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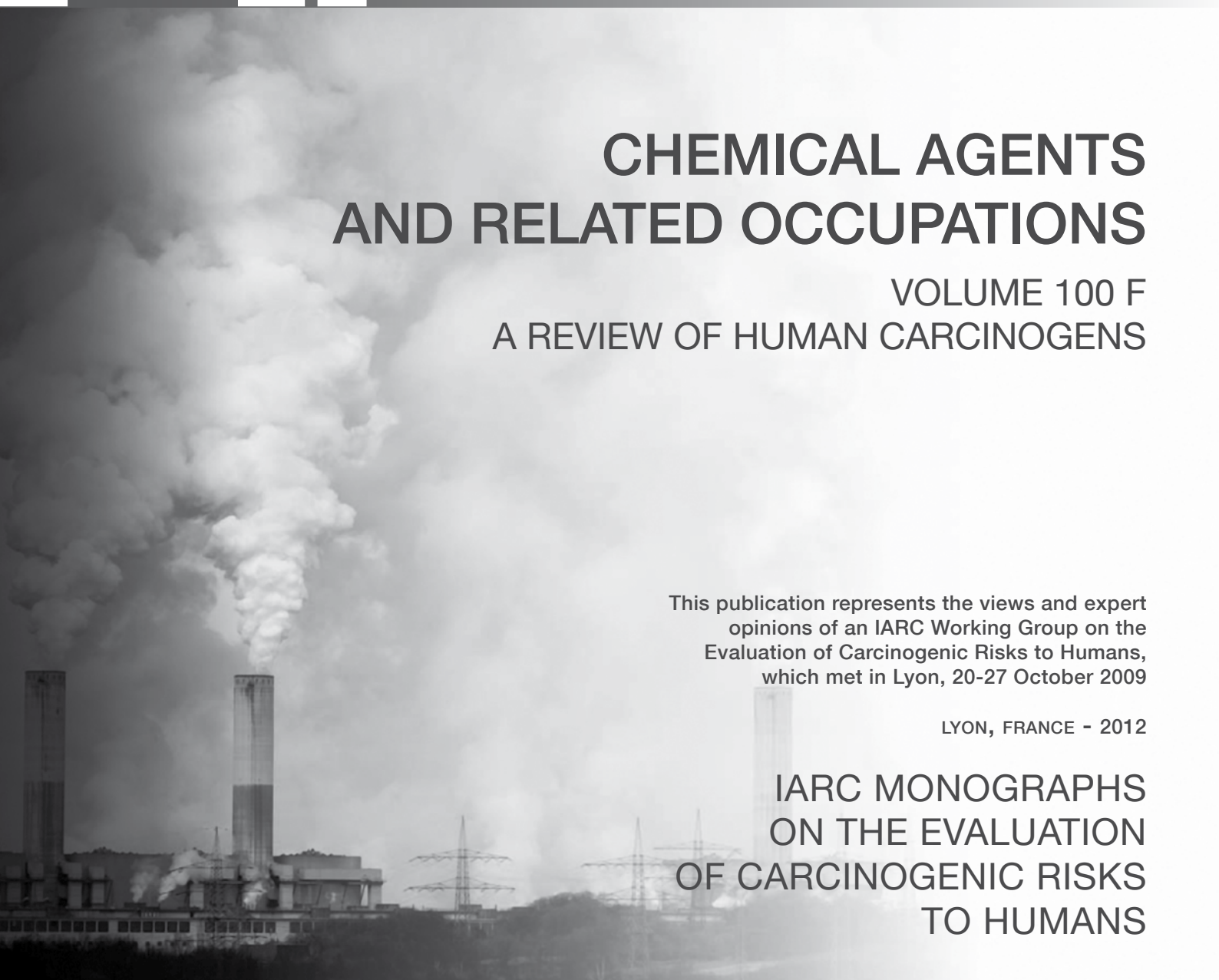

CHEMICAL AGENTS AND RELATED OCCUPATIONS

VOLUME 100 F
A REVIEW OF HUMAN CARCINOGENS

This publication represents the views and expert opinions of an IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, which met in Lyon, 20-27 October 2009

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IARC MONOGRAPHS ON THE EVALUATION OF CARCINOGENIC RISKS TO HUMANS

International Agency for Research on Cancer
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MINERAL OILS, UNTREATED OR MILDLY TREATED

Mineral oils were considered by previous IARC Working Groups in 1983 and 1987 (IARC, 1984, 1987). Since that time new data have become available, which have been incorporated in this *Monograph*, and taken into consideration in the present evaluation.

1. Exposure Data

1.1 Identification of the agent

Mineral oils (also known as base oils, mineral base oils or lubricant base oils) are chemical substances prepared from naturally occurring crude petroleum oil. Crude oil is distilled first at atmospheric pressure and then under high vacuum to yield vacuum distillates and residual fractions that can be further refined to mineral oils. Mineral oils refined from petroleum crude oils are complex and variable mixtures of straight and branched-chain paraffinic, naphthenic (cycloparaffinic), and aromatic hydrocarbons having carbon numbers of 15 or more and boiling points in the range of 300–600°C (IARC, 1984).

Mineral oils are described by several dozen generic "petroleum stream" Chemical Abstracts Service (CAS) numbers. Many mineral oils may have more than one CAS number because different refiners submitted slightly different descriptions for similar refining streams when CAS numbers were being assigned (both in the United States of America and Europe) (CONCAWE, 1997).

The hydrocarbon composition and physical characteristics of a mineral oil depend on both the composition of the original crude oil and the processes used during refining (e.g. solvent extraction, hydro-treatment) (CONCAWE, 1997). Production processes of mineral oils have changed substantially over time (IARC, 1987; Tolbert, 1997). In the past, many mineral oils were only mildly refined and contained significant levels of polycyclic aromatic hydrocarbons (PAHs). Acid treatment was initially used to remove PAHs and other impurities and to improve the technical properties of the finished oils. In recent decades, acid treatment has largely been replaced by extensive refining with solvent extraction and/or hydro-treatment, which has further reduced the level of PAHs and other contaminants. Mineral oils have been produced by means of the severe hydro-treatment procedure since the 1960s (Kane *et al.*, 1984; Mackerer *et al.*, 2003). Regulatory pressures in the USA further encouraged the move to highly refined mineral oils in the mid-1980s (Woskie *et al.*, 2003).

There are several assays that can be used to determine if a mineral oil is highly or severely refined (Mackerer *et al.*, 2003). Two useful

short-term assays that are widely used by mineral-oil manufacturers are the modified Ames test (ASTM, 1996) and the IP346 assay (Institute for Petroleum, 1985, 1993; CONCAWE, 1994). The modified Ames test measures the amount of extractable mutagenic activity in a mineral-oil sample; mineral oils with a mutagenicity index ≤ 1.0 in this assay are considered highly or severely refined. The IP346 assay measures the amount of material extractable in dimethyl sulfoxide (DMSO): mineral oils with a DMSO-extractable content < 3% in the IP346 assay are considered highly or severely refined. Naphthenic mineral oils tend to have higher non-mutagenic DMSO extractables and some naphthenic oils can give a false-positive result in the IP346 assay. The modified Ames test can give conclusive results if the outcome of the IP346 assay is high.

1.2 Uses

A wide variety of mineral oil-containing products including lubricants as well as products intended for non-lubricant purposes are manufactured for different applications. Lubricant products include engine oils, transmission fluids, gear oils, hydraulic fluids, as well as metalworking fluids (also known as metal-removal fluids). Metalworking fluids may be different from other mineral oil-containing products due to the types of additives used, the additive treatment rates, and contaminants – including those of microbial origin – that are associated with use. "Non-lubricant" products include agricultural spray oils, printing inks, tyre oils, etc. Oil mists or aerosols can arise from the use of mineral oil both as lubricant and as non-lubricant. In practice, oil aerosols may be generated by several mechanisms such as aeration, contact with a fast-moving surface, or by heating. Important applications associated with potential generation of oil aerosols are metal-working, textile machinery, rock drills, aerosol lubrication, agriculture sprays, concrete mould release agents, corrosion preventatives, printing inks, rubber extenders, lubricant-blending in open processes, and applications in food and pharmaceutical preparations (CONCAWE, 1986; Urbanus *et al.*, 2003; ACGIH, 2007). The particle size of the mists, aerosols or fogs is likely to differ for each of these processes (IARC, 1984).

1.3 Human exposure

1.3.1 Occupational exposure

There are several occupational environments in which an oil mist can be generated. In these situations the opportunities for dermal exposure or inhalation exposure, with concomitant ingestion, are substantial. Such occupations include metalworking, printing-press operating, and cotton- and jute-spinning (Tolbert, 1997). According to the US National Occupational Exposure Survey (1981–83), approximately 1 million workers (including approximately 390,000 women) in the USA were potentially exposed to mineral oil (NIOSH, 1990).

