Subject: Toxic Substances Control Act - Section 8(e) Substantial Risk Notification. September 20, 1990.
- Hernandez O. 1990. Note from Oscar Hernandez, Risk Analysis Branch, Existing Chemical Assessment Division, Office of Pollution Prevention and Toxics to Pre-RM1 Meeting Attendees. Subject: Metalworking Fluids, October 10, 1990.
- Kennedy S., Greaves F., Kriebel D., Elsen E., Smith T., Woskie S. 1989. Acute pulmonary responses among automobile workers exposed to aerosols of machining fluids. American Journal of Industrial Medicine 15: 627-641.
- McMahon P. October 12, 1990. Memorandum from Paul N. McMahon, CS13, Existing Chemical Assessment Division Office of Pollution Prevention and Toxics to David R. Williams Chemical Screening Branch, Existing Chemical Assessment Division, Office of Pollution Prevention and Toxics. Subject: Status Report 8EHQ-0990-1078.
- Mirer F. 1990. Letter from Franklin E. Mirer, PhD. International Union, United Automobile, Aerospace & Agricultural Implement Workers of America - UAW to charges Elkins, Office of Pollution Prevention and Toxics. June 28, 1990.
- Murphy J. November 28, 1990 Memorandum from James Murphy, Oncology Branch, Health and Environmental Review Division, Office of Pollution Prevention and Toxics to Pauline Wagner Toxic Effects Brandy, Health and Environmental Review Division, Office of Pollution Prevention and Toxics. Subject: Review of 8EHQ-0990-1078 (Initial) Report.
- Park R., Wegman D., Silverstein M., Malzlish N, Mirer F. 1988. Causes of death among workers in a bearing manufacturing plant. Am. J. Industrial Medicine. 13: 569-589.
- Robertson A., Weir D., Sherwood Burge P. 1988. Occupational asthma due to oil mists. Thorax 43: 200-205.

Silverstein M., Park R., Marmor M., Malzlish N., Mirer F., September 1988. Mortality among bearing plant workers exposed to metalworking fluids and abrasives. J. of Occupational Medicine. Vol 30. No 9; pages 706-714.

Smith K. Undated. RM1 Form from Kenon Smith, Regulatory Impacts Branch, Existing Chemical Assessment Division, Office of Pollution Prevention and Toxics.

Strassman-Sundy S. June 8, 1992. Telephone conversation between Sandra Strassman-Sundy, Risk Analysis Branch, Existing Chemical Assessment Division, Office of Pollution Prevention and Toxics and Daniel Fort, Economics and Technology Division, Office of Pollution Prevention and Toxics. Subject: Metalworking Fluid Use Cluster.

Stroup C. Undated. Note from Cindy Stroup, Design and Development Branch, Exposure Evaluation Division, Office of Pollution Prevention and Toxics to Lin Moos, Chemical Assessment Division, Office of Pollution Prevention and Toxics. Subject: Review of Epidemiologic Studies on UAW Exposures for Possible § 21 Petition.

Wagner P. December 3, 1990. Memorandum from Pauline Wagner, Toxic Effects Branch, Health and Environmental Review Division, Office of Pollution Prevention and Toxics to Oscar Hernandez, Risk Analysis Branch, Existing Chemical Assessment Division, Office of Pollution Prevention and Toxics. Subject: OTS SAT Health Hazard Review of Metalworking Fluids.

1



INTERNATIONAL UNION, UNITED AUTOMOBILE, AEROSPACE & AGRICULTURAL IMPLEMENT WORKERS OF AMERICA—UAW

OWEN F. BIEBER, *PRESIDENT*

BILL CASSTEVENS, *SECRETARY-TREASURER*

VICE-PRESIDENTS: ODESSA KOMER • ERNEST LOFTON • STAN MARSHALL • STEPHEN P YOKICH



June 28, 1990

Charles Elkins, Director  
Office of Toxic Substances  
Environmental Protection Agency  
401 "M" Street, SW  
Washington, DC 20460

Dear Mr. Elkins:

This letter follows our discussion of TSCA action regarding machining fluids, otherwise known as cutting fluids, cutting oils, metalworking fluids or coolants.

