European Food Safety Authority

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SCIENTIFIC OPINION

Scientific Opinion on the use of high viscosity white mineral oils as a food additive[1]

EFSA Panel on Food Additives and Nutrient Sources added to Food (ANS)[2, 3]

European Food Safety Authority (EFSA), Parma, Italy

ABSTRACT

The Panel on Food Additives and Nutrient Sources added to Food (ANS) provides a scientific opinion on the safety of high viscosity white mineral oils (HVMO) (CAS Registry Number 8042-47-5) when used as food additives. HVMO have previously been evaluated by the EC Scientific Committee for Food (SCF) (1995) and the Joint FAO/WHO Expert Committee on Food Additives (JECFA) (1995, 2002). The SCF allocated a Temporary Group ADI of 0-4 mg/kg bw/day for white paraffinic oils which included white mineral oils with a viscosity higher than 8.5 cSt at 100°C. In 2002, JECFA recommended an ADI of 0 – 20 mg/kg bw/day for HVMO. Dietary exposure to HVMO did not produce adverse effects in subchronic toxicity and chronic toxicity/carcinogenicity studies in rats. Infiltration of histiocytes (granulomas) in mesenteric lymph nodes and oil deposition in the liver were considered to be an indication of exposure to white mineral oils rather than an adverse effect. The NOAEL for HVMO was considered to be 1200 mg/kg bw/day, the highest dose tested. Using this NOAEL and applying an uncertainty factor of 100 the Panel established an ADI of 12 mg/kg bw/day for HVMO (kinematic viscosity ≥ 11 mm²/s (cSt) at 100 °C, a carbon number > 28 at 5 % distillation point and an average molecular weight > 500 g/mol). The Panel considered the dietary exposure to HVMO from current uses as well as proposed uses, and estimated that the potential dietary exposures for high level consumers (95^{th}/97.5^{th}) would reach up to approximately 13 mg/kg bw/day for adults and 19 mg/kg bw/day for children. The Panel considers these estimates to be very conservative since high levels of exposure from different sources, in consumers only, have been added up.

KEY WORDS

High viscosity white mineral oils; CAS Number 8042-47-5; Liquid paraffin; Paraffinum Liquidum.

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SUMMARY

Following a request from the European Commission to the European Food Safety Authority, the Scientific Panel on Food Additives and Nutrient Sources added to Food (ANS) was asked to evaluate the safety-in-use of high viscosity white mineral oils as food additives.

In 1995, the EC Scientific Committee for Food (SCF) (1995) evaluated the safety of mineral and synthetic hydrocarbon oils and waxes for use as food additives, in food processing and for use in food packaging materials. The SCF did not allocate an Acceptable Daily Intake (ADI) for those products which, in F344 rats, showed accumulation of hydrocarbons in the liver and lymph nodes associated with a granulomatous response, since it was felt that from the 90-day studies available at that time it was not possible to set a safe level for intake from food. These products included white mineral oils with a viscosity equal to or less than 8.5 cSt at 100°C. For the mineral hydrocarbon products which showed no or minimal accumulation and no toxicity within the duration of a 90-day study in rats the SCF allocated a Temporary Group ADI of 0-4 mg/kg bw for white paraffinic oils. These products included white mineral oils with a viscosity higher than 8.5 cSt at 100°C.

In 1995, the Joint FAO/WHO Expert Committee on Food Additives (JECFA) evaluated white mineral oils and waxes.

In the present evaluation, the Panel considered the dietary exposure to high viscosity white mineral oils (CAS Registry Number 8042-47-5) from current uses as well as proposed uses, calculating the exposure estimates in high level consumers from the different sources. For the high level consumer (95^{th}/97.5^{th}) the estimated potential dietary exposure to white mineral oils would reach up to approximately 13 mg/kg bw/day for adults and 19 mg/kg bw/day for children.

The Panel considers these estimates to be very conservative since high levels of exposure from different sources, in consumers only, have been added up. Therefore, the Panel is of the opinion that the exposures to white mineral oils might be substantially below the conservative estimates given above.

Data were provided showing that the physical and chemical characteristics of high viscosity mineral oils obtained either via the conventional method (i.e. solvent extraction followed by oleum treatment) or via the catalytic hydrogenation process are essentially similar. In addition, 90-day feeding studies in male and female Fischer 344 rats have shown that the toxicological characteristics of several corresponding mineral oils obtained via both methods are also similar. In these studies the high viscosity mineral oils did not induce any toxicologically significant effects. For a number of low(er) viscosity mineral oils (not included in this opinion) the well known toxic effects of low viscosity mineral oils were seen on the liver and lymph nodes, consisting of increased organ weights, presence of mineral hydrocarbons and granulomatous changes (liver) and histiocytosis (lymph nodes). The degree of toxicity was inversely related to the viscosity of the oil, whereas the method of refining had no influence on the toxicity of these lower viscosity mineral hydrocarbons.

Information on the toxicological properties of white mineral oils of lower viscosity than high viscosity mineral oils, and hence better bioavailability and potentially higher toxicity, were also considered in the opinion in order to make the toxicological database more complete. In particular studies on medium viscosity mineral oils, Class I, having only slightly lower viscosity than high viscosity mineral oils, provided important information for the safety evaluation of the high viscosity mineral oils.

From studies on absorption, distribution, metabolism and excretion and characterisation of the mineral hydrocarbons (MHC) in white oils with a viscosity representative for the high viscosity mineral oils under consideration, it can be estimated that approximately 3 % of the oils is systemically absorbed. Absorbed material is predominantly distributed via the lymphatic system to the liver, where it is metabolised via omega-oxidation to acidic compounds and eliminated in the urine.

Subchronic oral toxicity studies with white oils representative for high viscosity mineral oils, conducted in F344 rats, Long Evans rats and Beagle dogs, showed generally no effects up to doses of approximately 2000 mg/kg bw/day.

Based on the available data the Panel concluded that there would be no safety concern with respect to genotoxicity for high viscosity and Class I medium viscosity mineral oils.

In chronic toxicity/carcinogenicity studies with high viscosity or Class I medium viscosity white mineral oils, no carcinogenic effects were observed in F344 rats. There were no adverse effects on survival, body weight, food consumption, clinical signs, clinical chemistry, haematology, and no treatment-related adverse effects were seen at gross necropsy and histopathology. Infiltration of histiocytes (granulomas) in mesenteric lymph nodes and oil deposition in the liver were considered to be an indication of exposure to white mineral oils rather than an adverse effect. From these studies the No-Observed-Adverse-Effect-Level (NOAEL) for the high viscosity mineral oil was considered to be 1 200 mg/kg bw/day, the highest dose tested.

No specific reproductive or developmental studies of high viscosity mineral oils are available. However, available studies on low viscosity white mineral oils provide evidence for the lack of reproductive and developmental effects. Extrapolating from these findings, no reproductive or developmental toxicity would be expected with high or medium viscosity mineral oils.

From human studies it is concluded that mineral hydrocarbons have been observed in a number of human tissues and are believed to occur from both natural and man-made sources of mineral hydrocarbons in the diet. Published and unpublished reports dealing with studies of various white mineral oils (including high viscosity and Class I medium viscosity white oils) and waxes in both F344 and Sprague-Dawley rats were reviewed in 2001. The overall conclusions of this review were that granulomatous lesions are produced in F344 rats, especially in the livers, by feed containing certain low viscosity MHC but granulomatous lesions are not found in human tissues. This suggests a heightened and perhaps different type of toxic response in the rat compared to humans. The MHC-associated alterations in humans are present after a certain age in most, if not all, humans, and consist of intra-and-extra-cellular oil droplets with a minimal macrophage (including giant cells) response. These MHC-induced lesions were considered by the authors as incidental and inconsequential.

The Panel establishes an acceptable daily intake (ADI) of 12 mg/kg bw/day for high viscosity white mineral oils (kinematic viscosity $\geq$ 11 mm²/s (cSt) at 100 °C, a carbon number > 28 at 5 % distillation point and an average molecular weight > 500 g/mol). The ADI was based on the NOAEL of 1200 mg/kg bw/day, the highest dose level tested, in a long term toxicity and carcinogenicity study in F344 rats, applying an uncertainty factor of 100. For high viscosity white mineral oils this ADI replaces the Temporary Group ADI of 0-4 mg/kg bw/day formerly allocated by the SCF to white paraffinic oils derived from petroleum based hydrocarbon feedstocks.

The Panel notes that exposure to high viscosity white mineral oils at the ADI of 12 mg/kg bw/day would result in a daily exposure of less than 200 ng of total polycyclic aromatic hydrocarbons (PAHs) for a person weighing 60 kg. Compared to an estimated dietary exposure to total PAHs of 10 000 – 20 000 ng/person/day, which can be derived from the SCF assessment of PAHs in food (SCF 2002), the additional exposure to PAHs from the use of high viscosity white mineral oils as food additives is considered to be of no concern.

The Panel notes that conservative estimates indicate that the potential dietary exposure to white mineral oils in high consumers could be up to approximately 13 mg/kg bw/day for adults and 19 mg/kg bw/day for children and thus would be above the ADI.

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BACKGROUND AS PROVIDED BY THE EUROPEAN COMMISSION

The European Commission has received a request for the authorisation of high viscosity mineral oils under European Parliament and Council Directive 95/2/EC. This additive is used to exert different functions in a range of foodstuffs, e.g. as a glazing agent on confectionary, meat products, fruits and vegetables at use levels up to 950 mg/kg.

Before the introduction of the European legislation on food additives, mineral oils have historically been used as food additives, e.g. glazing agents, anti-foaming agents, binders and preservatives. Moreover, in some countries they are used as processing aids, for example as external lubricants and release agents. Legislation on such processing aid uses is not harmonized at European level and uses are subject to national legislation.

The European Commission requests the European Food Safety Authority to provide an opinion on the safety of high viscosity white mineral oils used as food additive, however the data submitted by the applicant shows that major exposure to high viscosity white mineral oils would arise from the use as processing aids, therefore, additionally the use as processing aids should be taken into account due to its contribution to overall exposure.

TERMS OF REFERENCE AS PROVIDED BY THE EUROPEAN COMMISSION

In accordance with Article 29 (1) (a) of Regulation (EC) No 178/2002, the European Commission asks the European Food Safety Authority to provide a scientific opinion, on the safety of high viscosity white mineral oils as a food additive.

ASSESSMENT

1. Introduction

The present opinion deals with the safety of high viscosity white mineral oils as food additives. Information on the toxicological properties of white mineral oils of lower viscosity than high viscosity mineral oils, and hence better bioavailability and potentially higher toxicity, were also considered in the opinion in order to make the toxicological database more complete. In particular studies on medium viscosity mineral oils, Class I, having only slightly lower viscosity than high viscosity mineral oils, provide important information for the safety evaluation of the high viscosity mineral oils.

White mineral oils are currently used in coating and packaging materials, during bakery and confectionery manufacture and in grain and seed dust control. Based on a usage pattern survey, the largest usage of food grade white mineral oils is in plastic manufacture. However, according to the petitioner, the majority of plastics are used in non-food applications and those that do come into contact with food show low levels of migration. Food machinery lubricants account for the next largest use of white mineral oils but, according to the petitioner, only traces would be expected to be found in food except for very highly processed foods in small units. Use of white mineral oil as dough divider is limited and is restricted to those industrial bakeries where older design equipment is still used. Other less important uses of white mineral oils include their use as/or in elastomers and other polymers, bakery release agents, jute batching oil and sausage skin lubricants. The use of white mineral oil for grain de-dusting is believed to be common in some non-EU countries, such as the USA, that export grain into the EU. In the EU, such practice has been reported only in France, as a minor application of white mineral oils (Tennant, 2001).