A small number of studies have evaluated respiratory morbidity from exposure to mineral-oil mist among newspaper pressmen, marine engineers, cable oilers, and tunnel blasters. Mineral-oil aerosol concentrations in these studies ranged from approximately 0.3 mg/m^3 (Bakke *et al.*, 2001) to about 3 mg/m^3 (Skyberg *et al.*, 1992; Svendsen & Hilt, 1997, 1999; Bukowski, 2003). Values of up to >20 mg/m^3 were recorded in earlier studies (Goldstein *et al.*, 1970).

Ambient mineral-oil mist concentrations were measured in the engine rooms of ships: the typical lubricating oil (b.p. 300–700°C) is a solvent-refined mineral oil containing paraffins, cycloparaffins, aromatic hydrocarbons, and additives. The air concentrations of oil mist in the engine rooms of different ships varied from not detectable to 0.53 mg/m^3 (mean 0.24 mg/m^3). The levels of hydrocarbons varied from 0.2 to

14.5 mg/m^3 (Svendsen & Børresen, 1999). [The level of refinement of these oils was not reported.]

1.3.2 Non-occupational exposure

The non-occupationally involved general population may be exposed to mineral oils through ingestion of contaminated foodstuffs. In a study conducted in Switzerland, Grob *et al.* (2001) analysed mineral oil in the fat or in a raw extract from animal feed or foodstuffs. The average concentration in the feed was 100 mg/kg, with a maximum of 1000 mg/kg, 25 mg/kg in animal body fat (maximum, 150 mg/kg) and 30 mg/kg in the fat phase of eggs (maximum, 80 mg/kg). Paraffin oil is used for feed production, which may account for part of the contamination problem (e.g. in eggs). [The level of refinement of these mineral oils was not reported.]

2. Cancer in Humans

2.1 Introduction

Mineral oils comprise a diverse set of agents used for a wide range of industrial operations. There is evidence that mineral oils vary in their potential to cause cancer with the degree of treatment or processing. Hydro-treatment and solvent extraction reduce the PAH content, and thus the carcinogenicity of the oils. Untreated and mildly treated oils have been classified as Group-1 carcinogens, with *sufficient evidence* from studies in humans that mineral oils (containing various additives and impurities) that have been used in occupations such as mule-spinning, metal machining and jute-processing are carcinogenic to humans.

A major challenge in making an overall assessment of the carcinogenicity of mineral oils is this diversity in processing, with incomplete information on the extent of processing in specific industrial applications. Mineral oils are typically used as part of a complex mixture for such applications as metalworking, lubrication, and cooling. The additional processing and combining with other agents makes attribution of risk specifically to mineral oils difficult (Woskie *et al.*, 2003).

2.2 Cancer of the skin/scrotum

The evidence from a series of case reports and case series for skin cancer, particularly of the scrotum, over the period from the early 1900s through the 1960s, was reviewed in *IARC Monograph* Volume 34 (IARC, 1984). Five large case series of mule-spinners had been reported, each with over 100 scrotal cancers (Green, 1910; Southam & Wilson, 1922; Henry & Irvine, 1936; Henry, 1947), with sizable numbers of cases in other exposed populations. Despite the inherent limitations in case series as a source of information, the numbers of cases observed, the rarity of scrotal cancer, and the intensity of the direct exposure of the skin in these jobs during that time period render these case series highly informative. Scrotal cancer is virtually pathognomonic for occupational exposure, in part as a result of these historical case series.

Over the intervening period since the 1960s nothing has challenged the assessment of *sufficient evidence* of human carcinogenicity based on the historical evidence pertaining to skin cancer. In a cohort of 792 Swedish metalworkers exposed to oil mist there were four cases of scrotal cancer, all among 242 men employed as turners, versus 0 expected overall (Järvholm *et al.*, 1981). The same group (Järvholm *et al.*, 1985) reported on a cohort of 682 bearing-ring industry workers and found working as a lathe operator to be associated with scrotal cancer (four observed, 0.3 expected, $P < 0.001$). Zhao *et al.* (2005) studied a cohort of 5049 male aerospace workers in the USA and found a significantly increased risk for skin melanoma (see Table 2.1 available at http://monographs.iarc.fr/ENG/Monographs/

vol100F/100F-14-Table2.1.pdf). Case series indicative of an increased risk for scrotal cancer continue to be published based on historical exposures. Pressmen working in a wax-manufacturing department in an oil refinery in the USA had a marked excess of scrotal cancer based on 11 cases in men working >10 years during the period 1937–56, which corresponds to a crude rate of 806 per 100,000 relative to a general population rate estimated at 0.15 per 100,000 (Hendricks *et al.*, 1959). Tool setters and tool fitters in the West Midlands area of England showed notably elevated risk for scrotal cancer over the period 1936–1976 (Waldron *et al.*, 1984).

Several epidemiological studies were able to detect the expected increased risk for skin cancer in general, or scrotal cancer in particular, but since these cancers are rarely fatal, studies based on cancer mortality were of limited use to address the question. Roush *et al.* (1982) studied squamous-cell carcinoma of the scrotum in a case–control study in Connecticut, USA, among men diagnosed between 1935 and 1973 (see Table 2.2 available at http://monographs.iarc.fr/ENG/Monographs/vol100F/100F-14-Table2.2.pdf). Occupations associated with exposure to cutting oils, including tool or machine setters, screw-machine operators, machinists, and machine operators, were examined and showed an odds ratio of 10.5 (95%CI: 4.0–36.9).

2.3 Other cancers

The more rigorous epidemiological studies pertain to the occupations in which mineral oils are used in various formulations and in different degrees, including metal workers, machinists, jute workers, and others. Given the time period and setting, the mineral oils studied were likely to be highly treated. At the time of the previous *IARC Monograph* there were several studies of workers in these industries, mostly based solely on job title and industry of employment and limited in detail regarding exposure (IARC, 1984). Exposure to mineral oil was inferred based solely on job title or self-reported exposure. Whereas dermal exposure is the primary route of exposure for skin/scrotal cancer, for other sites and under improved hygienic conditions, aerosols are of equal or greater concern.

Focusing on studies that made attempts to address exposure to mineral oil directly, there has been sporadic and inconsistent support for an association with bladder cancer (Ugnat *et al.*, 2004; Friesen *et al.*, 2009; see Table 2.3 available at http://monographs.iarc.fr/ENG/Monographs/vol100F/100F-14-Table2.3.pdf and Table 2.4 at http://monographs.iarc.fr/ENG/Monographs/vol100F/100F-14-Table2.4.pdf), stomach cancer (Zhao *et al.*, 2005; see Table 2.5 at http://monographs.iarc.fr/ENG/Monographs/vol100F/100F-14-Table2.5.pdf and Table 2.6 at http://monographs.iarc.fr/ENG/Monographs/vol100F/100F-14-Table2.6.pdf), rectal cancer (Gerhardsson de Verdier *et al.*, 1992; Eisen *et al.*, 2001; see Table 2.7 at http://monographs.iarc.fr/ENG/Monographs/vol100F/100F-14-Table2.7.pdf and Table 2.8 at http://monographs.iarc.fr/ENG/Monographs/vol100F/100F-14-Table2.8.pdf), pancreatic cancer (Yassi *et al.*, 2003), sinonasal cancers (Roush *et al.*, 1980), laryngeal cancer (Ahrens *et al.*, 1991; Eisen *et al.*, 1992), and lung cancer (Rønneberg *et al.*, 1988; Acquavella *et al.*, 1993; see Table 2.9, available at http://monographs.iarc.fr/ENG/Monographs/vol100F/100F-14-Table2.9.pdf and Table 2.10 at http://monographs.iarc.fr/ENG/Monographs/vol100F/100F-14-Table2.10.pdf). Individual studies have suggested that mineral oil may be related to a range of other cancers, including those of the larynx and pancreas, based on studies of metal-workers and related manufacturing occupations. For each of these, however, there are studies of equal or higher quality that do not show associations, and in many cases there are inconsistent results within the same study across exposure indices. There have been varyious interpretations of the strength of the

evidence linking exposure to metalworking fluids to a range of cancer sites (Tolbert, 1997; Calvert *et al.*, 1998; Mirer, 2003; Savitz, 2003). The diversity in exposures to other agents, including synthetic oils and contaminants, and the presence of accompanying unrelated occupational exposures make the relevance of many studies tenuous in the assessment of the carcinogenic hazards of exposures to mineral oils.

Lung cancer is the most extensively investigated cancer in these occupations. While there are several studies supporting an association with exposed workers in certain occupations (Coggon *et al.*, 1984; Rønneberg *et al.*, 1988; Acquavella *et al.*, 1993; Droste *et al.*, 1999; Zhao *et al.*, 2005), the exposures are not generally to mineral oils alone, given the use of other compounds in the metal-working trade (see Table 2.9, online), the most detailed study did not show an association (Schroeder *et al.*, 1997; Eisen *et al.*, 2001), and smoking was not controlled for in some of the studies that did show an association (Coggon *et al.*, 1984; Zhao *et al.*, 2005; see Table 2.10 online).