The UAW believes that recent evidence shows that these materials pose a cancer and respiratory hazard to workers. Several recent references are attached. These materials have long been known to pose a hazard to the skin.

The UAW believes that test rules are needed to evaluate the hazards of individual constituents of cutting fluids as well as the effects of combined exposure. Additional rules to control exposures are needed as well.

This letter is to alert you to our intention to submit a petition under Section 21 of TSCA.

Sincerely,

Franklin E. Mirer, Ph.D.  
Director  
Health and Safety Department  
International Union, UAW

FEM:maf  
opeiu494

**METHYL ISOBUTYL KETONE (MIBK)**  
**METHYL ETHYL KETONE (MEK)**

Project Officer: Agnes Revesz, ECAD/RAB  
ECCG meeting: Aug. 27, 1992  
DRAFT

BACKGROUND INFORMATION ON METHYL ISOBUTYL KETONE (MIBK)  
AND METHYL ETHYL KETONE (MEK).

**SUMMARY**

MEK and MIBK are TSCA §4 chemicals for which test rule data have been reviewed. In light of the current amount of Agency risk reduction activities, it is recommended that OPPT refer MEK and MIBK to these activities. In addition, an internal referral to the OPPT Paints Cluster and Lead-Encapsulate Cluster for further consumer risk review. Section 4 test data and the RM1 recommendations should be made available to the relevant Federal Agencies.

**1. HEALTH EFFECTS**

Interagency Testing Committee (ITC) Selection Rationale

The ITC in its 4th Report recommended that MIBK be tested for mutagenicity, teratogenicity, and chronic effects and that MEK be tested for chronic effects (with emphasis on neurotoxicity evaluation). Epidemiologic studies were recommended for both compounds.

Health effects testing recommendations were based on high exposure and a lack of adequate data on mutagenicity and chronic effects. In addition, acute neurologic effects (CNS depression and numbing of fingers and arms) were reported due to MEK. Environmental effects tests were not recommended because of the rapid chemical and biological degradation of MEK and MIBK in the environment.

TSCA Section 4 Studies

The EPA response to the ITC referral was that testing data provided by major US manufacturers of MIBK and MEK were sufficient to evaluate some of the health effects recommended for testing by the ITC. EPA accepted a testing program submitted by the Chemical Manufacturers Association (CMA) Ketones Program Panel. The proposed testing program included an inhalation teratology test and a 90-day subchronic toxicity study on MIBK and mutagenicity testing on both MIBK and MEK.<sup>1</sup> The subchronic inhalation study, performed by CIIT, was expected to provide sufficient data to determine the risks of chronic exposure to MEK. EPA decided that no epidemiological studies were warranted, since no toxic endpoints have been identified in the available data which would serve as a basis for testing.

**MIBK:** A proposed Multi-Substance Rule for the Testing of Neurotoxicity was promulgated under TSCA §4 on 3/4/91.<sup>2</sup> Ten organic solvents were selected to be included in the rule, based on five criteria, such as production level, occupational and consumer exposure, and vapor pressure. MIBK met several of these criteria and became one of the ten substances included in the rule. The TSCA Guidelines call for the following neurotoxicity tests: functional observational battery, motor activity, neuropathology, and the schedule-controlled operant behavior test. A literature review on MIBK tests revealed one developmental toxicity test in rats and mice, which reported a neurotoxic effect. It was determined, however, that the study did not satisfy neurotoxicity data needs. Therefore the proposed Multi-Substance Rule for the Testing of Neurotoxicity calls for state-of-the-art neurotoxicity testing for MIBK.

During the comment period for the proposed rule, industry has submitted new studies on the solvents included in the rule<sup>1</sup>. Thus new data are currently being evaluated by HERD which may have a bearing on the neurotoxicity testing requirements for MIBK to be included in the final rule.

#### RCRA/CERCLA Testing

The Office of Solid Waste and Emergency Response (OSWER) contracted for an oral subchronic study on MIBK in 1986 to be used as the basis for RCRA regulations. A review of the study by RAB is attached.<sup>3</sup>

#### **SUMMARY OF HEALTH EFFECTS TESTING FOR MEK AND MIBK**

The tests marked with an asterisk (\*) were submitted by the Chemical Manufacturers Association under the TSCA §4 agreement and were reviewed by HERD. However, several of the original HERD reviews<sup>4</sup> were lost since 1982/83, so the attached review package is incomplete.