2. Technical data

2.1. Identity of the substance

Chemical Name and characteristics

High viscosity mineral oils (P100) has the empirical formula: $C_nH_{2(n+1-z)}$ where n is equal to 22 - 60 and z to 0 - 5. The CAS Registry Number is 8042-47-5 and the average molecular weight: >500 g/mol.

High viscosity white mineral oils are almost exclusively composed of pure, high molecular weight saturated liquid hydrocarbons including isoalkane and branched cycloalkane molecules.

Linear alkanes (similar to heavy waxes), aromatic hydrocarbons and mono-unsaturated hydrocarbons are absent or present at very low trace levels.

Carbon numbers in the molecules range from approximately C22 to C60, with less than 5 % in the range C22 to C24. The distribution broadly follows a "gaussian" histogram with a maximum above C32.

About 45 to 70 % of the carbon atoms are part of an open chain structure, called "paraffinic carbons". The remaining third is part of a cyclic structure called "naphthenic carbons". The cyclic structures present are mostly 6-sided rings (cyclohexane-type); to a lesser extent 5-sided rings (cyclopentane-type). Fused rings are also present, with decreasing occurrence as the number of fused rings increases. More detailed characterisation has been reported by CONCAWE (1984) and API (1990).

White mineral oils of high viscosity are composed only of carbon (approximately 86 % carbon by weight) and hydrogen (approximately 14 % hydrogen by weight).

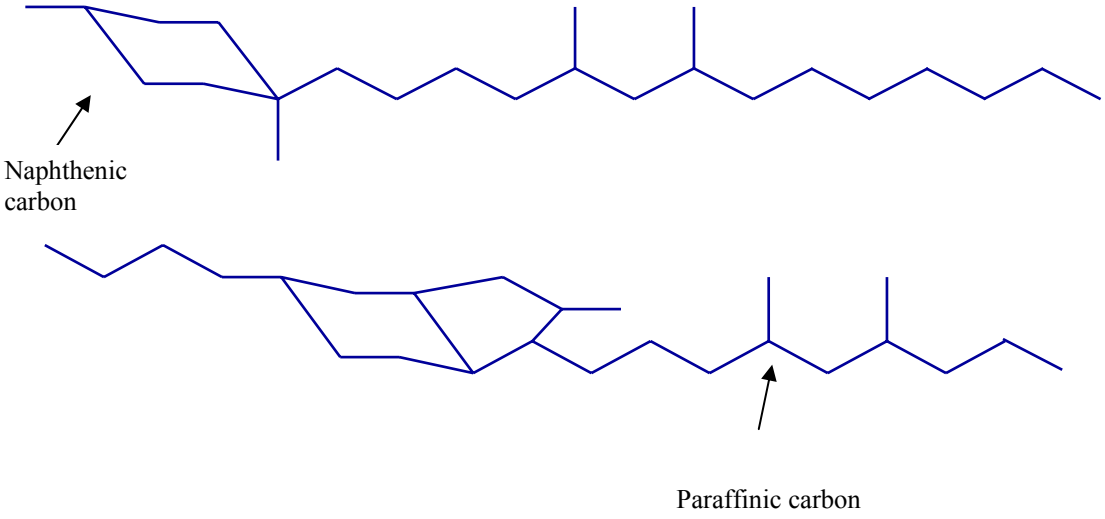

Figure 1. Schematic molecular structure (for illustration purposes)

Synonyms

White mineral oil, mineral oil (USP, FDA), liquid paraffin (European Pharm., Jap. Pharm.), paraffinum liquidum (INCI[4]), and mineral oil, high viscosity (Joint FAO/WHO Expert Committee on Food Additives (JECFA)), food-grade mineral oil, food-grade white oil, food-grade vaseline.

The present submission is only for the viscosity class described as "white mineral oil, high viscosity", excluding medium-viscosity Class I, II and III and low viscosity mineral oils (see Table 1).

The classification of mineral oils is given in Table 1.

Table 1. Classification of mineral oils

Name	Viscosity at 100°C mm²/s	Viscosity at 40°C mm²/s	Average molecular weight (g/mol)	Carbon number at 5% distillation-point
High viscosity mineral oil (P100)	>11	>99.8	>500	>28
Medium and low viscosity mineral oil, Class I	8.5 – 11		480 – 500	>25
P70 P70H	9.0 8.6	70 7	480 480	27 27
Medium and low viscosity mineral oil, Class II	7.0 – 8.5		400 – 480	>22
N70(H)	7.7	70	420	23
Medium and low viscosity mineral oil (Class III mineral oil)	3.0 – 7.0		300 – 340	|17

[4] International Nomenclature of Cosmetic Ingredients

P15(H)	3.5	15	350	17
N15(N)	3.5	15	330	17

P100 oil, crude: paraffinic, viscosity (40 °C): 100 mm^2/s, P70 oil, crude: paraffinic, viscosity (40 °C): 70 mm^2/s, P70(H) oil, crude: paraffinic, viscosity (40 °C): 70 mm^2/s, hydrotreated (catalytic hydrogenation);N70(H) oil, crude: naphthenic, viscosity (40 °C): 70 mm^2/s, hydrotreated (catalytic hydrogenation; P15(H) oil, crude: paraffinic, viscosity (40 °C): 15 mm^2/s, hydrotreated (catalytic hydrogenation); N15(H) oil, crude: naphthenic, viscosity (40 °C): 15 mm^2/s, hydrotreated (catalytic hydrogenation)

Chemical Description

The petitioner defines high viscosity white mineral oils as a mixture of highly refined paraffinic and naphthenic liquid hydrocarbons with a boiling point above 350 ˚C; obtained from mineral crude oils through various refining steps (e.g. distillation, extraction and crystallisation) and subsequent purification by acid and/or catalytic hydro-treatment.

Description of physical state

White mineral oils (high viscosity) are colourless, transparent, oily viscous liquids. They are described as odourless and tasteless, and are less dense than water. The oils are insoluble in water; sparingly soluble in alcohol; soluble in hydrocarbons, ketones, esters and chlorinated solvents, and in vegetable and animal oils.

Purity

The petitioner states that the purity is more than 99.9 %, qualified by control of substances other than heavy saturated hydrocarbons.

Impurities

Aromatic hydrocarbons

Residues of aromatic hydrocarbons are restricted by the limit test "Readily Carbonisable Substances" (absence of reaction with hot, concentrated sulphuric acid) and are lower than the acceptance limit of 1000 mg/kg set by the European Pharmacopoeia (2005). The Panel noted that by current standards this test is very crude and methods using HPLC or GC/MS are now available which obtain a better measure of the levels of contamination with aromatic hydrocarbons.

Polycyclic Aromatic hydrocarbons (PAHs)

Residues of polycyclic aromatic hydrocarbons (PAHs) are restricted by selective extraction and measurement of UV absorption. According to the petitioner, residues are lower than the acceptance limit of 200 to 300 µg/kg, expressed as the sum of all PAHs including alkylated PAHs, as set by the European Pharmacopoeia (2005, Haenni *et al*., 1962). The Panel noted that the indicated technique for measuring levels of PAHs is non-specific and HPLC with fluorescence detection or GC/MS is preferred as it gives a better insight into contamination with specific PAHs which are of more interest than total levels.

Residual solvents

According to the petitioner, processing solvents may include: phenol (rarely used), liquid sulphur dioxide (rarely used), 2-furfural, N-methylpyrrolidone (NMP), methyl ethyl ketone (MEK), methyl isobutyl ketone (MiBK), toluene, liquid propane, ethanol, 1-propanol and 2-propanol.

However, according to the petitioner, in practice, the processes used are such that processing solvents are quantitatively removed. High viscosity white mineral oils also comply with the limits set for Residual Solvents in the European Pharmacopoeia (European Pharmacopoeia, 2005).

Heavy metals

According to the petitioner, high viscosity white mineral oils are essentially free from metal impurities. Inductively Coupled Plasma (ICP) and Atomic Absorption spectrometries have typically shown levels below 1 mg/kg for arsenic (As), lead (Pb), mercury (Hg), nickel (Ni) and cadmium (Cd).

2.2. Specifications

The specifications proposed by the petitioner is given in Table 2.

Table 2. Proposed specifications for high viscosity mineral oils (P100 oil)

Assay	Average molecular weight: no less than 500 g/mol Carbon number at 5 % distillation point: not less than 28[1] (the boiling point at the 5 % distillation point is higher than 396 °C) Kinematic viscosity: not less than 99.8 mm²/ at 40°C and not less than 11 mm²/s at 100 °C
Description	Colourless, transparent, oily liquid; odourless
Identification	Solubility: insoluble in water, sparingly soluble in ethanol, soluble in ether Burning: burns with bright flame and with a paraffin-like characteristic smell
Purity	more than 99.9 %
Acidity or alkalinity	Neutral to acids and bases
Carbonizable substances	After 10 min shaking a 5g sample with sulphuric acid in a tube at the temperature of a boiling water bath, the sulphuric acid is not darker than a very slightly coloured reference.
Polycyclic aromatic hydrocarbons	The UV absorbance of a dimethylsulfoxide extract of the white mineral oil (high viscosity) is not higher than a reference.
Solid paraffins	The white mineral oil (high viscosity) is clear after 4 hr storage at 0 °C
Heavy metals	Arsenic, Lead, Nickel, Cadmium and Mercury Not more than 1 mg/kg each (JECFA, 1995)

[1] Not more than 5 % of molecules with carbon number less than 25.

The Panel noted that the specifications proposed by the petitioner were based on crude physical tests and some equally crude chemical tests (e.g. for PAHs) and felt there was scope for determining more specific parameters better related to the potential presence of contaminants.

2.3. Manufacturing process

The manufacturing process is described in detail by the petitioner. The raw materials used are crude mineral oils. The manufacturing process can be summarised as follows:

(i) The crude mineral oils are selected, de-salted by water washing and in a first distillation refining stage at atmospheric pressure the various atmospheric distillates are separated.

(ii) The fraction that does not boil under atmospheric pressure is heated to 350 to 380°C and subjected to vacuum distillation typically operated at about 0.01 MPa.

(iii) The distillate obtained after step (ii) is further refined either by solvent extraction (using phenol, liquid sulphur dioxide, furfural and N-methylpyrrolidone) or by hydrocracking.

(iv) The refinate of step (iii) contains most of the saturated hydrocarbons from the initial distillate. It is further purified either by solvent dewaxing or by catalytic dewaxing resulting in an almost complete removal of linear waxes and in a reduction of little-branched isoparaffins.

(v) Final purification is achieved either via the so-called oleum process or by a hydrogenation process.

- In the oleum process the feedstock as obtained from previous steps is reacted with an excess of sulphur trioxide or fuming sulphuric acid (oleum). After reaction, the reactants separate into a hydrocarbon layer and a sulphuric sludge layer, which contains most of the water-soluble sulfonic acids and by-products formed. These are settled by gravity or centrifugation.