The case–control studies have typically been better able to address confounding, whereas the cohort studies have tended to examine exposure in more detail. However, even in the most sophisticated studies, it was not possible to isolate highly-treated from untreated or mildly-treated oils, nor are mineral oils used in isolation from other agents. As noted in several reviews (Tolbert, 1997; Woskie *et al.*, 2003), in metal-working there is concomitant exposure to a range of chemicals including biocides, metal dusts, and by-products of oil heating. Even in the study of the Michigan automobile-manufacturing workers – the most detailed study of metal-workers – the authors identified categories of exposure to straight-chain and soluble lubricating fluids, but were not able to separate or characterize mineral-oil exposures in particular (Eisen *et al.*, 1992).

2.4 Synthesis

There is consistent evidence that untreated or mildly-treated mineral oils cause cancer of the skin, specifically of the scrotum, in humans. The association is highly unlikely to be due to chance, bias, or confounding, given the large case series, supportive epidemiological studies, the rarity of scrotal cancer, and the intensity of exposure during the period of interest.

There were insufficient data regarding cancer at other sites to draw conclusions on the carcinogenicity in humans for untreated, mildly-treated, or highly-treated mineral oils. Recent studies did address highly-treated mineral oils, but were limited in their assessment of this agent, instead addressing all aspects of the work environment. Exposure to mineral oils in metal-working and other industries has not been easy to assess, and other agents of concern are known to be present in such work environments. Given these limitations in assessing exposure to mineral oils, and the lack of consistency in study findings by cancer site, the evidence for carcinogenicity of highly-treated mineral oils remains insufficient to draw conclusions.

3. Cancer in Experimental Animals

Petroleum-derived base oils and formulated products have been tested for their potential carcinogenicity in mice and other experimental animals, by skin application, in feeding studies, by inhalation exposure, and by subcutaneous and intra-peritoneal injection. In *IARC Monograph* Volume 33 (IARC, 1984), the Working Group divided petroleum materials into eight classes plus two subclasses (6.2, 7.2) based on the extent of refinement. Class 8 covers petroleum-derived materials not otherwise classified, and this category is not considered in this *Monograph*. This categorization scheme is still useful and applied here despite the fact that the terminology used

to describe the material tested in recent studies may not be easily conducive to allocate it to a given class. Table 3.1 presents the most representative animal cancer bioassays with mineral oils evaluated in *IARC Monograph* Volume 33 (IARC, 1984), as well as studies published since that time.

3.1 Earlier studies

Vacuum-distillate fractions [class 1], either naphthenic or paraffinic in nature, produced a significant skin-tumour response. De-waxing of these distillates did not appreciably alter their activity (Halder *et al.*, 1984; IARC, 1984; Kane *et al.*, 1984). Early studies demonstrated that both light and heavy fractions of paraffinic oils induced benign and malignant skin tumours (Twort & Ing, 1928). De-waxed paraffinic distillates induced both benign and malignant skin tumours in mouse skin (Gradiski *et al.*, 1983). Jute-batching oil induced benign and malignant skin tumours and promoted tumours in mice pre-treated with 7,12-dimethylbenz[*a*]anthacene (Roe *et al.*, 1967).

Acid-treated oils [class 2] of either naphthenic or paraffinic origin, induced benign and malignant skin-tumour responses (Twort & Lyth, 1939; Bingham *et al.*, 1965; Bingham & Horton, 1966), unless severe acid treatment had been applied (Twort & Lyth, 1939).

Solvent-refined oils (raffinates) [class 3], either naphthenic or paraffinic in nature, generally did not produce skin tumours (Gradiski *et al.*, 1983). However, in one study skin application of solvent-extracted paraffinic oil induced one malignant tumour, which suggests possible skin tumour-inducing activity (Doak *et al.*, 1983).

Hydro-treated oils [class 4], principally paraffinic in nature, induced a moderate incidence of skin tumours when treatment of the distillates was mild (Halder *et al.*, 1984; Kane *et al.*, 1984), while no tumour was induced by severely hydro-treated oils. The combination of mild hydro-treatment and solvent extraction appears to reduce or eliminate skin tumorigenicity.

White oils and petrolatums [class 5], which are produced from oils that have undergone the most severe acid and/or hydro-treatment, showed no activity in the skin-tumour bioassay (Doak *et al.*, 1983). Single subcutaneous injection of three different grades of medicinal petrolatum into mice induced no treatment-related tumours during the following 18 months (Oser *et al.*, 1965). Similarly, a lifetime study in rats involving subcutaneous injection of liquid paraffin and yellow petrolatum did not show local tumours, except a single osteosarcoma near the site of yellow petrolatum injection (Schmähl & Reiter, 1953). Intra-peritoneal injection of two highly refined food-grade mineral oils into certain strains of mice induced plasma-cell neoplasms and reticulum-cell sarcomas (Potter & Boyce, 1962; Bober *et al.*, 1976). Mice receiving repeated intra-peritoneal injections of liquid paraffin developed peritoneal reticulum-cell sarcomas, plasma-cell leukaemia, myeloid leukaemia and lymphocytic leukaemia (Rask-Nielsen & Ebbesen, 1965). In two feeding studies in which three different samples of medicinal-grade petrolatum and liquid paraffin were fed to rats for two years at either 2% or 5% of the diet, no significant increase in tumour incidence was observed (Schmähl & Reiter, 1953; Oser *et al.*, 1965). Although the experimental design was considered inadequate and the exposure period was short, inhalation of light white naphthenic aerosol (100 mg/m^3) by mice, rats, hamsters, and rabbits from 6–13 months did not produce a significant increase in tumours in any of the species tested (Wagner *et al.*, 1964).

Solvent extracts [class 6.1], which are by-products of solvent refining and sometimes called aromatic oils, induced a significant increase in incidence of skin tumours (Gradiski *et al.*, 1983). The same response was produced with highly concentrated aromatic extracts of medicinal-grade petrolatums (Kane *et al.*, 1984).

Table 3.1 Carcinogenicity studies of mineral oils in experimental animals

Species, strain (sex) Duration Reference	Route Oil Type Dosing regimen, Animals/group at start	Incidence and/or multiplicity of tumours (%)	Significance	Comments
Rats, Fisher (M, F) 104 wk Shoda *et al.* (1997)	Oral administration of 0, 2.5 or 5% liquid paraffin (class 1) in the diet. Controls received basal diet 50 animals/sex/group	All neoplastic lesions were similar to those that occur spontaneously; no significant difference was detected.	NS	Granulomatous inflammation was observed on the mesenteric lymph nodes, but this was not associated with any neoplastic lesion.
Chester-Beatty stock mice (M) 84 wk Roe *et al.* (1967)	Skin application 14 applications of 0.25 ml of JBO (class 1) during 9½ wk Untreated, JBO, DMBA, JBO + DMBA 24 animals/group	Mice with malignant tumours Untreated 0/24, JBO 6/24*, DMBA 2/24, JBO + DMBA 11/24**	* $P = 0.01$ ** $P = 0.004$	DMBA Benzo[*a*]pyrene content of JOB < 1 mg/kg.
Mice, C3H, C57BL, and Rockland Farm (M, F) 310 d Gilman & Vesselinovitch (1955)[1]	Skin application of soluble cutting oil (class 7.1) 3×/wk Different mouse strains were untreated or treated with 1 of 2 undiluted or diluted oils containing additives. 20–40 animals/group	Oil, strain:% mice with skin tumours,% carcinomas Controls: 0,0 1 Undiluted, C3H: 61,22 1 Diluted, C3H: 19,3 2 Undiluted, C3H: 58,19 2 Undiluted, C57BL: 27,3 2 Undiluted, RF: 33,7	NR	Sulfurized mineral-oil base from straight-run distillate in 40% water emulsion. Usually further diluted with eight parts of water before use.
Mice, CFLP (F) 104 wk Grimmer *et al.* (1982b) [1]	Skin application of used gasoline-engine oil (class 7.2), twice/wk of 0.1 ml of 3:1 mixture of acetone/ cyclohexane containing doses of 0, 0.625, 1.875, 5.625 mg of engine oil artificially aged 65 animals/group	Papillomas/carcinomas,% tumour-bearing mice 0/1, 1.5 3/0, 4.6 8/9, 26.6 14/29, 69.4	Dose-related increase $P < 0.01$	No comparison with unused oil, but the strong dose-response and the large number of animals per group are noted
Mice, Swiss Albino (F) 1 d initiation, 30 wk promotion study Agarwal *et al.* (1985)	Topical application of JBO (class 1) and six of its reconstituted fractions. Mice were initiated with single application of 100 µl of vehicle, JBO, or one of six reconstituted fractions. This was followed by 5 µg TPA 3×/wk for 30 wk 10 animals/group	Treatment: papilloma + keratoacanthoma/mice Untreated: 0/10 Vehicle control: 0/9 JBO: *4/7 (57%) 6 Fractions: 4/9 (44%), 0/3, 0/5, 1/9 (11%), 2/6 (33%), 3/8 (37%) DMBA (positive control): 7/7 (100%)	*[$P = 0.01$]	Tumours were considered benign. JBO obtained from Indian refinery. Chemical analysis not given, but physicchemical characteristics were provided. Fourteen original fractions combined to six, which were tested in a tumour initiation–promotion assay. Cause of death of missing animals not indicated.