**MIBK: Mutagenicity\*:**

1. Ames test - negative;
2. Mouse lymphoma test - positive without metabolic activation, negative with it;
3. BALB/3T3 mouse embryo cell transformation - positive without activation, possibly positive with activation;
4. Cytogenicity (mouse micronucleus) - negative
5. Unscheduled DNA synthesis - suggestive but equivocal.

The results were taken from HERD reviews.<sup>4</sup>

**Inhalation teratology\*** testing in mice and rats. HERD review results: MIBK causes significant developmental effects in mice and rats at the 3000 ppm dose level (fetal death, reduced fetal weight, delayed ossification), but not at lower doses (1000, 300 ppm). Toxic effects in the dams of both species were observed at the 3000 ppm level, but not at the lower doses. Thus the LOAEL is 3000 ppm<sup>5</sup>.

**90-Day subchronic inhalation study\*** in male and female mice and rats. HERD review results: Increased liver weights but no microscopic lesions found. At the given exposure levels (0, 50, 250, and 1000 ppm) and conditions no conclusive toxicity was found. NOAEL: 50 mg/kg/day. (CMA-sponsored study performed at Bushy Run.)

**90-Day subchronic gavage study (OSWER)** in male and female rats. The study showed kidney toxicity at the high dose (1000 mg/kg/day and to a lesser degree at the mid-dose (250 mg/kg/day), and possible CNS effects at the high dose. The apparent NOAEL is 50 mg/kg/day.<sup>3</sup>

**MEK:**

**Mutagenicity\*:** The same five mutagenicity tests were performed as for MIBK; the HERD reviewer found all tests negative, except the UDS test, which was deemed positive.

**13-week inhalation subchronic (CIIT) study** submitted by the CMA subsequent to the ITC recommendations. The study in mice and rats (1,250 - 5,000 ppm 6 hr/day, x 5 for 13 weeks) showed virtually no effects at any exposure level. No neurological changes were noted through either behavioral observations or histologic examinations. Because of the lack of effects, CIIT decided it would be inappropriate to proceed with long-term testing. EPA consequently found that the study was adequate to predict the chronic toxicity of MEK.<sup>6</sup>

An extensive literature review showed no indications that MEK alone induced neuropathological effects.<sup>6</sup> MEK may act synergistically with methyl-n-butyl ketone or n-hexane, which by themselves are neurotoxic agents. However, neurotoxicity of MEK by itself has not been demonstrated.<sup>7</sup>

**Other studies:** An extensive examination of all health effects of MIBK are described in the final draft of the United Nations Environmental Programme (UNEP) Environmental Health Criteria Document.<sup>7</sup>

## 2. EPA PROGRAM/REGULATORY INTERESTS AND RISK REDUCTION ACTIVITIES

OPPT: 33/50 Program (Risk reduction by voluntary industry action; both MEK and MIBK)  
"Chemical Advisory" -- UNEP Draft Environmental Health Criteria Document for MEK<sup>7</sup>  
TSCA Sect. 4, 8a (PAIR), 8d (MEK and MIBK)

OPP: FIFRA (Active Ingredients of Registered Pesticides (MEK only))

OAR: CAA 111 (Standards of Performance for New Stationary Sources of Emission; MEK and MIBK)  
CAA 112 (National Emission Standards for Hazardous Air Pollutants; MEK and MIBK)

OSWER: CERCLA (MEK and MIBK)  
Paragraph C - Pretreatment Pollutants (for MIBK only)  
Office of Water Regulations and Standards  
EPCRA Sect. 313 list (MEK and MIBK)  
RCRA (MEK and MIBK)

## 3. ACTIONS BY OTHER AGENCIES/INSTITUTIONS

<b>MEK:</b>	OSHA PEL:	200 ppm or 590 mg/m <sup>3</sup>
	ACGIH TWA:	200 ppm or 590 mg/m <sup>3</sup>
	ACGIH STEL:	300 ppm or 885 mg/m <sup>3</sup>
<b>MIBK:</b>	OSHA PEL:	100 ppm or 410 mg/m <sup>3</sup>
	ACGIH TWA:	50 ppm or 205 mg/m <sup>3</sup>
	ACGIH STEL:	75 ppm or 300 mg/m <sup>3</sup>

## 4. ORGANIZATION FOR ECONOMIC COOPERATION AND DEVELOPMENT (OECD) SCREENING INFORMATION DATA SET (SIDS) ACTIONS

As part of the SIDS program, dossiers, which summarize available data and identify data gaps are being prepared. After data gaps have been identified, voluntary testing may take place within the OECD SIDS effort. OECD decision meetings have been scheduled for 1993.