- In the hydrogenation process, in a first step, specific catalysts (as described by the petitioner in the application dossier) operating under high temperatures (about 350°C) and high hydrogen pressure (typically above 12 MPa) are used. The reaction product is a colourless white oil of technical grade. It contains only traces of sulphur, and typically less than 1 %, of aromatic hydrocarbons, mostly 1-ring aromatics. These residual aromatic hydrocarbons are further hydrogenated at high temperature (200 to 300°C) using a more active hydrogenation catalyst (as described by the petitioner in the application dossier).

The final product is separated from unreacted hydrogen, stored and analysed.

The Panel noted that previous evaluations of mineral oils produced by the catalytic hydrogenation and the so-called "oleum" process had concluded that both oils might not be equivalent in terms of chemical composition and toxicity (AFSSA, 2005). However, for this application the petitioner has provided data that show that the physical and chemical characteristics of high viscosity mineral oils products obtained either via the conventional method (i.e. solvent extraction followed by oleum treatment) or via the catalytic hydrogenation process are essentially similar. This conclusion was based on the analysis of corresponding pairs of high viscosity mineral oils differing not only with respect to the final purification step but also with respect to being paraffinic or naphthenic. A similar conclusion could be reached for corresponding pairs of low viscosity mineral oils (CONCAWE, 1984). In addition, the petitioner provided data, based on 90-day feeding studies in male and female Fischer 344 rats, showing that the toxicological characteristics of several corresponding mineral oils obtained via both methods are also similar (CONCAWE, 1993; see section 3.3).

2.4. Methods of analysis in food

The petitioner adequately describes the methods used for the chemical and physical-chemical identification and characterisation of high viscosity white mineral oils.

The extraction of high viscosity white mineral oils from food products is done by solvent extraction from liquids, and by Soxhlet extraction from adequately homogenised solids. Food lipids and ester waxes can be removed from the fatty extract either by chemical treatment or by direct purification using column chromatography or HPLC.

The methods described by the petitioner in the application also refer to data published in the literature (Grob *et al*., 1997; Castle *et al*., 1993a and 1993b; Castle *et al*., 1994a, b,c; Lanzon *et al*., 1994). Detection levels range from 2 to 50 mg/kg according to the type of food investigated (UK Food Standards Agency, 2003; Lanzon *et al*., 1994). The fatty extract is analysed by GC/FID (Gas Chromatography with Flame Ionisation Detector) calibrated with n-alkanes solutions in the C25-C60 range. The Panel noted that the analysis of mineral oils in foods is very complex, and even after extensive clean-up the hydrocarbons appear as a complex envelope of peaks in capillary GC/MS. The lack of a suitable chromophore makes the analysis prone to interference from co-extracted compounds and the absence of suitable standards makes the analysis at best only semi-quantitative.

Microbiological data

The petitioner considers that microbiological data are of no relevance given the conditions of manufacture which involve high temperatures and aggressive chemical conditions. The Panel accepts this argument.

2.5. Stability, reaction and fate in food

The petitioner states that, stored in closed containers at ambient temperature under suitable conditions (i.e. protected from high exposure to heat, light, air and humidity), the high viscosity white mineral oils have shelf lives in excess of 36 months.

When added to food products, high viscosity white mineral oils remain essentially stable. High viscosity white mineral oils contained in food products processed at high temperatures and in low oxygen concentrations would be stable.

Very high temperatures (e.g. frying at 160 °C) in the presence of air would initiate oxidation, of high viscosity white mineral oils although at a much slower rate, when compared to the oxidation of fatty materials from vegetable or animal origin.

Due to the absence of chemical reactivity, effects on colour, odour and taste, effects on nutrients are not anticipated by the petitioner and have not been described in the literature.

2.6. Case of need and proposed use

The proposed uses and use levels of high viscosity white mineral oils as food additives are listed in Table 3 and the potential uses as processing aids reported by the petitioner are tabled in Annex I.

Table 3. Proposed applications of high viscosity white mineral oils as additives in food products

Type of food	Application	Technological function (main, sec.)	White oil useful properties	Currently Permitted in EU	Proposed Use level	Existing Legislations and limits
Concentrates of flavouring, spices condiments, nutrients excluding confectionery	Capsules and tablets	Firming agent Preservative, Glazing agent	Neutral organoleptic properties Water repellence Stability	No	6000 mg/kg max	FDA21CFR §172.878, 0.6 % max of capsule or tablet

Special dietary food	Capsules and tablets	Firming agent Preservative, Glazing agent	Neutral organoleptic properties Water repellence Stability	No	6000 mg/kg max	FDA21CFR §172.878, 0.6 % max of capsule or tablet
Confectionery		Glazing agent	Neutral organoleptic properties, Stability	No	2000 mg/kg max	FDA21CFR §172.878, 0.2 % max of confectionery
Meat	Hot melt coating on frozen meat	Glazing agent	Water repellence, stability	No	950 mg/kg of meat max	FDA21CFR §172.878, 0.095 % max of meat
Fruits and vegetable[1]	Protective coating for raw fruit and vegetable	Preservative	Water barrier Bacteriostatic Absence of odour and colour Stability	No	400 mg/kg max	FDA21CFR §172.878, GMP
Potatoes	Wash water for sliced potatoes	Anti-foaming agent	Low density and surface tension, stability	No	80 mg/kg of water max	FDA21CFR § 173.340 0.008 % in water

[1] According to the petitioner, the coating of raw fruit and vegetables may be applied to different commodities such as citrus, oranges, pineapples, apples, pears, peaches, nectarines, melons, avocados, cucumbers, sweet potatoes, turnips, tomatoes, plums, rutabagas, cherries, summer squash, hot peppers etc.

2.7. Information on existing authorisations and evaluations

White mineral oils (high viscosity) are permitted for use in Plastic materials and articles intended to come into contact with foodstuffs, Directive 2002/72/EC (EC, 2002).

European Union evaluation

In 1995, the EC Scientific Committee for Food (SCF) (SCF, 1995) evaluated the safety of mineral and synthetic hydrocarbon oils and waxes for use as food additives, in food processing and for use in food packaging materials. The SCF conservatively based their decision on the results from 90-day studies in F344 rats, since there was no information on whether humans are more or less sensitive to mineral hydrocarbons (MHC) than this animal model.

The SCF did not allocate an ADI for those *'products which, in F344 rats, showed accumulation of hydrocarbons in liver and lymph nodes associated with granulomatous response'* since it was felt that from the 90 day studies available at that time it was not possible to set a safe level for intake from food. These products included paraffin and synthetic waxes with viscosity below 11 cSt at 100°C, and white mineral oils with viscosity less than 8.5 cSt at 100°C.

For the MHC *'products which showed no or minimal accumulation and no toxicity within the duration of a 90-day study'* the SCF allocated a Temporary Group ADI of 0-4 mg/kg bw for white paraffinic oils derived from petroleum based hydrocarbon feedstocks meeting the following specifications: viscosity not less than 8.5 cSt at 100°C; carbon number, not less than 25 at the 5 % boiling point; average molecular weight not less than 480 g/mol. This ADI was based on '*a 90-day no-effect level of 2% in the diet for the P100(H) oil and the 90-day minimal effect level of 2% in the diet for increased liver weight for the P70(H) oil*', using a safety factor of 500. The ADI was considered temporary, pending submission of a two-year chronic toxicity/carcinogenicity study on P70(H) oil which is a medium viscosity mineral oil.

JECFA evaluation

In 1995, JECFA (FAO/WHO 1995) evaluated white mineral oils and waxes and recommended ADI's for their use as food additives. JECFA conducted a review of Glazing Agents: Medium and Low Viscosity White Oils in 1998 and revisited their 1995 evaluation in June 2002 in the light of new studies available.

Based on these studies JECFA recommended the following Acceptable Daily Intakes (ADIs) for MHCs (JECFA, 2002) (Table 4):

Table 4. Recommended ADI values for MHCs by JECFA (2002)

	Mineral Oil (High Viscosity) (P100)	**Class I (P70)**	**Mineral Oil (Medium and Low Viscosity)**	**Class III [P15(H) and [N15(H)]**
Viscosity (cSt / 100 C)	> 11	8.5 - 11	Class II [N70(H)]	3.0 - 7.0
Carbon No. - 5 % BP	> 28	> 25	> 22	> 17
Average Molecular Weight	> 500	480 - 500	400 - 480	300 - 400
ADI (mg/kg bw/day)	0-20	0 - 10	0 - 0.01 (T)	0 - 0.01 (T)

(T) = temporary ADI

2.8. Exposure

Known and anticipated exposure

White mineral oils of high and low viscosity have historically been used as processing aids in Europe and as food additives and processing aids in the USA.

The petitioner provided exposure estimates from two comprehensive dietary studies in the USA and Europe (Feich, 1998; Tennant, 2001). Dietary exposure to mineral hydrocarbons (MHCs) was estimated from information on concentrations in foods and quantities consumed. Food-related usage patterns of mineral hydrocarbons and their potential levels in food were identified in a review of the scientific literature and from information provided by industry and other investigations.

USA

The petitioner provided exposure data indicating the use and use levels permitted in the USA. The data show a potential mean dietary exposure to white mineral oils in the USA for the total population of 0.43 mg/kg bw/day. About 40 % of this potential exposure (0.18 mg/kg bw/day) was from medium and high viscosity mineral oils used in polystyrene and bakery pan-release oils. The present USA study indicated that for the overall population, on average 18 % of the potential exposure to white mineral oils came from confectionary (glazing) and 17 % from fruit and vegetables (coating). The approved uses of MHCs as hot-melt coating for frozen meats and for some applications such as processing aids were demonstrated to be very minor in terms of volume of MHC sales and they were eliminated from further consideration (Heimbach *et al.*, 2002).

Europe

The petitioner provided current potential exposure estimates, for consumers only, of white mineral oils (high and low viscosity), used as processing aids for the UK (Tennant, 2001) using the raw food consumption data from the UK National Dietary and Nutrition Surveys (NDNS). The data were derived from 7 or 4 day intake records within a population of adults aged 16-64 (Gregory *et al*., 1990) and pre-school children aged 1.5-4.5 years (Gregory *et al*., 1995). The total mean potential exposure to white mineral oils used as processing aids was 0.39 mg/kg bw/day for adults and 0.75 mg/kg bw/day for pre-school children. At the high level (97.5th percentiles) these estimates were 0.91 and 1.77 mg/kg bw/day, respectively. Of the overall exposure, the mean adjusted potential exposure from industrial bread and imported cereals was 0.09 mg/kg bw/day for adults and 0.17 mg/kg bw/day for children and the high level exposure (97.5th percentile) was 0.20 and 0.39 mg/kg bw/day, respectively. The Panel noted that this adjusted high level of exposure is an underestimate of exposure for consumers that always select industrially produced bread and food made from imported cereals. The Panel also noted that the use levels applied in the UK for processing aids [e.g. polyethylene in sliced meat (7 mg mineral oil per kg), divider oils in bread (243 mg/kg), jute batching in chocolate (7 mg/kg), temporary skins in sausages (28 mg/kg) and grain de-dusting in imported cereals (40-110 mg/kg)] did not take all the possible processing aid uses as listed in Annex 1, into account.

The Panel made an approximate estimate of the potential exposure to white mineral oils from its proposed uses as a food additive while applying the maximum use levels to the consumption data from the UK and France for children and adults, and from Italy for adults only.