Table 3.1 (continued)

Species, strain (sex) Duration Reference	Route Oil Type Dosing regimen, Animals/group at start	Incidence and/or multiplicity of tumours (%)	Significance	Comments
Mice, Swiss Albino (F) 40 wk, plus 14 wk tumour promotion. Agarwal *et al.* (1988)	Topical application of 50 µl JBO-P (Class 1), one of four JBO-P fractions or vehicle 3×/wk for 40 wk. JBO-P fractions were designed to limit PAH type content. Controls and three groups treated with fractions were further treated 3×/wk for 14 wk with 5 µg TPA; 20 animals/group	Oil: tumour incidence (+TPA) Untreated: 0/20 (0/12) Vehicle: 0/20 (0/14) JBO-P: 12/20 JBO-P reconstituted: 10/20 JBO-P PAH free: 2/20 (0/7) JBO-P 2–3-ring PAH: 0/20 (0/9) JBO-*P* > 3-ring PAH: 0/20 (7/7)	[NS]	All tumours were considered benign and identifiable as squamous-cell papillomas and keratoacanthomas. Source of JBO same as in Agarwal *et al.* (1985).
Mice, Swiss EOPS (F) 18 mo Gradiski *et al.* (1983) [1]	Topical application of 0.05 ml, 3×/wk for 1 mo and 0.05 ml, twice/wk for 11 mo of paraffinic distillates (class 1), Mineral ("White oil" (F) and 5 (A-E) solvent extractions (class 6) of Middle East crude oil containing different levels of PAHs and benzo[*a*]pyrene Oil,% PAH/B[*a*]P ppb A, 43.5 /1100; B, 9.15/270 C, 3.08/33; D, 2.06/1; E, 0.80/0.2; F, 0.26/NP Groups A-F, 30 animals/group; 60 controls	Tumours classified as benign, malignant, or benign & malignant for oils A-F Controls: 0, 0, 0; A: 10, *5, 10; B: 8, 2, 3; C: 1, 0, 0; D: 0, 0, 0 E: 0, 0, 0; F: 0, 0, 0 Aromatic extract (class 6.1) produced 15 malignant tumours in 30 mice	*[$P = 0.0032$]	Malignant tumours were squamous cell carcinomas, sarcomas, and mixed tumours. Oil refinement considered same as commercially used in mineral-oil production. Dermal application of oils had marked irritating effect. Benign tumours were acanthosic, papillomatous, hyperkeratotic.
Mice, SPF, CFLP (F) 104 wk Grimmer *et al.* (1982a)[1]	Topical application of 0.1 ml, twice/wk of used engine oil (class 7.2) 1) Untreated 2) Solvent, 3) Used oil, 0.6, 1.8, 5.6 mg 4) PAH free, 0.5, 1.7, 5.1 mg 5) PAH (2, 3) 0.04, 0.1, 0.4 mg 6) PAH (> 3 ring) 6, 20, 60 ug 7) Recons oil, 0.6, 1.8, 5.6 mg 8) B[*a*]P 3, 7, 15 ug Mice/group at start (NR), total 1300 animals	Papilloma/Carcinoma 1) 0/0 2) 0/1 3) 3/0, 8/9, 14/29 4) 0/1, 0/2, 1/0 5) 2/2, 1/1, 4/2 6) 0/0, 7/2, 20/13 7) 1/2, 4/2, 16/19 8) 6/20, 6/44, 6/54	Tumour induction time using log-rank test and Wilcoxon test show significant effect of used oil, >3-ring PAH, reconstituted oil, and B[*a*]P. *P*-value not provided.	Oil aged in gasoline-driven car. Oil dissolved in cyclohexane and PAH extracted with nitro-methane. Tumours occurred only at site of treatment and were described as papillomas and carcinomas. Authors concluded that >3-ring PAH content accounted for 70% carcinogenicity and B[*a*]P content accounted for 18%. Tumour incidence may be misleading as the number of mice/group was unknown.

Table 3.1 (continued)

Species, strain (sex) Duration Reference	Route Oil Type Dosing regimen, Animals/group at start	Incidence and/or multiplicity of tumours (%)	Significance	Comments
Mice, Swiss (F, M) Lifespan Lijinsky *et al.* (1966)[1]	Skin application of 60 µl petrolatum or 20 µl fractionated solutions in iso-octane Amber Petrolatum (National Formulary grade) (class 5) twice/wk fractionated into aliphatic and aromatic fractions. Controls received 20 µl iso-octane 30 treated animals/group; 50 controls	Material: Total tumours/carcinomas (F, M) Isooctane: 0/0, 2/1 Petrolatum: 2/0, 3/0 Filtrate: /0, 0/0 Adsorbate: 26/9[a], 3/0 Nitromethane: 10/1, 31/9[b] Cyclohexane: 8/5[c], 4/1	[a][P < 0.0001; carcinomas (F)] [b][P < 0.0001; carcinomas (M)] [c][P < 0.0059; carcinomas (M)]	Skin tumours were papillomas, kerato-acanthomas and malignant squamous-cell carcinomas. Internal tumours within limits of controls.
Mice, C3H (M) 24 mo. McKee *et al.* (1989)	Skin application of 37.5 µl of naphthenic crude oil (class1), light and heavy vacuum distillates of the crude, and hydro-treated (mild or severe) (class 4) products, twice/wk for 24 mo. White mineral oil (- control) B[*a*]P (+ control) 1. unrefined light 2. hydro-treated light mild 3. hydro-treated light severe 4. unrefined heavy 5. hydro-treated heavy mild 6. hydro-treated heavy severe 7. unrefined heavy (viscous) 8. hydro-treated heavy mild 9. hydro-treated heavy severe 40 animals/group	Number of mice with carcinoma/papilloma White mineral oil: 0/0 B[*a*]P: 21/1* 1. 20/0* 2. 0/0 3. 0/0 4. 21/3* 5. 0/0 6. 0/0 7. 1/1 8. 0/0 9. 0/0	*[$P < 0.0001$]	

Table 3.1 (continued)

Species, strain (sex) Duration Reference	Route Oil Type Dosing regimen, Animals/group at start	Incidence and/or multiplicity of tumours (%)	Significance	Comments
Mice, Swiss (F) 15 wk Mehrotra *et al.* (1987)	Topical application of JBO-C (class 1) 3×/wk for 15 wk Tumour promotion assay groups: 1. Untreated 2. Acetone, 0.1 ml 3. JBO-C, 50 µl 4. TPA, 15 nmole in 0.1 ml acetone 5. Urethane, 1mg/g bw in 50 µl saline 6. Urethane+JBO-C 7. Urethane+TPA 8. 3MC, 4 µg/g 9. 3MC once+JBO-C 10. 3MC once+TPA 15 animals/group	Mice in groups 1, 2, 3, 4, 5, and 7 did not develop tumours. Group 6 had 3 squamous cell papillomas and 1 keratoacanthoma. Group 7 had 3 squamous-cell papillomas and 2 keratoacanthomas. Group 9 had 2 squamous-cell papillomas, 1 keratoacanthoma, and 1 malignant fibrosarcoma. Group 10 had 1 fibroma and 2 keratoacanthomas.	Probability of tumour development was determined as P = r/n (r = mice with tumours, n = total of mice). Statistical methods described, but no P-value provided. Results of statistical analysis not presented.	TPA or 3MC were administered once subcutaneously as initiators. Groups 2, 3, 4 promotion; 5, 6 initiation; 4, 5, 9, 10 initiation+promotion. Although not stated that results were statistically significant, authors concluded that JBO-C acted as tumour promoter following initiation by 3MC or urethane.
Mice, Swiss (F) Study 1, 20 wk; study 2, 14 wk Mehrotra *et al.* (1988)	Topical application JBO-P (class 1) 3×/wk for 20 wk (Exp. 1) or 14 wk (Exp. 2) Experiment 1 a. 50 µl acetone b. 5 µl B[*a*]P in 50 µl acetone c. 30 µl neat JBO-P Experiment 2 a. 1mg/g urethane in 50 µl saline, single s.c. b. ureth.+30 µl paraffin c. ureth.+30 µl crot oil d. ureth.+30 µl JBO-P e. 30 µl neat JBO 10 animals/group	Experiment 1 a. 0/10 b. 3 /9 (33%) c. 8/9 (89%) Experiment 2 a. 0/10 b. 0/10 c. 6/10 (60%) d. 5/9 (56%) e. 2 /10 (20%)	NR	Most tumours are benign squamous-cell papillomas and keratoacanthomas. One JBO-P and 2 B[*a*]P exposed mice developed malignant squamous-cell carcinomas. Results indicate that JBO-P is tumorigenic and acts as a tumour promoter. The short duration of the exposure was noted.