### EPA Assessments of SIDS Phase 2 Chemicals:

**MEK and MIBK:** The SIDS dossier is considered complete with regard to both ecotoxicity and health effects. At the August 6, 1992 SIDS meeting it was decided the no further testing is needed of these chemicals.

## 5. TSCA SECTION 4 OUTSTANDING ISSUE

A TSCA §4 final generic Multi-Substance Rule for Testing of Neurotoxicity is currently in preparation. The rule will require neurotoxicity testing on MIBK by industry. Neurotoxicity test results obtained through this venue will complete the data set needed for the full evaluation of MIBK.

### SUMMARY/CONCLUSION

MEK: The rationale for the initial testing was the lack of mutagenicity and chronic toxicity data in the light of widespread exposures. Four of five mutagenicity tests were negative and a 13-week subchronic study showed no conclusive toxicity.

MEK is also used in various lead-based paint encapsulant formulations. In connection with this use, a Structure-Activity Team report summary indicated a low concern level for MEK at all routes of absorption.

In light of the many risk reduction activities already in place by the Agency (e.g., 33/50 project, CAA 112, Chemical Advisory) and testing review under the SIDS program, we recommend that:

- no further action be taken by OPPT on MEK at this time, other than that new TSCA Section 4 test results be made available to other agencies as general information;
- review MEK as a lead encapsulate in paints;
- review MEK as part of an OPPT paint cluster;
- share the RM1 recommendations with other relevant Federal agencies.

MIBK: The rationale for the testing recommendation for MIBK was identical to that for MEK. Mutagenicity testing showed a mixture of positive and negative results; a 90-day subchronic inhalation study showed no relevant effects, although a previous oral subchronic test had slight kidney effects at 250 mg/kg/day. An inhalation developmental toxicity test indicated toxic effects in two species at the high dose (3000 ppm) only.

Considering Agency risk reduction activities for MIBK [described under MEK], we recommend that this information package be made available to other agencies as well as to SIDS. A specific note should be sent to OSHA regarding the developmental toxicity information (NOAEL: 1000 ppm; LOAEL: 3000 ppm<sup>5</sup>, which is 30 times the PEL and 60 times the ACGIH TWA, making a recommendation for

lowering of the PEL and adding the developmental toxicity findings to the MSDS.

Since MIBK is on the TSCA §4 multiple neurotoxicity rule, the findings should be reevaluated upon receiving test data pursuant to this rule.

There is a need to characterize consumer exposure to MIBK due to the extensive use of MIBK in paint formulations. MIBK should be referred to an OPPT paint cluster for evaluation of potential consumer risks. [Note that consumer exposure information may become available through the OECD/SIDS program but not necessarily in the immediate future.]

As for MEK, it is recommended that we share the RM1 decisions on MIBK with other Federal agencies, including CPSC.

## REFERENCES

1. MIBK and MEK Decision to Adopt Negotiated Testing Program. 48 FR 44905.
2. Multi-Substance Rule for the Testing of Neurotoxicity. (Proposed rule.) 56 FR 9105.
3. Vasant Malshet: Review of the Subchronic Toxicity Study on MIBK in Sprague-Dawley Rats.
4. HERD mutagenicity tests review and 90-day inhalation toxicity study review.
5. Tyl RW et al., Fund & Appl Toxicol 8:310-327 (as referenced in the HERD review).
6. MIBK and MEK: Response to the Interagency Testing Committee. 47 FR 5825.
7. International Programme on Chemical Safety: Environmental Health Criteria for Methyl Ethyl Ketone. (Draft, Feb. 2, 1992).