For children in the UK, the estimate could only be based on reported mean consumption of the food groups proposed for the applications as food additives (see Table 3) in young people aged 4-18 years (Gregory *et al*., 2000) and pre-school children aged 1.5-4.5 years (Gregory *et al*., 1995). The mean potential dietary exposure to white mineral oils from all proposed uses as a food additive would be 125 mg/day in pre-school children and 216 mg/day in young people, corresponding to approximately 8.3 mg/kg bw/day and 5.1 mg/kg bw/day, respectively (Table 5).

For France, the estimates in children (aged 3-14 years) were based on raw individual food consumption data of the INCA Survey[5] (Volatier, 2000). Since every subject is a consumer of one or more of the included food categories the overall exposure for consumers only and the total population does not differ. The potential mean dietary exposure to white mineral oils used as food additives for children would be approximately 8 mg/kg bw/day. For high consumers, the potential dietary exposure (based on the 2 highest 95th percentile contributors of consumers only and the mean consumption of the other food categories) was estimated to be approximately 13 mg/kg bw/day in children (Table 5).

Table 5. Potential estimated dietary exposure to white mineral oils from selected food categories in children (mg/kg bw/day)[1]

Food item	**Maximum proposed use level (mg/kg)**	**Consumption (g/day)**				**Potential exposure to white mineral oil from proposed use (mg/kg bw/day)**			
		UK		France		UK		France	
		Pre-school children	Young people	Children		Pre-school children	Young people	Children	
		Mean	Mean	Mean	95th perc.	Mean	Mean	mean	95th perc.[2]
Confectionery	2000	20	30	31	87	2.67	1.43	2.00	5.61
Fruit and	400	50	55	101	268	1.33	0.52	1.30	3.46
Vegetables	400	39	73	76	165	1.04	0.70	0.98	2.13
Meat	950	52	110	111	173	3.29	2.49	3.40	5.30

[5] Enquête Individuelle et Nationale sur les Consommations Alimentaires

Potatoes	80 in washing water for sliced potatoes					Ngible	Ngible	Ngible	Ngible[3]
All sources						8.33	5.14	7.68	13.19

[1] mean body weight pre-school children UK 15 kg; mean body weight young people UK 42 kg; mean body weight children France 31 kg.
[2] based on the 2 highest 95th percentile contributors of consumers only and the mean consumption of the other food categories
[3] Ngible = exposure considered negligible

For adults, data from the Concise European Food Consumption Database for exposure assessments have been used (EFSA, 2008). As was the case for children, every subject is a consumer of one or more of the included food categories. The data in Table 6 show that the mean dietary exposure to white mineral oils used as food additives in a 60 kg adult ranges between 5 and 6 mg/kg bw/day. For high consumers the potential dietary exposure varied from approximately 9.3 mg/kg bw/day in Italy to 10.7 mg/kg bw/day in France (Table 6).

Table 6. Potential estimated dietary exposure to white mineral oils from selected food categories in adults (mg/kg bw/day)[1]

Food item	**Maximum proposed use level (mg/kg)**	**Consumption (g/day)**						**Potential exposure to white mineral oil from proposed use (mg/kg bw/day)**					
		UK		France		Italy		UK		France		Italy	
		mean	95th perc.	Mean	95th perc.	mean	95th perc.	Mean	95th perc.[2]	Mean	95th perc.[2]	mean	95th perc.[2]
Confectionery	2000	27	88	31	87	19	55	0.90	2.93	1.03	2.90	0.63	1.83
Fruit and	400	95	331	132	410	203	460	0.63	2.21	0.88	2.73	1.35	3.07
Vegetables	400	138	306	146	297	249	470	0.92	2.04	0.97	1.98	1.66	3.13
Meat	950	161	329	202	376	137	264	2.55	5.21	3.20	5.95	2.17	4.18
Potatoes	80 in washing water for sliced potatoes							Ngible	Ngible	Ngible	Ngible	Ngible	Ngible
All sources								5.00	9.69	6.08	10.70	5.81	9.29

[1] assumed mean body weight 60 kg
[2] based on the 2 highest 95th percentile contributors of consumers only and the mean consumption of the other food categories

For potatoes, the application refers to the use of a maximum of 80 mg/kg of wash water for sliced potatoes with the water being eliminated at the end of the process. The potential exposure from this source is likely to be minor and was therefore not considered by the Panel.

For the use of white mineral oils as a firming agent in capsules and tablets, the UK data indicate that 24 % of adults, 14 % of young people and 17 % of pre-school children consume food supplements. High consumers (97.5th percentile) use 2 (young people) to 7 units (pre-schoolchildren and adults) per day. The data do not discriminate between tablets or capsules. Assuming that the average capsule shell weighs 100-150 mg and that tablets weigh 1.2-1.5 g (EFSA, 2004), supplements may contribute up to 4.2 mg/kg bw/day white mineral oils in pre-school children, 0.4 mg/kg bw/day in young people and 1.05 mg/kg bw/day in adults.

Taking into account the estimated potential exposure to white mineral oils from current uses as processing aids (as provided by the petitioner) as well as proposed uses for food additives (estimated

by the Panel) and adding up exposure estimates for the different sources for high consumers, the potential exposure to white mineral oils would reach up to approximately 19.2 mg/kg bw/day in children[6] and 12.7 mg/kg bw/day in adults[7].

The Panel recognises that the presented estimates are conservative because (i) high levels of exposure from different sources in consumers only have been considered, (ii) it was assumed that white mineral oils were present at the maximum use levels in all proposed foods and (iii) the calculations are based on very broad food categories. In the estimations all types of fruit were considered (i.e. fresh fruit, dried fruit, fruit mousse and compote). Also, all types of vegetables, vegetable sauces, nuts and pulses were taken into account. Further, for fruit and vegetables, it is assumed that all fruit and vegetables were treated with white mineral oils and that all putatively edible rinds were consumed. In the present calculations it is also assumed that all meat consumed originated from frozen meat and that the consumption of meat referred to all meat and meat products, including offal, sliced cold meat and meat dishes. In reality, only a small proportion of meat might come from frozen meat and be coated as such. However, the Panel does not have better data at the moment to enable a more refined exposure assessment to be performed.

3. Biological and toxicological data

3.1.1. Introduction

The petitioner reiterates that this food additive notification is for high viscosity white mineral oils (CAS R. N. 8042-47-5). Food safety information for other white mineral oils and waxes (low viscosity) and refined petroleum products are also considered for comparative purposes.

Key physical properties of P100 and P70 white oils, including alkane distribution, are provided in Table 7. Properties of a blend of eight commercially available paraffinic medium viscosity white oils (P70[a]) are also provided for comparison (Table 7).

Table 7. Properties of some white mineral oils

	P70[a]	**P70**	**P100 (high viscosity)**
Avg. MW	475	485	510
Viscosity at 40°C and 100°C (cSt) respectively	NA[b] – 8.71	69.5 - 8.79	99.8 - 11.0
Avg. C number at 5 % BP	25	27	28
Avg. C number range (peak C number)	18 - 44 (32)	27 - 43 (34)	28 - 45 (36)
% <C20	0	0	0
% C20 - C32	50	35	34.6
% >C32	50	65	66.4

[a] Blend of eight commercially available paraffinic medium viscosity Class 1 white oils

[b] Not available

[6] 1.77 mg kg/bw from processing aids + 4.2 mg kg/bw from food supplements + 13.19 mg kg/bw from selected food categories (table 3)

[7] 0.91 mg kg/bw from processing aids + 1.05 mg kg/bw from food supplements + 10.7 mg kg/bw from selected food categories (table 4)

3.1.2. Absorption, distribution, metabolism and excretion

Studies on the absorption, distribution, metabolism and elimination of high viscosity (P100) and Class 1 medium viscosity (P70) white oils, using specific radiolabelled compounds, have not been conducted. The petitioner is of the opinion that the absorption, distribution, metabolism and elimination of these substances can be inferred from studies conducted on similar hydrocarbon products (e.g., hydrogenated poly-1-decene) and studies of hydrocarbon markers that are representative of the MHCs present in tissues following exposure to high viscosity (referred to as P100) and Class I medium viscosity (referred to as P70) white oils.

Gastrointestinal absorption of white oils is dependent on the physical properties and molecular composition of the oil, with no absorption occurring for hydrocarbon fractions above C32. This is confirmed in studies of hydrogenated poly-1-decene, a structurally similar hydrocarbon product (Huntingdon Life Sciences, 2000). In addition, less than 5 % of the carbon fraction above C28 is expected to be absorbed (Albro and Fishbein, 1970). Based on extrapolations from absorption data on aliphatic hydrocarbons, the gastrointestinal absorption of P70 and P100 oils is estimated to be approximately 3 % of the administered dose.

In studies on absorption of aliphatic hydrocarbons in the rat (Albro and Fishbein, 1970) simple mixtures of these compounds were administered by gastric intubation at dose levels of up to 500 mg/kg bw/day. The percentage retention of the aliphatic hydrocarbons was inversely proportional to the number of carbon atoms and ranged from 60 % for C14 compounds to 5 % for C28 compounds. No absorption was detected for carbon numbers greater than C30. The major site of absorption was found to be the small intestine.

The absorption, distribution, metabolism and elimination of hydrogenated poly-1-decene, a hydrocarbon structurally related to P100 white oils, was investigated in rats given a single oral dose (30, 210, or 1500 mg/rat) of radiolabelled hydrogenated poly-1-decene (Huntingdon Life Sciences, 2000). Less than 1 % of the dose was absorbed, which is consistent with the low proportion of saturated hydrocarbons <C30 present in the compound. Tissue concentrations in the lymph nodes, fat, kidney and spleen were <0.1 % of the dose. Only the liver had concentrations >0.1 % of the dose, which decreased to non-detectable after 24 hrs. Highest tissue concentrations were observed in the gastrointestinal tract and represented unabsorbed material. Faecal elimination was 102 %, 94.9 % and 91.7 % of the 30, 210 and 1500 mg/rat oral doses, respectively. Urinary elimination (mean 0.16 % of the dose) and bile excretion (mean 0.01 % of the dose) were very low.

Scotter *et al*., (2003) conducted detailed mineral MHC analysis of tissues following oral administration of various white oils, including P70, for 90 days. No histopathological evidence of MHC accumulation was detected in any tissues from F344 rats fed 2 % P70 oil (mean dose = 2116 mg/kg bw/day) for 90 days. MHC in the small intestine and faeces were similar to the original test material and had an alkane distribution of C25-C45 with a maximum at C31-32. In contrast, the alkane distribution of MHC detected in tissue extracts ranged from C22-C34 with a maximum at C28, except for the kidneys where it ranged from C18-C32 with a maximum at C24. These results suggest that a C26 hydrocarbon marker would be a reasonable surrogate to represent the absorption, distribution, metabolism and elimination of white oils, including P70 and P100 oils.