Table 3.1 (continued)

Species, strain (sex) Duration Reference	Route Oil Type Dosing regimen, Animals/group at start	Incidence and/or multiplicity of tumours (%)	Significance	Comments
Mice, C3H, (M) 2 yr Nessel *et al.* (1998)	Topical application of mineral oil (MO), heavy (class 5) clarified oil (HCO), straight-run kerosene (SRK), straight-run gas oil (SRGO), light cycle oil (LCO) 50 µl of MO or HCO at 100% 2x/wk 50 µl of SRK, SRGO, LCO at 100% 2x/wk, at 50% 4x/wk, or at 28.5% 7x/wk 50 animals/group	MO and SRK 0 HCO, 42 carcinomas, 3 keratoacanthomas, 37 papillomas SRG, 8 carcinomas, 4 fibrocarcinomas SRGO, 2 carcinomas, 3 papillomas LCO, 12 carcinomas, 5 fribrosarcomas, 14 papillomas	sHCO, SRK, and LCO, $P < 0.01$ SRGO, $P < 0.05$	Large, well-designed study addressing the role of dermal irritation in carcinogenesis. Diluted oils produced reduced irritation and fewer tumours with significant tumour formation in 100% or 50% solutions only. Results support conclusion that non-irritating oils with low PACs are not tumorigenic
Mice, CD-1 (M) 54 wk Nessel *et al.* (1999)	Topical application of C10-C14 normal paraffins (NP) (class 1); steam-cracked gas oil (SCGO); light refined paraffinic (LRPO), or jet fuel (JF) Tumour promotion initiated with 25 µg DMBA and promoted with 25 µl TPA (+ control) or 75 µl of NP at 100% twice/wk, at 50% 4×/wk, or at 28.5% 7×/wk, or 75 µl SCGO, LRPO, or JF at 100% twice/wk or at 28.5% 7×/wk 30 animals/group	Control 0/30 DMBA + TPA 29/30 (97%) ** DMBA 1/30 NP 15/30 (50%) **, 1/30 (3%), 3/30 (10%) SCGO 17/30 (56%) **, 9/30 (30%) ** LRPO 7/30 (23%) *, 0/30 JF 11/30 (37%) **, 0/30	*$P < 0.05$ vs control ** $P < 0.01$ vs control	Large, well-designed tumour-promotion study. Undiluted (100%) solutions more irritating and tumorigenic than diluted solutions (28.5%). Most tumours were papillomas and to a lesser extent squamous-cell carcinomas
Mice, DBA/2, CBA (F) 24 mo Rask-Nielsen & Ebbesen (1965)[1]	Intra-peritoneal injections of high-visocosity oil (Primol D & Bayol F) (class 5) Three injections of 0.5 ml Primol D to mice at 10, 15, and 21 wk 36 DBA/2 and 12 CBA	DBA/2 mice: 15 (42%) had peritoneal-cell sarcomas, 3 had plasma-cell leukaemia, 3 myeloid leukaemia, 2 lymphocytic leukaemia. CBA mice: 1 had reticulum-cell sarcoma, and 1 had lymphocytic leukaemia	NR	No mention of controls IC and C3H mice injected with Bayol F developed oil-granulomas but not plasma-cell tumours (Hermann, 1966)

Table 3.1 (continued)

Species, strain (sex) Duration Reference	Route Oil Type Dosing regimen, Animals/group at start	Incidence and/or multiplicity of tumours (%)	Significance	Comments
Mice, BALB/c (F) 14 mo Potter & Boyce (1962)[1]	Intraperitoneal injections of two refined mineral oils US Pharmacopeia (Bayol F and Primol D) (class 5) Mice received Bavol F as single injection of 0.4 or 0.5 ml, or three injections of 0.5 ml at intervals of two months. 40 or 32 animals/group One group of >56 mice received injections of Primol D	Bavol F: 8, 2, 22 plasma-cell neoplasms in each of the three groups receiving injections. Primol D: plasma-cell neoplasms in 13/56 (23%) mice Corn-oil control: no neoplasms	NR	Tumour morphology same as those induced by mixture of Freund's adjuvant and *Staphylococcus* (Potter & Robertson, 1960) Tumours appeared to arise from mesenteric oil-granulomas (Potter & MacCardle, 1964)
Mice, BALB/c (F) 7 or 12 mo Bober *et al.* (1976)[1]	Intra-peritoneal injections of mineral oil Primol D (class 5) Mice received three 0.5 ml injections of oil or saline. Two wk after oil injection mice were immunized with plaque-forming units of bacteriophage T2	Plasma-cell tumours from Primol D alone: Experiment 1, 0/21 Experiment 2, 7/27 (26%)		Injections of bacterial endotoxins enhanced the incidence of tumours in BALB/c mice injected with Primol D. Effect of oil alone was inadequately described. Experiments 1 and 2 differed on source of mice and study duration; 7 and 12 mo, respectively.

bw, body weight; d, day or days; DMBA, 7,12-dimethylbenz[*a*]anthracene; F, female; JBO, jute-batching oil (mineral oil obtained from the distillation of crude petroleum); M, male; MC, methylcholanthrene; mo, month or months; NR, not reported; NS, not significant; TPA, 12-*O*-tetradecanoylphorbol-13-acetate; vs, versus; wk, week or weeks

High-boiling fractions from catalytically cracked oils [class 6.2] – also classified as aromatic oils – induced increasing numbers of skin tumours in mice with increasing boiling-ranges above 370°C. Further fractionation established that the activity is maximal for oils boiling at 500–520°C and is concentrated in the aromatic fraction of the oils. High-boiling, catalytically cracked oils also produced skin tumours in rabbits and monkeys (Smith *et al.*, 1951). Additional studies confirmed the increased tumorigenic activity of oils with boiling ranges 370–500°C. Promoting activity was also detected for some oil fractions in mice and rabbits (Shubik & Saffiotti, 1955; Saffiotti & Shubik, 1963).

Unused gasoline-engine oil [class 7.1] applied in several studies to mouse skin did not give a tumorigenic response with the exception of one single tumour (Saffiotti & Shubik, 1963; Kane *et al.*, 1984). Mice exposed via inhalation to unused diesel-engine oil for 11 months exhibited no increase in tumour incidence (Lushbaugh *et al.*, 1950). In contrast, unused cutting oils (also class 7.1), which are often formulated products consisting of blends of base oils and chemical additives, produced skin tumours (Gilman & Vesselinovitch, 1955; Jepsen *et al.*, 1977).

Used gasoline-engine oil [class 7.2] had stronger tumorigenic activity than unused oil; solvent extraction of polyaromatic hydrocarbons almost eliminated the tumorigenic activity (Grimmer *et al.*, 1982a). Similarly, used cutting oil [also class 7.2] tended to be more active than a comparable, unused oil (Gilman & Vesselinovitch, 1955; Jepsen *et al.*, 1977).

3.2 Studies published since the previous evaluation

Studies conducted since *IARC Monograph* Volume 33 (IARC, 1984) show a marked improvement in experimental design and reporting, and confirmed previous findings. Exposure to batching oil [class 1] induced benign and malignant skin tumours and promoted tumour formation in mice pre-treated with urethane (Mehrotra *et al.*, 1987; 1988). Subsequent studies with the same oil reported only benign tumours in mice treated with jute-batching oil, which occurred with and without pre-treatment with 7,12-dimethylbenz[*a*]anthacene (Agarwal *et al.*, 1985). Additionally, in mice treated dermally with fractions of the same jute-batching oil for 40 weeks, the PAH-containing fractions induced tumours only when treatment was followed by 12-*O*-tretradecanoylphorbol-13-acetate (Agarwal *et al.*, 1988). Unrefined naphthenic crude oil applied to the skin of mice induced papillomas and carcinomas (McKee *et al.*, 1989). Dietary exposure to liquid paraffin did not induce an increased tumour incidence (Shoda *et al.*, 1997).

Both mild and severe hydro-treatments of naphthenic oils [class 4] eliminate the tumorigenicity, which is associated with a decrease in PAH content (McKee *et al.*, 1989). Despite the association, PAH content alone was not considered predictive of carcinogenicity.

Most tumours observed after exposure to white oils and petrolatums [class 5] produced from oils that have undergone the most severe acid and/or hydrogen treatment, were papillomas and to a lesser extent squamous cell carcinomas (Nessel *et al.*, 1998, 1999).

4. Other relevant data

4.1 Humans

A group of 31 male glassmakers (smokers and non-smokers) and a group of suitably matched controls exposed to aerosols of mineral oils were examined for chromosomal abnormalities in peripheral blood lymphocytes. Chromosomal damage, including chromatid breaks, chromosome breaks, and chromosome exchanges

(di-centrics and reciprocal translocations) were increased in the exposed workers compared with controls (Srám *et al.*, 1985).

Workers from a cold-rolling steel plant (smokers and non-smokers) exposed to mineral oils were examined for mutagenic activity in the urine by means of *Salmonella typhimurium* strain TA98 in the presence of an exogenous source of metabolic activation. There was a significant difference in urinary mutagenicity between the exposed workers and the controls. While among non-smokers the mutagenic activity was not increased in exposed compared with unexposed workers, the overall results suggested a synergistic effect of smoking and exposure to mineral oils (Pasquini *et al.*, 1985).

Overall, there is weak evidence on the mechanism underlying the effects of exposures to mineral oils in humans. This evidence is based on genotoxic (mutagenic) activity of mineral oils in bacteria and a single cytogenetic study of glassworkers exposed to aerosols of mineral oils.

4.2 Experimental systems

Samples of vacuum distillates (class 1), solvent-refined oils (class 3), hydro-treated oils (class 4), used hardening oil (class 7.2) and used crankcase oils (class 7.2) were mutagenic in *Salmonella typhimurium* in the presence and absence (class 7.2 only) of an exogenous source of metabolic activation. Samples of a white oil (class 5), a refined steel-hardening oil (class 7.1) and of unused crankcase oils (class 7.1) were not mutagenic in *S. typhimurium* strain TA98 in the presence or absence of exogenous metabolic activation (IARC, 1984, 1987).

Naphthenic distillates (raw or acid-treated) were tested for mutagenicity in the *S. typhimurium* assay in the presence and absence of an exogenous source of metabolic activation. With metabolic activation, both untreated and acid-treated naphthenic distillates were mutagenic. The naphthenic distillates contained approximately 12% (w/w) polycyclic aromatic hydrocarbons (Granella & Clonfero, 1991). A series of 15 high-viscosity mineral oils obtained from naphthenic distillates, including used, recycled and pooled oils, were examined for mutagenic activity in the *S. typhimurium* assay with strains TA98 and TA100 in the presence and absence of an exogenous source of metabolic activation. Four of the samples (three acid-treated naphthenic oils and one recycled fraction of a used oil) showed significant mutagenic activity in the presence metabolic activation (Granella *et al.*, 1995).

An extensive evaluation of the mutagenic activities of 13 mineral oils obtained from various processes was conducted with a modified *S. typhimurium* assay. The modification consisted of extracting the mineral-oil samples with dimethyl sulfoxide and increasing the concentrations of both $NADP^+$ and the liver post-mitochondrial fraction (S9). The mutagenic activities of the mineral-oil samples were significantly correlated with the amount of 3–7-ring polycyclic aromatic compounds for a subgroup of oil samples (Blackburn *et al.*, 1984; Roy *et al.*, 1988).

Six mineral-oil samples were evaluated in a *S. typhimurium* assay activated with washed liver microsomes from Aroclor-1254-induced rats. Five of the six samples were mutagenic. The results showed an empirical correlation between increasing mutagenicity index, carcinogenicity and the polycyclic aromatic hydrocarbon content of the oils (Brooks *et al.*, 1995).

Three mineral-oil samples (N11, N1, and R1) and several fractions of the N1 oil – obtained from silica-gel column chromatography and high-performance liquid chromatography – were evaluated by means of ^{32}P-postlabelling for their ability to form DNA adducts after a single dermal application on the skin of TO mice. Both the R1 and N1 oils had formed unidentified DNA adducts at 24 hours. The 2–3-ring fraction produced more adducts than the 4–6-ring fraction of N1. The adduct levels first increased

and then decreased with time after treatment (Ingram *et al.*, 2000).

5. Evaluation

There is *sufficient evidence* in humans for the carcinogenicity of untreated or mildly treated mineral oils. Untreated or mildly treated mineral oils cause cancer of the skin (observed in the scrotum).

There is *sufficient evidence* in experimental animals for the carcinogenicity of untreated vacuum distillates, acid-treated oils, and aromatic oils, including extracts from solvent treatment of distillates and the high-boiling fraction of catalytically cracked oils [classes 1, 2 and 6].

There is *sufficient evidence* in experimental animals for the carcinogenicity of mildly hydrotreated oils [class 4].

There is *sufficient evidence* in experimental animals for the carcinogenicity of used gasoline-engine oil [class 7.2].

There is weak evidence on the mechanism underlying the effects in humans of exposures to mineral oils. This evidence is based on genotoxic (mutagenic) activity of mineral oils in bacteria and a single cytogenetic study of glassworkers exposed to aerosols of mineral oils.

Untreated and mildly treated mineral oils are *carcinogenic to humans (Group 1).*

References

ACGIH (2007). Documentation of the TLVs and BEIs with Other Worldwide Occupational Exposure Values - 2007, CD-ROM, Oil Mist, Mineral (2001), Cincinnati, OH.

Acquavella J, Leet T, Johnson G (1993). Occupational experience and mortality among a cohort of metal components manufacturing workers. *Epidemiology (Cambridge, Mass.)*, 4: 428–434. doi:10.1097/00001648-199309000-00008 PMID:11560339

Agarwal R, Kumar S, Shukla Y *et al.* (1985). Quantification of tumour initiating effect of jute batching oil and its distillates over mouse skin. *Cancer Lett*, 28: 281–290. doi:10.1016/0304-3835(85)90036-9 PMID:4052997

Agarwal R, Shukla Y, Kumar S, Mehrotra NK (1988). Evaluation of carcinogenic effect of jute batching oil (JBO-P) fractions following topical application to mouse skin. *Arch Toxicol*, 62: 406–410. doi:10.1007/BF00288342 PMID:3250371

Ahrens W, Jöckel KH, Patzak W, Elsner G (1991). Alcohol, smoking, and occupational factors in cancer of the larynx: a case-control study. *American Journal of Industrial Medicine*, 20: 477–493. doi:10.1002/ajim.4700200404 PMID:1785612

ASTM (1996). *Determining Carcinogenic Potential of Virgin Base Oils in Metalworking Fluids* (E 1687-95) West Conshohocken, PA

Bakke B, Ulvestad B, Stewart P *et al.* (2001). Effects of blasting fumes on exposure and short-term lung function changes in tunnel construction workers. *Scand J Work Environ Health*, 27: 250–257. doi:10.5271/sjweh.612 PMID:11560339

Bingham E & Horton AW (1966). Environmental carcinogenesis: Experimental observations related to occupational cancer. *Advances in Biology of Skin*, 7: 183–193.

Bingham E, Horton AW, Tye R (1965). The carcinogenic potency of certain oils. *Arch Environ Health*, 10: 449–451. PMID:14247342

Blackburn GR, Deitch RA, Schreiner CA *et al.* (1984). Estimation of the dermal carcinogenic activity of petroleum fractions using a modified Ames assay. *Cell Biol Toxicol*, 1: 67–80. doi:10.1007/BF00125566 PMID:6401126

Bober LA, Kranepool MJ, Bojko C *et al.* (1976). Endotoxin enhancement of plasma cell tumor development in mice given injections of mineral oil. *Cancer Res*, 36: 1947–1949. PMID:773532

Brooks TM, Priston RA, Wright AS, Watson WP (1995). Evaluation of modified bacterial mutagenicity assays for the genotoxicity testing of mineral oils. *Mutagenesis*, 10: 409–415. doi:10.1093/mutage/10.5.409 PMID:8544754

Bukowski JA (2003). Review of respiratory morbidity from occupational exposure to oil mists. *Appl Occup Environ Hyg*, 18: 828–837. PMID:14555435

Calvert GM, Ward E, Schnorr TM, Fine LJ (1998). Cancer risks among workers exposed to metalworking fluids: a systematic review. *American Journal of Industrial Medicine*, 33: 282–292. doi:10.1002/(SICI)1097-0274(199803)33:3<282::AID-AJIM10>3.0.CO;2-W PMID:9481427

Coggon D, Pannett B, Acheson ED (1984). Use of job-exposure matrix in an occupational analysis of lung and bladder cancers on the basis of death certificates. *J Natl Cancer Inst*, 72: 61–65. PMID:6363790

CONCAWE (1986). Health Aspects of Worker Exposure to Oil Mists. Report No. 86/69.