Mackerer *et al*., (unpublished data) and Low (1992) examined the pharmacokinetics and tissue distribution in F344 rats of radiolabelled markers for the naphthenics (cycloparaffins), isoparaffins and n-paraffins in white oils. Rats were fed a high dose (2 % w/w in the diet – one hr feeding) of a naphthenic white oil with a (low) viscosity of 25.6 mm^2/sec (at 40 ^oC), consisting of 73 % naphthenics, 22 % isoparaffins, and 5 % n-paraffins. The white oil was spiked with trace levels of radiolabelled markers for either the naphthenics (i.e. a tritiated mixture of 5 cycloparaffins: trans-decalin ($C_{10}H_{18}$); perhydrophenanthrene ($C_{14}H_{24}$); 1, 3-dimethyl-2-(3, 7-dimethyloctyl) cyclohexane ($C_{18}H_{36}$); 2, 3-dimethyl-5(4-methylpentyl)-decahydronaphthalene ($C_{18}H_{34}$); and cholestane ($C_{27}H_{48}$), or

the isoparaffins (i.e., a tritiated mixture of 4 components: 2, 4, 6-trimethylheptane ($C_{10}H_{22}$); 2, 6, 11-trimethyldodecane ($C_{15}H_{32}$); 2, 6, 10, 14-tetramethylpentadecane ($C_{19}H_{40}$; pristane); and 2, 6, 10, 15, 19, 23-hexamethyltetracosane ($C_{30}H_{62}$); squalane), or the n-paraffins (^{14}C-16,17-dotriacontane; $C_{32}H_{66}$), Three rats from each test group were sacrificed at 2, 4, 8, 16, 24, 48 and 72 hr after completion of the one-hr single-dose feeding and tissues (liver, spleen, mesenteric lymph nodes, brain, heart, adipose tissue, and lung), blood, and excreta were collected.

Markers for the three hydrocarbon classes (n-paraffins, isoparaffins and naphthenics) were absorbed from the intestinal tract but only trace levels were deposited in the spleen, kidney, brain, heart and lung. Elevated levels of radioactivity were found in the liver, mesenteric lymph nodes, and adipose tissue. In adipose tissue and lymph nodes, radioactivity increased and reached a plateau over the 72 hr study duration. Markers for the three classes were eliminated at the same rate from the blood ($t_{1/2}$ varying between 58-77 hr) and from the liver ($t_{1/2}$ varying between 29-37 hr). Most of the radiolabel from the marker compounds was excreted via the faeces and represented unabsorbed material. A total of 8 % of the total administered radiolabels in the three markers was found in the urine by 72 hr post-dose. The authors suggested that a single cycloparaffinic hydrocarbon marker, eicosanyl cyclohexane [C26], as recently evaluated by Halladay *et al*., (2002), could be used as a surrogate for comparative studies of the absorption, distribution, metabolism and elimination of white oils in the rat and perhaps for other species including humans.

Halladay *et al*., (2002) characterised the kinetics and distribution of a representative C26 MHC, [^{14}C]1-eicosanylcyclohexane ($C_{26}H_{52}$), in Sprague Dawley (SD) and F344 strains of rat. Rats were given either a high (1.80 g/kg bw/day) or a low (0.18 g/kg bw/day) dose of MHC in olive oil (1:4, v/v) containing [^{14}C]-$C_{26}H_{52}$ as a tracer. Blood, urine, faeces, liver, and mesenteric lymph nodes were analysed for $C_{26}H_{52}$ and radiolabeled metabolites. F344 rats had a higher C_{max} of $C_{26}H_{52}$, a longer time to C_{max}, and a greater area under the systemic blood concentration-time curve compared with SD rats. After 24 hr, F344 rats had a higher level of $C_{26}H_{52}$ in the liver than SD rats; at 96 hr, 3 and 0.1 % of the dose was retained in the livers of F344 and SD rats, respectively. Faecal excretion was the major route of elimination for both rat strains (70–92 % of the dose), and represented unabsorbed material. Urinary excretion (8–17 % of the dose), was faster in the SD rat with most of $C_{26}H_{52}$ metabolites recovered by 16 h. In contrast, F344 rats did not excrete the same amount of $C_{26}H_{52}$ metabolites until 72 to 96 h post-dose. The major urinary metabolites of $C_{26}H_{52}$ in both rat strains were identified as 12-cyclohexyldodecanoic acid and 10-cyclohexyldecanoic acid, consistent with omega-oxidation of saturated hydrocarbons to their corresponding acids. Based on the pharmacokinetic parameters and disposition profiles, the data indicate inherent strain differences in the total systemic exposure, rate of metabolism, and hepatic and lymph node retention of $C_{26}H_{52}$, which may be associated with the different strain sensitivities to the formation of liver granulomas and mesenteric lymph nodes (MLN) histiocytosis.

MHC analysis in selected tissues (liver, mesenteric lymph nodes, spleen and kidney) was also conducted as part of a chronic toxicity/carcinogenicity study of P70 and P100 mineral oil in Fischer 344 rats following 2 years of administration in the diet (Trimmer *et al*., 2004). The study design included an evaluation of the deposition and a reversibility of tissue hydrocarbon concentrations in female rats (n=5/dose) fed 0, 60, 120, 240 or 1200 mg/kg bw/day for 12 months, followed by a 12-month recovery period. Additional groups of five female animals fed the highest test dose (1200 mg/kg bw/day) were added to evaluate tissue hydrocarbon concentrations at 3, 6, 12, 18 and 24 months in both phases of the study.

Quantifiable amounts of hydrocarbon were detected in the livers of all treated animals. In P70 treated rats, the MHC concentrations for animals administered 60, 120 and 240 mg/kg bw/ per day at 12 and 24 months were 1200–1500 µg/g tissue, which were similar to each other and were approximately 60 % of those of animals at 1200 mg/kg bw/day (1800 and 2300 µg/g tissue, respectively). For P100 treated rats, liver concentrations at 12 and 24 months were similar in all treated groups (800–900 and 1200–1400 µg/g tissue, respectively), suggesting that a steady-state level had been reached. Hepatic concentrations of MHC in animals receiving the highest dose reached nearly a maximum within 3

months and increased slowly up to 24 months of treatment. After cessation of treatment, the hepatic concentrations for both oils had dropped substantially by 6 months and had returned to near background levels by 12 months. The amount of MHC in the kidneys, spleens and mesenteric lymph nodes of most animals treated with the higher doses was below the practical limit of reliable quantification.

From these studies it can be concluded that approximately 3 % of P100 and P70 oils is systemically absorbed. Absorbed material is predominately distributed via the lymphatic system to the liver, where it is metabolised via omega-oxidation to acidic compounds which are eliminated in the urine. Characterisation of MHC in tissue extracts following a 90 day exposure to P70 suggests that the small amount of MHC retained in tissues has an alkane distribution ranging from C22-C34 with a maximum at C28. Following chronic exposures of rats to P70 or P100 oils, near maximal MHC concentrations in the liver are reached within 90 days. A further slow increase up to 24 months after treatment was observed. MHC levels return to near background levels within 6 months after exposure ceases. F344 rats have a greater tendency to absorb and retain MHC compared to SD rats, which may explain the unique sensitivity of F344 rats to white mineral oils compared to other rat strains.

3.2. Toxicological data

3.2.1. Acute oral toxicity

No information was provided on the acute toxicity of high viscosity mineral oil in animals.

3.2.2. Short-term and subchronic toxicity

Several subchronic feeding studies on a wide range of white oils and waxes, including P70 and the high viscosity P100 white oils, have been conducted in F344 rats (Smith *et al*., 1996, Scotter *et al*., 2003). A summary of these studies is given below with a special focus on results obtained with P70 and P100 white oils.

In a study aimed at comparing the toxicity of different mineral oils, groups of 20 male and female F344 rats were fed for three months on diets containing 0, 20, 200, 2000 or 20000 mg/kg diet of each of seven different mineral oils, ranging from low to high viscosity and selected to cover the variables: type of oil (paraffinic versus naphthenic) and method of refining (oleum treatment versus hydrogenation). P100 oil did not induce any histopathological effects. P70 oil also did not produce any adverse effects, although there was some evidence of mineral hydrocarbons presence in the liver and mesentheric lymph nodes. For mineral oils of lower viscosity the well known effects on the liver and lymph nodes were seen, consisting of increased organ weights, presence of mineral hydrocarbons and granulomatous changes (liver) and histiocytosis (lymph nodes). The degree of toxicity was inversely related to the viscosity of the oil, whereas the method of refining had no influence on the toxicity of these lower viscosity mineral hydrocarbons (Concave 1993).

P100 and P70 were administered in the diet to groups of F344 rats (20/sex) at levels of 0.002 %, 0.02 %, 0.2 % or 2 % for 90 days (equivalent to 1.7, 17, 173 or 1815 mg/kg bw/day for male rats and 2.0, 19, 190 and 1951 mg/kg bw/day for female rats) (Smith *et al*., 1996). The study was conducted according to OECD Guidelines (408). Control groups included rats (60/sex) fed the control diet and rats (20/sex) fed diets containing 2 % coconut oil. Additional groups of 10 males and 10 females were fed diets containing 2 % test article or 2 % coconut oil for 90 days followed by a 28-day recovery period on control diet. All tissues from the high-dose and control groups were processed and examined by light microscopy, as were limited tissues from all intermediate-dose animals. Histopathological examination of tissues from P70 treated animals was limited to the liver and mesenteric lymph nodes of rats in the main study.

There was no effect on body weight gain or clinical signs of toxicity in rats treated with P70 or P100 at any test dose. In the main study, food consumption was increased by approximately 10 % in both sexes at the 2 % level. Increased organ weights were recorded for the kidney, liver, spleen, and lymph nodes at the 2 % dose level. The organ weight changes were generally more marked in female rats than in males. No treatment-related changes were seen in haematological parameters in P70 or P100 treated rats. Raised ALT (Alanine transaminase), gamma-GT (Gamma-glutamyl transpeptidase) and AP levels (alkaline phosphatase) were seen intermittently in male and female dose groups but there was no clear dose-related effect. Histopathological examination of tissues from rats administered P100 oil was indistinguishable from controls at any dose level in either sex. In P70 treated rats, the only significant histopathological finding was an increased incidence of pigmented macrophages in the lymph nodes of male rats receiving the oil at the 2 % level. Tissue levels of MHCs were determined in the kidney, liver, mesenteric lymph node and perirenal fat of rats treated at the 2 % dose level. No increased levels of MHCs were detected in tissues from P100 treated rats. In P70 treated rats, residues of MHC material were found in the liver and mesenteric lymph nodes of both male and female rats and in the kidneys of female rats.

In the above studies, the No-Observed-Adverse-Effect-Level (NOAEL) for P100 oil was 2 % (equivalent to 2000 mg/kg bw/day). The NOAEL for the P70 oil was considered by the authors to be 0.2 % (equivalent to 200 mg/kg bw/day), since only minor effects of doubtful biological significance, were seen at this dose level (Smith *et al*., 1996).

Scotter *et al*., (2003) conducted 28 day and 90 day feeding studies on various mineral oils and waxes, including P70 oil, to confirm the findings of previous feeding studies and to extend these observations to a wider range of tissue samples for histopathological examination and chemical analysis. Female Fischer 344 rats (12/group) were fed diets for either 28 or 90 days containing 2 % P70 mineral oil (mean dietary dose of 2600 mg/kg bw/day for 28 day treatment groups and 2100 mg/kg bw/day for 90 day treatment groups). Respective control groups received a standard diet containing < 0.01 % MHC by weight. Kidney, liver, mesenteric and cervical lymph nodes, small intestine and spleen from all animals were evaluated histopathologically, and the MHC content was measured in the kidney, liver, mesenteric and cervical lymph nodes and small intestine. There was no effect on body weight gain or other clinical signs of toxicity. Food consumption was statistically significantly increased throughout most of the treatment period of each study. Spleen weights were increased with P70(H)[8] oils in the 28 day treatment group, but not in the 90 day treatment group. The weights of the other tissues were not affected by treatment. There were no histopathological changes detected in any of the tissues for P70 treated rats. Low levels of MHCs were detected in the small intestine (1.1 % w/w), heart (0.16 % w/w) and kidney (2.62 % w/w). Livers from P70 treated rats were not analysed; no MHCs were found in the other tissues. Qualitative analysis of the carbon number range of the MHCs in tissue samples from rats treated with P70 oil suggested that material in the alkane range of C20–C34 was preferentially retained, confirming observations from previous studies.