CONCAWE (1994). The Use of the Dimethyl Sulphoxide (DMSO) Extract by the IP346 Method as an Indicator

of the Carcinogenicity of Lubricant Base Oils and Distillate Aromatic Extracts. Report Number 94/51.

CONCAWE (1997). Lubricating Oil Basestocks Product Dossier. Report No. 97/108.

Doak SM, Brown VK, Hunt PF *et al.* (1983). The carcinogenic potential of twelve refined mineral oils following long-term topical application. *Br J Cancer*, 48: 429–436. PMID:6615701

Droste JH, Weyler JJ, Van Meerbeeck JP *et al.* (1999). Occupational risk factors of lung cancer: a hospital based case-control study. *Occupational and Environmental Medicine*, 56: 322–327. doi:10.1136/oem.56.5.322 PMID:10472306

Eisen EA, Bardin J, Gore R *et al.* (2001). Exposure-response models based on extended follow-up of a cohort mortality study in the automobile industry. *Scand J Work Environ Health*, 27: 240–249. PMID:11560338

Eisen EA, Tolbert PE, Monson RR, Smith TJ (1992). Mortality studies of machining fluid exposure in the automobile industry I: A standardized mortality ratio analysis. *American Journal of Industrial Medicine*, 22: 809–824. doi:10.1002/ajim.4700220604 PMID:1463027

Friesen MC, Costello S, Eisen EA (2009). Quantitative exposure to metalworking fluids and bladder cancer incidence in a cohort of autoworkers. *American Journal of Epidemiology*, 169: 1471–1478. doi:10.1093/aje/kwp073 PMID:19414495

Gerhardsson de Verdier M, Plato N, Steineck G, Peters JM (1992). Occupational exposures and cancer of the colon and rectum. *Am J Ind Med*, 22: 291–303. doi:10.1002/ajim.4700220303 PMID:1519614

Gilman JPW & Vesselinovitch SD (1955). Cutting oils and squamous-cell carcinoma. II. An experimental study of the carcinogenicity of two types of cutting oils. *Br J Ind Med*, 12: 244–248. PMID:13240030

Goldstein DH, Benoit JN, Tyroler HA (1970). An epidemiologic study of an oil mist exposure. *Arch Environ Health*, 21: 600–603. PMID:5475423

Gradiski D, Vinot J, Zissu D *et al.* (1983). The carcinogenic effect of a series of petroleum-derived oils on the skin of mice. *Environ Res*, 32: 258–268. doi:10.1016/0013-9351(83)90110-X PMID:6315389

Granella M, Ballarin C, Nardini B *et al.* (1995). Mutagenicity and contents of polycyclic aromatic hydrocarbons in new high-viscosity naphthenic oils and used and recycled mineral oils. *Mutat Res*, 343: 145–150. doi:10.1016/0165-1218(95)90080-2 PMID:7791808

Granella M & Clonfero E (1991). The mutagenic activity and polycyclic aromatic hydrocarbon content of mineral oils. *Int Arch Occup Environ Health*, 63: 149–153. doi:10.1007/BF00379080 PMID:1889886

Green RM (1910). Cancer of the scrotum. *Boston Medical and Surgical Journal*, 163: 792–797.

Grimmer G, Dettbarn G, Brune H *et al.* (1982b). Quantification of the carcinogenic effect of polycyclic aromatic hydrocarbons in used engine oil by topical application onto the skin of mice. *Int Arch Occup Environ Health*, 50: 95–100. doi:10.1007/BF00432496 PMID:7085089

Grimmer G, Naujack K-W, Dettbarn G *et al.* (1982a). Studies on the carcinogenic action of used engine lubricating motor oil (Ger.). *Erdöl Kohle*, 35: 466–472.

Grob K, Vass M, Biedermann M, Neukom HP (2001). Contamination of animal feed and food from animal origin with mineral oil hydrocarbons. *Food Addit Contam*, 18: 1–10. doi:10.1080/02652030010003503 PMID:11212542

Halder CA, Warne TM, Little RQ, Garvin PJ (1984). Carcinogenicity of petroleum lubricating oil distillates: effects of solvent refining, hydroprocessing, and blending. *Am J Ind Med*, 5: 265–274. doi:10.1002/ajim.4700050403 PMID:6720690

Hendricks NV, Berry CM, Lione JG, Thorpe JJ (1959). Cancer of the scrotum in wax pressmen. I. Epidemiology. *AMA Arch Ind Health*, 19: 524–529. PMID:13636467

Henry SA (1947). Occupational cutaneous cancer attributable to certain chemicals in industry. *British Medical Bulletin*, 4: 389–401.

Henry SA & Irvine ED (1936). Cancer of the scrotum in the Blackburn registration district, 1837-1929. *The Journal of Hygiene*, 36: 310–340. doi:10.1017/S0022172400043667

Hermann G (1966). [Plasmocytic tumors and ascites induced by Bayol F in the BALB-c mouse] *Pathol Biol*, 14: 657–669. PMID:5328283

IARC (1984). Polynuclear aromatic hydrocarbons, Part 2, carbon blacks, mineral oils (lubricant base oils and derived products) and some nitroarenes. *IARC Monogr Eval Carcinog Risk Chem Hum*, 33: 1–222. PMID:6590450

IARC (1987). Overall evaluations of carcinogenicity: an updating of IARC Monographs volumes 1 to 42. *IARC Monogr Eval Carcinog Risks Hum Suppl*, 7: 1–440. PMID:3482203

Ingram AJ, Phillips JC, Davies S (2000). DNA adducts produced by oils, oil fractions and polycyclic aromatic hydrocarbons in relation to repair processes and skin carcinogenesis. *J Appl Toxicol*, 20: 165–174. doi:10.1002/(SICI)1099-1263(200005/06)20:3<165::AID-JAT625>3.0.CO;2-E PMID:10797468

Institute for Petroleum (1985). IP Standards for Petroleum and Its Products. Part I – Methods for Analysis and Testing. 2, 346.1.

Institute for Petroleum (1993). Determination of Polycyclic Aromatics in Unused Lubricating Base Oils and Asphaltene Free Petroleum Fractions – Dimethyl Sulfoxide Extraction Refractive Index Method. IP 346/92. In: Standard Methods for Analysis and Testing of Petroleum and Related Products, Vol. 2, Chichester, John Wiley & Sons.

Järvholm B, Fast K, Lavenius B, Tomsic P (1985). Exposure to cutting oils and its relation to skin tumors and

premalignant skin lesions on the hands and forearms. *Scand J Work Environ Health*, 11: 365–369. PMID:4071002

Järvholm B, Lillienberg L, Sällsten G *et al.* (1981). Cancer morbidity among men exposed to oil mist in the metal industry. *J Occup Med*, 23: 333–337. PMID:7241245

Jepsen JR, Stoyanov S, Unger M *et al.* (1977). Cutting fluids and their effects on the skin of mice. *Acta pathol microbiol scand*, 85: 731–738.

Kane ML, Ladov EN, Holdsworth CE, Weaver NK (1984). Toxicological characteristics of refinery streams used to manufacture lubricating oils. *Am J Ind Med*, 5: 183–200. doi:10.1002/ajim.4700050304 PMID:6702826

Lijinsky W, Saffiotti U, Shubik P (1966). Skin tumorigenesis by an extract of amber petrolatum. *Toxicol Appl Pharmacol*, 8: 113–117. doi:10.1016/0041-008X(66)90107-4 PMID:5921887

Lushbaugh CC, Green JW Jr, Redemann CE (1950). Effects of prolonged inhalation of oil fogs on experimental animals. *A.M.A. Archives of Industrial Hygiene and Occupational Medicine*, 1: 237–247.

Mackerer CR, Griffis LC, Grabowski JS Jr, Reitman FA (2003). Petroleum mineral oil refining and evaluation of cancer hazard. *Appl Occup Environ Hyg*, 18: 890–901. PMID:14555442

McKee RH, Daughtrey WC, Freeman JJ *et al.* (1989). The dermal carcinogenic potential of unrefined and hydrotreated lubricating oils. *J Appl Toxicol*, 9: 265–270. doi:10.1002/jat.2550090411 PMID:2778262

Mehrotra NK, Kumar S, Agarwal R, Antony M (1987). Jute batching oil: a tumor promoter on mouse skin. *Environ Res*, 42: 12–23. doi:10.1016/S0013-9351(87)80003-8 PMID:3803329

Mehrotra NK, Kumar S, Antony M (1988). Carcinogenic property of JBO(P) variety of jute batching oil. *Drug Chem Toxicol*, 11: 181–193. doi:10.3109/01480548808998221 PMID:3402349

Mirer F (2003). Updated epidemiology of workers exposed to metalworking fluids provides sufficient evidence for carcinogenicity. *Appl Occup Environ Hyg*, 18: 902–912. PMID:14555443

Nessel CS, Freeman JJ, Forgash RC, McKee RH (1999). The role of dermal irritation in the skin tumor promoting activity of petroleum middle distillates. *Toxicol Sci*, 49: 48–55. doi:10.1093/toxsci/49.1.48 PMID:10367341

Nessel CS, Priston RA, McKee RH *et al.* (1998). A comprehensive evaluation of the mechanism of skin tumorigenesis by straight-run and cracked petroleum middle distillates. *Toxicol Sci*, 44: 22–31. doi:10.1093/toxsci/44.1.22 PMID:9720137

NIOSH (1990). *National Occupational Exposure Survey (1981-83).* Cincinnati, OH: US Department of Health and Human Services, Public Health Service, National Institute for Occupational Safety and Health. http://www.cdc.gov/noes/noes4/m0603sco.html

Oser BL, Oser M, Carson S, Sternberg SS (1965). Toxicologic studies of petrolatum in mice and rats. *Toxicol Appl Pharmacol*, 7: 382–401. doi:10.1016/0041-008X(65)90140-7 PMID:14288812

Pasquini R, Monarca S, Sforzolini GS *et al.* (1985). Mutagenicity studies and D-glucaric acid determination in urine of workers exposed to mineral oils. *Int Arch Occup Environ Health*, 56: 275–284. doi:10.1007/BF00405269 PMID:3905625

Potter M & Boyce CR (1962). Induction of plasma-cell neoplasms in strain BALB/c mice with mineral oil and mineral oil adjuvants. *Nature*, 193: 1086–1087. doi:10.1038/1931086a0 PMID:14488296

Potter M & MacCardle RC (1964). HISTOLOGY OF DEVELOPING PLASMA CELL NEOPLASIA INDUCED BY MINERAL OIL IN BALB/C MICE. *J Natl Cancer Inst*, 33: 497–515. PMID:14207859

Potter M & Robertson CL (1960). Development of plasma-cell neoplasms in BALB/c mice after intraperitoneal injection of paraffin-oil adjuvant, heart-killed Staphylococcus mixtures. *J Natl Cancer Inst*, 25: 847–861. PMID:13737512

Rask-Nielsen R & Ebbesen P (1965). Reticular neoplasms induced in DBA-2 and CBA mice by intraperitoneal injections of mineral oil. *J Natl Cancer Inst*, 35: 83–94. PMID:5318200

Roe FJC, Carter RL, Taylor W (1967). Cancer hazard from mineral oil used in the processing of jute. *Br J Cancer*, 21: 694–702. PMID:4294613

Rønneberg A, Andersen A, Skyberg K (1988). Mortality and incidence of cancer among oil exposed workers in a Norwegian cable manufacturing company. Part 2. Mortality and cancer incidence 1953–84. *Br J Ind Med*, 45: 595–601. PMID:3179234

Roush GC, Kelly JA, Meigs JW, Flannery JT (1982). Scrotal carcinoma in Connecticut metalworkers: sequel to a study of sinonasal cancer. *Am J Epidemiol*, 116: 76–85. PMID:7102658

Roush GC, Meigs JW, Kelly JA *et al.* (1980). Sinonasal cancer and occupation: a case-control study. *Am J Epidemiol*, 111: 183–193. PMID:7355881

Roy TA, Johnson SW, Blackburn GR, Mackerer CR (1988). Correlation of mutagenic and dermal carcinogenic activities of mineral oils with polycyclic aromatic compound content. *Fundam Appl Toxicol*, 10: 466–476. doi:10.1016/0272-0590(88)90293-X PMID:3286347

Saffiotti U & Shubik P (1963). Studies on promoting action in skin carcinogenesis. *National Cancer Institute Monograph*, 10: 489–507.

Savitz DA (2003). Epidemiologic evidence on the carcinogenicity of metalworking fluids. *Appl Occup Environ Hyg*, 18: 913–920. PMID:14555444

Schmähl D & Reiter A (1953). Studies on carcinogenesis by liquid paraffin, yellow vaseline and wool fat. *Arzneimittelforschung*, 3: 403–406. PMID:13093484

Schroeder JC, Tolbert PE, Eisen EA *et al.* (1997). Mortality studies of machining fluid exposure in the automobile industry. IV: A case-control study of lung cancer. *American Journal of Industrial Medicine*, 31: 525–533. doi:10.1002/(SICI)1097-0274(199705)31:5<525::AID-AJIM5>3.0.CO;2-S PMID:9099353

Shoda T, Toyoda K, Uneyama C *et al.* (1997). Lack of carcinogenicity of medium-viscosity liquid paraffin given in the diet to F344 rats. *Food Chem Toxicol*, 35: 1181–1190. doi:10.1016/S0278-6915(97)00105-1 PMID:9449224

Shubik P & Saffiotti U (1955). The carcinogenic and promoting action of low boiling catalytically cracked oils. *Acta Unio Int Contra Cancrum*, 11: 707–711. PMID:13326679

Skyberg K, Ronneberg A, Christensen CC *et al.* (1992). Lung function and radiographic signs of pulmonary fibrosis in oil exposed workers in a cable manufacturing company: a follow up study. *British Journal of Industrial Medicine*, 49: 309–315. PMID:1599868

Smith WE, Sunderland DA, Sugiura K (1951). Experimental analysis of the carcinogenic activity of certain petroleum products. *A M A Arch Ind Hyg Occup Med*, 4: 299–314. PMID:14867943

Southam AH & Wilson SR (1922). Cancer of the scrotum: the etiology, clinical features, and treatment of the disease. *British Medical Journal*, 2: 971–973. doi:10.1136/bmj.2.3229.971

Srám RJ, Holá N, Kotěsovec F, Nováková A (1985). Cytogenetic analysis of peripheral blood lymphocytes in glass workers occupationally exposed to mineral oils. *Mutat Res*, 144: 277–280. doi:10.1016/0165-7992(85)90064-8 PMID:4069144

Svendsen K & Børresen E (1999). Measurements of mineral oil mist, hydrocarbon vapor, and noise in engine rooms of ships. *Appl Occup Environ Hyg*, 14: 186–191. doi:10.1080/104732299303151 PMID:10453633

Svendsen K & Hilt B (1997). Exposure to mineral oil mist and respiratory symptoms in marine engineers. *Am J Ind Med*, 32: 84–89. doi:10.1002/(SICI)1097-0274(199707)32:1<84::AID-AJIM10>3.0.CO;2-2 PMID:9131215

Svendsen K & Hilt B (1999). Lung function disturbances and chest X-ray abnormalities among marine engineers. *Am J Ind Med*, 35: 590–594. doi:10.1002/(SICI)1097-0274(199906)35:6<590::AID-AJIM6>3.0.CO;2-D PMID:10332512

Tolbert PE (1997). Oils and cancer. *Cancer Causes & Control*, 8: 386–405. doi:10.1023/A:1018409422050 PMID:9498901

Twort CC & Ing HR (1928). Mule-spinners' cancer and mineral oils. *Lancet*, 211: 752–754. doi:10.1016/S0140-6736(00)96837-5

Twort JM & Lyth R (1939). The concentration of carcinogenic materials in mineral oils bydistillation processes. *The Journal of Hygiene*, 39: 161–169. doi:10.1017/S0022172400011785

Ugnat AM, Luo W, Semenciw R, Mao YCanadian Cancer Registries Epidemiology Research Group (2004). Occupational exposure to chemical and petrochemical industries and bladder cancer risk in four western Canadian provinces. *Chronic Dis Can*, 25: 7–15. PMID:15554606

Urbanus JH, Lobo RC, Riley AJ (2003). European hazard classification advice for crude oil-derived lubricant base oils compared with the proposed mineral oil mist TLV. *Appl Occup Environ Hyg*, 18: 815–817. PMID:14555432

Wagner WD, Wright PG, Stokinger HE (1964). Inhalation toxicology of oil mists. I. Chronic effects of white mineral oil. *Am Ind Hyg Assoc J*, 25: 158–168. PMID:14125868

Waldron HA, Waterhouse JA, Tessema N (1984). Scrotal cancer in the West Midlands 1936–76. *Br J Ind Med*, 41: 437–444. PMID:6498107

Woskie SR, Virji MA, Hallock M *et al.* (2003). Summary of the findings from the exposure assessments for metalworking fluid mortality and morbidity studies. *Appl Occup Environ Hyg*, 18: 855–864. PMID:14555438

Yassi A, Tate RB, Routledge M (2003). Cancer incidence and mortality in workers employed at a transformer manufacturing plant: update to a cohort study. *American Journal of Industrial Medicine*, 44: 58–62. doi:10.1002/ajim.10237 PMID:12822136

Zhao Y, Krishnadasan A, Kennedy N *et al.* (2005). Estimated effects of solvents and mineral oils on cancer incidence and mortality in a cohort of aerospace workers. *American Journal of Industrial Medicine*, 48: 249–258. doi:10.1002/ajim.20216 PMID:16167347