The Panel considers that the NOAEL for P70 oil in this study is 2100 mg/kg bw/day.

Subchronic 90-day feeding studies were conducted on highly refined white mineral oils to determine any potential for toxicity in Long Evans rats (20/sex/ dose) and Beagle dogs (4/sex/ dose). The study was conducted according to the appropriate OECD Test Guidelines. Four white oils were tested, including one Class II paraffinic white mineral oil (65.9 cSt at 40 C°, i.e. P65 white oil). Each oil was fed both to the rats and the dogs at dietary concentrations of 300 and 1500 mg/kg diet, respectively, equivalent to 21 and 108 mg/kg bw/day for the male rat, 25 and 125 mg/kg bw/day for the female rat, 10 and 50 mg/kg bw/day for the male dog, and 10 and 52 mg/kg bw/day for the female dog. No treatment-related effects of toxicological importance were detected in daily observations for general health or in periodic assessments of food consumption and body weight, haematology, serum clinical chemistry, and urinalysis. Observations in dogs suggested that the white oils produced mild laxative

[8] P70(H) oil, crude: paraffinic, viscosity (40 °C): 70 mm^2/s, hydrotreated (catalytic hydrogenation)

effects. Gross and histopathological examinations, as well as measurements of organ weights, did not reveal any macroscopic or microscopic changes that could be due to treatment. In addition, special staining by Oil Red O of liver, mesenteric lymph nodes, spleen, gastrointestinal tract, stomach, and kidneys indicated no evidence of oil or lipid deposition. A special re-examination of tissues from female and male rats, in response to more recent conflicting data from the F344 strain, found no histopathological signs of macrophage accumulation and/or microgranuloma formation in liver, spleen, or mesenteric lymph nodes (Smith *et al*., 1995).

It can be concluded from the subchronic studies conducted in F344 rats, that the NOAEL for P70 and P100 white oils is approximately 2000 mg/kg bw/day according to Smith 1996.

3.2.3. Genotoxicity studies

3.2.3.1. In Vitro Studies

P100 white mineral oil was tested in the Modified Ames assay in bacteria (Exxon Mobil Biomedical Sciences, 2001). The study was conducted according to the appropriate OECD Test Guidelines (471). In this study, the Mutagenicity Index (MI) of P100 was 0.1, which indicates essentially no induction of gene mutations.

3.2.3.2. In Vivo Studies

Specific *in vivo* genotoxicity tests on P70 and P100 have not been conducted. However, less refined base stock mineral oils of the same viscosity and molecular weight range as these white oils have been tested and were not genotoxic in the rat bone marrow cytogenetic assay (CONCAWE, 1984).

A series of five paraffinic base stocks (viscosity range from less than 4 cSt at 100^{o} C to approximately 19 cSt at 100^{o} C respectively) and two naphthenic base stocks (viscosity range from less than 4 cSt at 100^{o} C to approximately 29 cSt at 100^{o} C respectively), were tested in the rat bone marrow cytogenetic assay (CONCAWE, 1984). Male and female Sprague-Dawley rats (5/sex/dose) were given by gavage 500 to 2000 mg/kg bw/day paraffinic base oils and 500 to 5000 mg/kg naphthenic base oils for 5 days. Corn oil control samples and a positive control chemical, triethylenemelamine (TEM) were tested concurrently. The percentage of aberrant bone marrow cells from treated rats were at or below corn-oil treated control levels, indicating a lack of cytogenicity for these oils. Negative findings in these base stock oils, all of which are less refined than white mineral oils, supports the lack of genotoxicity in white mineral oils.

These studies suggest that high viscosity and Class 1 medium viscosity white oils do not show genotoxic effects.

3.2.4. Chronic toxicity and carcinogenicity

3.2.4.1. Studies in mice

Two groups of 30 mice had white mineral oil applied to their skin three times weekly at 15 mg/application for 311 and 478 days respectively. No tumours were found (Esso Research, 1960). White mineral oils have been used as negative controls (non-tumorigenic material) for many carcinogenicity studies of other petroleum products (Biles *et al*., 1988; McKee *et al*., 1987a, 1987b,).

These studies were all done in groups of 40 to 50 mice by skin painting or delivery to the skin for the animal's lifetime. No carcinogenic effects were observed.

3.2.4.2. Studies in rats

Chronic toxicity/carcinogenicity of a blend of Class I medium viscosity white oils (P70)

A blend of white mineral oil (mineral oil, medium viscosity, Class I), equal quantities of eight commercially available paraffinic white mineral oils obtained from eight member companies of the Japan Liquid Paraffin Industry, was fed in the diet to Fischer 344 rats (Shoda *et al*., 1997). The oils complied with the requirements of the Japanese food additive standards and the Japanese Pharmacopoeia. Five of the component white mineral oils had been derived from petroleum by acid treatment, and the other three had been derived by hydrotreatment. The physical properties of the blended mineral oil were intermediate between those of P70H and N70H[9]. The study was conducted in accordance with OECD chronic toxicity/carcinogenicity testing guidelines (OECD Guideline 453, 1981). Groups of 50 male and 50 female Fischer 344 rats were fed diets containing 2.5 % or 5 % of the composite medium-viscosity white mineral oil (equivalent to 1250 and 2500 mg/kg bw/day), continually for 104 weeks. Body weights and food consumption were measured throughout the study. At the end of the study, the animals were killed and blood samples were collected for haematological and clinical chemical measurements. A full necropsy was performed on all animals; the major organs were weighed and a range of tissues, including the liver, mesenteric lymph node, heart and spleen, were taken for histological examination.

The food consumption and body weights of animals of each sex given 5 % mineral oil were slightly increased. The frequency of clinical signs, mortality and haematological parameters were unaffected by treatment. In the group given 5 %, the absolute weights of the liver and kidney were increased in males and the absolute and relative weights of the submaxillary gland were reduced in females. The increased absolute organ weights were attributed to the slightly increased body weights of males at this concentration. The absolute and relative weights of the heart and spleen were unaffected by treatment. A variety of tumours developed in all groups, including the control group, but all the neoplastic lesions were histologically similar to those known to occur spontaneously in Fischer 344 rats, and no statistically significant increase in the incidence of any tumour type was found for either sex in the treated groups. An increased grade of small granulomatous foci of macrophages was observed in the mesenteric lymph nodes of both sexes at 2.5 and 5 % in comparison with the respective control groups (Shoda *et al*., 1997). The authors did not consider this finding to be a toxic effect but rather an indication of over exposure to white oil. Thus, the NOAEL in this study was considered to be 2500 mg/kg bw/day.

Chronic toxicity/carcinogenicity of high viscosity (P-100) and Class I medium viscosity (P-70) white oils

Parallel studies were conducted to assess the long-term toxic and carcinogenic effects of P70 mineral oil (medium viscosity, Class I) and P100 mineral oil (high viscosity) in male and female Fischer 344 rats after 2 years administration in the diet (Trimmer *et al*., 2004). The study design also included an evaluation of the reversibility or persistence of the biological effects associated with a 12 months exposure, after a 12-month recovery period. The studies were conducted in accordance with OECD chronic toxicity/carcinogenicity testing guidelines (OECD Guideline 453, 1981) and in compliance with US Food and Drug Administration Good Laboratory Practice Regulations and the OECD Principles of Good Laboratory Practice. Five groups were used for each study: a control group and

[9] N70(H) oil, crude: naphthenic, viscosity (40 °C): 70 mm^2/s, hydrotreated (catalytic hydrogenation)

groups given concentrations in the diet corresponding to a dose of 60, 120, 240 or 1200 mg/kg bw/day. The concentrations in the diet were adjusted to achieve a constant target dose throughout the study. Groups of 50 male and 50 female animals were used in the main (24 month) study, with additional groups of 30 male and 30 female animals for the reversibility phase (treatment for 12 months followed by 12 months on control diet). Of the 30 animals of each sex per group in the reversibility phase, 10 animals of each sex per group were killed after the 12 month feeding period. Additional small groups of at least five female animals were added to evaluate tissue hydrocarbon concentrations at 3, 6, 12, 18 and 24 months in both phases of the study.

The parameters investigated included body weight, food consumption, clinical observations, serum chemistry, haematology, ophthalmology, urine parameters and organ weights, including mesenteric lymph nodes. Analyses for MHC were performed on the liver, kidneys, mesenteric lymph nodes and spleen from female animals. Detailed histopathological examination of 48 tissues, including the liver, spleen, mesenteric and mandibular lymph nodes, Peyer's patches, kidney, bone marrow and male and female reproductive tissues was conducted for all animals in the control group and at the highest dose in the main (2 year) study and at the 12 month sacrifice. From animals at 60, 120 or 240 mg/kg bw/day in the main study, only the lungs, liver, mesenteric lymph nodes, spleen and kidneys were examined; the mesenteric lymph nodes and livers of animals in all groups in the recovery study were also examined. Immune function was not tested, but standard end-points considered to reflect immune function (i.e. total and differential leukocyte count, albumin:globulin ratio, the weights and histological appearance of the thymus, spleen and mesenteric lymph nodes, histopathological evaluation of Peyer's patches and bone-marrow cellularity) were assessed.

Administration of either oil to Fischer 344 rats in the diet for 24 months did not affect survival. No treatment-related effects were seen on clinical signs, body weight, food consumption, food conversion efficiency, ophthalmic, haematological, serum chemical or urinary parameters, and no treatment-related changes were seen at gross necropsy. Dietary administration of both oils was associated with increased weight of mesenteric lymph nodes and increased grade of infiltrating cell histiocytosis; increased incidence and grade of vacuolation of periportal hepatocytes; increased incidence of combined cystic degeneration or angiectasis of the livers from male rats (with no dose–response relationship); and a quantifiable, reversible accumulation of MHCs in the liver to a similar level regardless of dose but dependent on the type of mineral oil. Neither P-70 nor P-100 oil was carcinogenic in this assay.

Treatment-related non-neoplastic lesions in this study were seen in the mesenteric lymph nodes. The incidence of infiltrating cell histiocytes occurred at or near 100 % with both oils, and was similar in both control and all test groups after 24 months and 12 months of treatment. The grade, but not the incidence, of infiltrating cell histiocytosis of the mesenteric lymph nodes was increased in all treated groups after 24 months of treatment with P70 white oil, and was reported as "mild" versus the "minimal" severity observed in controls. Similar severity scores were seen in animals at the highest dose, the only group assessed, at the 12 month sacrifice and after the 12 month recovery period. For P-100 oils, a slight increase in severity score from "minimal" to "mild" was observed after 24 months of exposure: no changes were seen after 12 months of exposure.

A few other non-neoplastic lesions were observed in this study but were not considered to be biologically important, e.g., a dose-related increase in the incidence and grade of vacuolation of periportal hepatocytes was observed in the livers of males in all treated groups after 12 and 24 months of exposure. In view of the nature and severity of the response, the investigators did not consider the increased grade of vacuolation to be indicative of an adverse effect but rather a marker of prolonged administration of white oil. An increased incidence of combined angiectasis[10] and cystic degeneration (focal sinusoidal dilatation) was also observed in all treated male groups compared to the control group at the 24 month sacrifice. This lesion was of minimal grade, and the incidence was similar in all

[10] Gross dilatation and often lengthening of a blood or lymph vessel.

treated groups, and is a common finding in F344 rats. An increased incidence of mononuclear cell leukaemia was observed in treated females. However, this was not considered treatment-related, as the incidence in treated groups was not dose-related and was within the range for other control female Fischer F344 rats.

Although effects were observed in the mesenteric lymph nodes and the liver, even at the lowest dose level, these did not progress to more serious changes and were not detrimental to the life or health status of the rat. These effects are considered to be more an indication of exposure to white oils rather than adverse effects. Thus, the NOAEL for both oils in this study was considered to be 1200 mg/kg bw/day.

It can be concluded that, in chronic toxicity/carcinogenicity studies conducted with high viscosity (P100) and Class I medium viscosity (P70 and the blend of P70 oils) white oils, no carcinogenic effects were observed in any of the studies in F344 rats or in skin painting studies in mice. Non-neoplastic effects were limited to infiltration of histiocytes in mesenteric lymph nodes and oil deposition in the liver. These effects are considered by the authors to be an indication of white oil exposure rather than an adverse effect. There were no adverse effects on survival, body weight, food consumption, clinical signs, clinical chemistry, haematology, and no treatment-related changes were seen at gross necropsy. The NOAEL for these white oils is considered to be 1200 mg/kg bw/day, the highest dose tested.

3.2.5. Reproduction and developmental toxicity

Specific reproductive and developmental studies on high viscosity (P100) and Class I medium viscosity (P70) white oils have not been conducted. However, chronic toxicity studies, as reviewed above, did not find any histopathological changes on male and female reproductive organs (i.e. ovaries, oviducts, uterus (corpus, cervix), vagina, testes, prostate, or seminal vesicles). Additionally, reproductive and developmental studies, referred to below, that used low viscosity white oils as a solvent control are available and have consistently shown no evidence of reproductive or developmental effects in rats.

A United States Pharmacopeia (USP) grade mineral oil (low viscosity not specified, CAS RN 8042-47-5) was used as the vehicle control in a study on kerosene conducted according to the OECD Test Guideline 421 (Schreiner *et al*., 1997). In addition to the vehicle control group, the study design included a sham-treated control group. A dose of 1 mL/kg bw (approximately 1g/kg bw) of the mineral oil was applied daily to the skin of male and female Sprague Dawley rats. Female rats were dosed from 14 days prior to mating to day 20 of gestation. Males were treated for a total of 8 weeks, beginning prior to mating and continuing until final female sacrifice on days 4-6 of lactation. While the 8 weeks dosing of males is longer than that required by OECD Test Guideline 421, the study authors thought it improved the study's ability to detect effects on the reproductive system. No mortality, clinical signs of toxicity, or effects on body weight, food consumption, or absolute organ weights were observed. No microscopic changes were observed in the reproductive organs of parental animals. There was no effect on the mean number of corpora lutea, implantation sites, and live pups per litter, nor were any gross anomalies observed. Pups showed comparable body weights and weight gains to those of sham-treated controls. The viability index on postpartum day four was ≥ 93 %.

3.2.5.1. One-generation reproduction study

A low viscosity white mineral oil (Primol 185, a N40 white oil[11]) was used as a solvent control in a study to determine the effects of two EDS[12] coal liquids in a 13 week subchronic single generation reproduction study (McKee *et al*., 1987b). Male and female Sprague-Dawley rats were given white oil at a dose of 5 mL/kg bw, 5 days a week for 13 weeks. Following confirmed mating, the mated females were maintained without further dosing through gestation and lactation to post-partum day 21. Detailed maternal physical examinations and body weight measurements were made on days 0, 7, 14 and 21 of gestation and on days 0, 4, 14 and 21 of lactation. All dams and surviving litters were sacrificed and grossly examined on day 21 of lactation. Each of the offspring was examined for external malformations. All pups were then sacrificed, necropsied and subjected to visceral organ and brain examinations. The general condition of offspring and dams was good throughout the weaning period. Gross observations of pups and dams were generally unremarkable. In the white oil (solvent control) group, four malformed pups were found in four litters. Two of the pups had tail abnormalities, one had a depression in the sternum and the fourth had a short snout. These malformations are known as background pathology in developing Sprague-Dawley rats and were not regarded as treatment-related.

3.2.5.2. Developmental/teratogenicity study

A low viscosity white oil CAS RN 8012-95-1 (Primol 185a N40 white oil) was used as the solvent control in two separate studies, one for each of two test materials (McKee *et al*., 1987b). Two groups of animals (n=50 and 25) were administered white oil by gavage at a dose of 5 mL/kg bw, every day during gestation, day 6 to day 19 inclusive. Body weights and clinical signs of toxicity were recorded on days 0, 6, 10 and 20 of gestation. On day 20 of gestation, all animals were killed and examined for gross changes. Each gravid uterus was removed and weighed. The number, location and viability of each foetus and the number of implant sites were recorded. Fetuses were removed, weighed and the crown-rump lengths measured. All live and dead foetuses that had not been resorbed were examined for external malformations. Approximately half of the foetuses from each litter were decapitated and the heads preserved for subsequent examination for abnormalities. The viscera were also examined for malformations under low power magnification. The remaining foetuses were stained with Alizarin red and subsequently examined for skeletal abnormalities. No organs, other than the uteri were weighed and no organs were examined histologically in this study. In the control group containing 50 animals, three malformed foetuses were found in three litters; one had an extra lumbar vertebra, one had a discrete area of ossification in the area of the junction of the frontal and nasal bones, one had moderately dilated lateral ventricles of the brain. Three malformed foetuses were also found in three litters of the other control group. These were, a vertebral arterial canal of a cervical process fully ossified in two foetuses and angulated ribs in a third foetus. The authors considered these malformations to be minor and that the findings were within the normal ranges for the strain of rat.

It can be concluded that, although there are no specific reproductive or developmental toxicity studies of high viscosity (P100) or Class I medium viscosity (P70) white oils, the studies described above performed with low viscosity white mineral oils are useful in providing evidence of the lack of reproductive or developmental effects for white oils.

3.2.6. Other studies

3.2.6.1. Observations in humans

[11] white oils meeting the standards of the S. Pharmacopoeia (USP) and the FDA regulations for direct food contact (21 CFR 172.878 and 21 CFR 178.3620(a)).
[12] Exxon Donor Solvent (EDS) coal liquefaction system i.e. a direct liquefaction procedure

MHCs have been found visually, chemically, and analytically in a number of human tissues at autopsy and biopsy. For decades, the presence of MHC oils has been observed in human liver, spleen, lymph nodes and other tissues, and it is believed to occur from both natural and man-made sources of MHCs in the diet. Stryker (1941) proposed that deposits of mineral oil in tissues such as the lung, liver, spleen, etc. are associated with histopathological changes in these same tissues. The nomenclature, severity and causality of tissue MHC and histopathological changes have varied, but there does not appear to be any major controversy in the published literature. These conclusions are essentially supported by various investigators (Rose, 1966; Boitnott, 1966; Liber, 1967; Boitnott, 1970; Dincsoy, 1982; Cruickshank, 1984a; Wanless, 1985; Fleming *et al.,* 1998).

The histopathology findings from tissues have been variously described in the literature. Follicular lipidosis (oil globules in follicles of the spleen), lipogranuloma of the liver, lipophage clusters, hepatic granulomata, histiocytosis, etc., have all been associated with the presence of oil in tissues. Klatskin (1977) described problems in interpreting hepatic granulomata and indicated that they did not pose a diagnostic problem unless the pathologist was unfamiliar with their appearance. He indicated that mineral oil lipogranulomata persist for years, but do not appear to progress, and that the hepatic lipogranulomata may have no clinical or diagnostic significance. Cruickshank (1984b) reported cellular reactions in the lymph nodes that were not considered granulomatous due to the absence of fibroblasts or significant fibrosis. Fleming *et al*., (1998) compared the lipogranulomas associated with the ingestion of mineral oil reported in humans, to the morphology of the hepatic lesions seen in the Fischer rat studies treated with certain MHC products. The lesions in humans were not believed to progress to lesions of clinical significance. The authors concluded that the majority, if not all, of the lesions in the rats were of no significance for humans (Fleming *et al*., 1998). A generalised conclusion from the literature of human mineral oil tissue deposition and concurrent histopathological changes is that that none of the investigations have clearly demonstrated any clinical significance due to the pathological changes and presence of oil.

3.2.6.2. Special pathology studies

In 2001, medical and veterinary pathologists (Carlton, *et al.,* 2001) reviewed published and unpublished reports dealing with studies of various white mineral oils (including high viscosity and Class 1 medium viscosity white oils) and waxes in both F344 and SD rats. They also studied histological slides from both subchronic and chronic studies of certain MHCs (90 day oral study of low melting point wax (LMPW) in female F344 and SD rats; 90 day studies of low viscosity (P15) and medium viscosity (P70) white oil and high melting point wax (HMPW) in male and female F344 rats; and a 24 month study of P70 white oil in male and female F344 rats). These pathologists also reviewed mineral oil-induced alterations in tissues from human patients (liver, hepatic lymph node and spleen). They agreed that certain MHCs produced lesions in the mesenteric lymph nodes and liver of the F344 rat and that these lesions were best described as microgranulomas/granulomas. The lesions were fundamentally similar in both organs, although varying in severity with dose and type of MHCs. They also agreed that hepatic lesions with inflammatory cell infiltration, necrosis, and fibrosis were produced only by feeding of LMPW and that the lesions were confined to F344 rats and were not found in SD rats. The most severe granulomatous lesions in the mesenteric lymph nodes were found in high dose LPMW-fed F344 rats. The microgranulomas were similar in subchronic and chronic studies. Also, little difference existed between controls and treated F344 rats in the incidence and severity of the lesions after 2 years of feeding P70 white oil. It was agreed that some slight reversibility existed for these lesions, but that the lesions observed in the liver and mesenteric lymph nodes of F344 rats exposed to MHCs, especially the LMPW, were morphologically different from changes observed in the lymph nodes, liver, and spleen of humans that were mineral oil-users. These changes in humans are usually found incidentally in tissues taken at biopsy or autopsy.

The overall conclusions drawn by the pathologists were that granulomatous lesions are produced in rats by MHC-feeding, especially in the livers of the F344 rat with certain MHCs, but are not found in human tissues. This suggests a heightened and perhaps different type of toxic response in the rat compared to humans. The MHC-associated alterations in humans are present after a certain age in

most, if not all cases, and consist of intra-and-extra-cellular oil droplets with a minimal macrophage (including giant cells) response. These MHC-induced lesions were considered by the authors as incidental and inconsequential.

4. Discussion

The present application is for the use of high viscosity white mineral oils (CAS RN 8042-47-5) as a food additive in a wide variety of food products. However, information on the toxicological properties of white mineral oils of lower viscosity than high viscosity mineral oils, and hence better bioavailability and potentially higher toxicity, were also considered in the opinion in order to make the toxicological database more complete. In particular studies on medium viscosity mineral oils, Class I, having only slightly lower viscosity than high viscosity mineral oils, provided important information for the safety evaluation of the high viscosity mineral oils.

The Panel considered the dietary exposure to high viscosity white mineral oils from current use as well as proposed use, adding up exposure estimates in high consumers for the different sources. The estimated potential total dietary exposure to white mineral oils would be up to approximately 13 mg/kg bw/day in adults and 19 mg/kg bw/day in children.

The Panel considers these estimates as very conservative since high levels of exposure from different sources, in consumers only, have been added up. Therefore, the Panel is of the opinion that the exposure to white mineral oils might be substantially below the conservative estimate given above.

The Panel noted that exposure to high viscosity white mineral oils at the proposed ADI of 12 mg/kg bw/day would result in a daily exposure of less than 200 ng of total PAHs for a person weighing 60 kg. Compared to an estimated dietary exposure to total PAHs of 10 000 – 20 000 ng/person/day, which can be derived from the SCF assessment of PAHs in food (SCF 2002), the additional exposure to PAHs from the use of high viscosity white mineral oils as food additives is considered to be of no concern.

Data were provided showing that the physical and chemical characteristics of high viscosity mineral oils obtained either via the conventional method (i.e. solvent extraction followed by oleum treatment) or via the catalytic hydrogenation process are essentially similar. In addition, 90-day feeding studies in male and female Fischer 344 rats have shown that the toxicological characteristics of several corresponding mineral oils obtained via both methods are also similar. In these studies the high viscosity mineral oils did not induce any toxicologically significant effects. For a number of low(er) viscosity mineral oils (not included in this opinion) the well known effects of low viscosity mineral oils were seen on the liver and lymph nodes, consisting of increased organ weights, presence of mineral hydrocarbons and granulomatous changes (liver) and histiocytosis (lymph nodes). The degree of toxicity was inversely related to the viscosity of the oil, whereas the method of refining had no influence on the toxicity of these lower viscosity mineral hydrocarbons.

From ADME studies and the MHC characterisation of white oils with a viscosity representative of the high viscosity mineral oils under consideration, it can be estimated that approximately 3 % of the oils is systemically absorbed. Absorbed material is predominantly distributed via the lymphatic system to the liver, where it is metabolised via omega-oxidation to acidic compounds and eliminated in the urine.

Subchronic oral toxicity studies with white oils representative for high viscosity mineral oils, conducted in F344 rats, Long Evans rats and Beagle dogs, showed generally no effects up to doses of approximately 2000 mg/kg bw/day.

Genetic toxicity studies indicate that high viscosity and medium white oils are neither mutagenic nor genotoxic.

Based on the available data the Panel concluded that there would be no safety concern with respect to genotoxicity for high viscosity and Class I medium viscosity mineral oils.

In chronic toxicity/carcinogenicity studies with high or Class I medium viscosity white mineral oils no carcinogenic effects were observed in any of the studies in F344 rats. There were no adverse effects on survival, body weight, food consumption, clinical signs, clinical chemistry, haematology, and no treatment-related changes were seen at gross necropsy and histopathology. Infiltration of histiocytes in mesenteric lymph nodes and oil deposition in the liver were considered to be an indication of exposure to white mineral oils rather than an adverse effect. From these studies the NOAEL for the high viscosity oil was considered to be 1200 mg/kg bw/day, the highest dose tested.

No specific reproductive or developmental studies of high viscosity mineral oils are available. However, available studies on low viscosity white mineral oils provide evidence for the lack of reproductive and developmental effects. Extrapolating from these findings, no reproductive or developmental toxicity would be expected with high or medium viscosity mineral oils.

From human studies it is concluded that MHCs have been observed in a number of human tissues and are believed to occur from both natural and man-made sources of MHCs in the diet. Carlton *et al*., (2001) reviewed published and unpublished reports dealing with studies of various white mineral oils (to include high viscosity and Class 1 medium viscosity white oils) and waxes in both F344 and SD rats. The overall conclusions of the authors were that granulomatous lesions are produced in rats by MHC-feeding, especially in the livers of the F344 rat with some of the low viscosity MHCs, but are not found in human tissues. This suggests a heightened and perhaps different type of toxic response in the rat compared to humans. The MHC-associated alterations in humans are present after a certain age in most, if not all, cases and consist of intra-and-extra-cellular oil droplets with a minimal macrophage (including giant cells) response. These MHC-induced lesions were considered by the authors as incidental and inconsequential.

From the overall toxicological database, the Panel selected the NOAEL of 1200 mg/kg bw/day, the highest dose level tested, in a long term toxicity and carcinogenicity study in F344 rats, to form the basis of the ADI for high viscosity mineral oils. The Panel notes that given that this study was conducted with both high viscosity and medium viscosity mineral oils class I, the derived ADI could have been potentially applicable as a group ADI to high viscosity (kinematic viscosity ≥ 11 mm²/s (cSt) at 100 °C, a carbon number > 28 at 5 % distillation point and an average molecular weight > 500 g/mol) and medium viscosity mineral oils class I (kinematic viscosity 8.5 - 11 mm²/s (cSt) at 100 °C, a carbon number > 25 at 5 % distillation point and an average molecular weight of 480 - 500 g/mol) but acknowledged that medium viscosity mineral oils are not covered by the terms of reference.

CONCLUSIONS

The Scientific Panel on Food Additives and Nutrient Sources added to food establishes an acceptable daily intake (ADI) of 12 mg/kg bw/day for high viscosity white mineral oils (kinematic viscosity ≥ 11 mm²/s (cSt) at 100 °C, a carbon number > 28 at 5 % distillation point and an average molecular weight > 500 g/mol). The ADI was based on the NOAEL of 1200 mg/kg bw/day, the highest dose level tested, in a long term toxicity and carcinogenicity study in F344 rats, applying an uncertainty factor of 100. For high viscosity white mineral oils this ADI replaces the Temporary Group ADI of 0-4 mg/kg bw/day formerly allocated by the SCF to white paraffinic oils derived from petroleum based hydrocarbon feedstocks.

The Panel notes that conservative estimates indicate that the potential dietary exposure to white mineral oils in high consumers would reach up to approximately 13 mg/kg bw/day in adults and 19 mg/kg bw/day in children and thus would be above the ADI.

DOCUMENTATION PROVIDED TO EFSA

1. Application dossier. Submitted by the 'European Oil Company Organisation for Environment, Health and Safety' (CONCAWE), Belgium.

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ANNEX 1

Possible Uses Of White Oil (High Viscosity) As Processing Aids

Type of food	Application	Technological function	White oil useful properties	Currently Permitted in EU	Proposed use level	Existing Legislations and limits
Aromas, dyes and preservatives		Release agent,	Neutral organoleptic properties Affinity with oily substances, Hydrolytic stability		QS	
Bakery products	Surfaces and dividers	Release agent	Thermal and oxidation stability, Lubricity	No	1500 mg/kg max (1)	USA FDA 21CFR§172.878 0.15%max of bakery product
Beer, cider, colas	Caps on top of glass bottle to avert breakage at forming	Lubricant,	Lubrication, absence of odour and colour	No	0.03 mg/cm^2	USA FDA 21CFR§178.3910(b), 0.2 mg/sq inch of caps Japan, QS
Confectionery	Surfaces and dividers	Release agent Sealing agent	Neutral organoleptic properties Stability		2000 mg/kg max	USA FDA 21CFR §172.878, 0.2% max of confectionery
Confectionery	slices	Release agent,	Neutral organoleptic properties Stability	Yes	QS	Fr Afssa opinion N° 2002-SA-0030, 20.01.03, quantum satis/GMP
Fruits and vegetable	Dehydrated fruit and vegetable surface	Release agent	Stability, water repellence	No	200 mg/kg max	USA FDA 21CFR §172.878, 0.02% max of dehydrated fruits and vegetables
Egg	White solid	Release agent	Lubricity	No	1000 mg/kg max	USA FDA 21CFR §172.878, 0.1% max of egg white solid

Vinegar and wine	Float on fermentation fluid during manufacture/storage (removed in final product)	Preservative Anti-foaming agent	Neutral Organoleptic Low surface tension Bacterial resistance Low density Low oxygen transfer	No	GMP	FDA21CFR §172.878, GMP,
Cereal grains	Grain surface Rice, corn, barley, rye, wheat, soybean, oats, sorghum	Dedusting agent	Stability, absence of rancid odour High flash point	No	200 mg/kg max	FDA21CFR §172.878, 0.02% max 0.08% max, rice (P100)
Starch	Molding starch surface in confectionery	Release agent	Water repellence, lubricity, stability	No	3000 mg/kg max	USA FDA 21CFR §172.878, 0.3% max of molding starch
Noodles	On handling surfaces	Release agent	Water repellence, lubricity, stability, organoleptic	No	QS	
Meat	Raw meat on handling surfaces	Glazing agent Lubricant	Water repellence, lubricity, stability, neutrality, bacteriostatic	Yes	25 mg/kg max	Opinion FA4700-48/01 of the Danish veterinary and Food Administration, 25 mg/kg meat max
Meat products	Sausage skin	External lubricant	Water repellence, lubricity, stability, organoleptic, germ resistance	Yes	10% in skin	BGVV 44 XLIV (Germany)
Sorbic acid		Antidusting agent	Neutral organoleptic properties Affinity with oily substances, Hydrolytic stability	No	0.25% max of sorbic acid	USA FDA 21CFR §172.878
Sugar	During sugar extraction and crystallisation	Defoamant	Low surface tension Neutrality	Yes	QS (Limit not specified)	Fr. Arrêté 8/02/89, JORF24/02/89
Yeast		Release agent Binder Lubricant	Hydrolytic stability	No	0.15% max of yeast	USA FDA 21CFR §172.878,
Wine and spirits		Lubricant, preservative	Lubricity, organoleptic neutrality, stability	Yes	QS	Specific supplier/cork approval (France)
Miscellaneo	In cleaning agents	Fat solvent	Neutrality,	Yes	2% in	Fr. Arrêté

us foodstuffs	for food contact surfaces	stability, low polarity	cleaning agent	8/9/1999

GLOSSARY / ABBREVIATIONS

ADI	Acceptable Daily Intake
ADME	Absorption, Distribution, Metabolism, Excretion
ANS	Scientific Panel on Food Additives and Nutrient Sources added to Food
bw	Body Weight
CAS RN	Chemical Abstract Service Registry Number
EC	European Commission
EDS	Exxon Donor Solvent
EFSA	European Food Safety Authority
EMEA	European Medicines Agency
EU	European Union
FAO/WHO	Food and Agriculture Organization/World Health Organization
FDA	U.S. Food and Drug Administration
GC/FID	Gas Chromatography with Flame Ionisation Detector
GC/MS	Gas Chromatography Mass Spectrometry
HMPW	High Melting Point Wax
HPLC	High Performance Liquid Chromatography
ICP	Inductively Coupled Plasma
INCA	Enquête Individuelle et Nationale sur les Consommations Alimentaires
INCI	International Nomenclature of Cosmetic Ingredients
JECFA	Joint FAO/WHO Expert Committee on Food Additives
LMPW	Low Melting Point Wax
MHC	Mineral Hydrocarbon
NDNS	UK National Dietary and Nutrition Surveys
NOAEL	No Observed Adverse Effect Level
OECD	Organisation for Economic Cooperation and Development
PAHs	Polycyclic Aromatic Hydrocarbons
SCF	Scientific Committee for Food
USP, FDA	U.S. Pharmacopeia
UV	Ultra Violet