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ORAL TOXICITY OF MINERAL OILS AND RELATED COMPOUNDS

A review

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Summary

Mineral oils are distillation products of petroleum consisting mainly alkanes (paraffinic oils, P) and/or cycloalcanes (naphthenic oils, N) the number of carbon atoms being ≥ 17. Mineral spirits is a generic name for petroleum distillates having 8 – 13 carbon atoms.

Mineral oils have a wide range of uses in materials that come to contact with foods and considerable amount of them have also been detected in recycled paper and board. Mineral spirits are used mainly as solvent, and the human exposure is generally inhalatory.

The acute oral toxicity of both mineral oils and mineral spirits is low, and most animal studies have not indicated any specific concerns. Mineral oil associated granulomas, particularly in the liver, are occasionally found in human autopsy materials, but they have been considered as clinically insignificant. Mineral spirits are known to produce several transient neurological effects.

In 1990'ies, however, feeding studies with low- and medium viscosity mineral oils demonstrated a range of pathological findings, mainly granulomatous lesions in the mesenteric lymph nodes and liver associated with effects on several clinical chemistry parameters in Fisher 344 rats. Based on these observation Acceptable Daily Intakes (ADIs) of 0 – 0.01 mg/kg bw/day have been calculated for these types of mineral oils. It is, however, acknowledged, that these ADIs are in practice exceed by more than 20-fold because of the ubiquitous intake from various sources.

Subsequent studies indicate that the observed adverse effect are highly specific for Fischer 344 rats and are either absent or only marginally present in other rat strains or animal species. The present ADI values therefore need reconsidering.

Any exposure to mineral spirits via food or packaging materials is probably limited to occupational situations, the consumer exposure being negligible.

1. Introduction

Mineral oils are distillation products of petroleum consisting mainly alkanes (paraffinic oils, P) and/or cycloalcanes (naphthenic oils, N). After refining, the purification can include an acid treatment (oleum method) or catalytic hydrogenation. Linear paraffinic oil has a general alkane structure (C_nH_{2n+2}), but cyclic, branched and alkylated oils have naturally different compositions. Mineral oils can be further classified according to their viscosity (Table 1)

Table 1. Classification of mineral oils according to viscosity (adapted from WHO 2002)

Type	Kinematic viscosity at 100 °C (mm^2s^{-1})	Average molecular mass	C-number
High viscosity paraffinic oil (P100)*	≥ 11	>500	>29
Medium and low viscosity, class I -paraffinic oils (P70) -hydrogenated oils (P70H)	8.5 -11	480 - 500	≥ 25
Medium and low viscosity, class II -hydrogenated naphthenic oils (N70H)	7.0 – 8.5	400 - 480	≥22
Medium and low viscosity oils, class III -hydrogenated paraffinic oil (P15H) -hydrogenated naphthenic oil(N15H)	3.0 – 7.0	300 - 400	≥17

- The number in parenthesis indicates the viscosity in centistokes at 40 °C

High viscosity paraffin oils with the C number 20 ≤ 40, and which are solid at room temperature, are often called paraffins or paraffin waxes. Compounds at the other end of the scale, having C-numbers in the range of $C_8 – C_{13}$, are called mineral spirits.

Physicochemically mineral oils are characterized by their high hydrophobicity and low reactivity.

In addition to mechanical and industrial uses mineral oils are used in cosmetics, skin care, packaging, confectionery etc. Due to their use in printing inks mineral oils can also be present in recycled paper and board, where quantities as high as 300 – 1000 $mgkg^{-1}$ of mineral oils (C number < 28) have been reported (Biedermann & Grob, 2010), and the suitability of these type of materials for food packaging has been questioned.

The average daily intake of mineral oils from food in the United Kingdom and in the USA has been estimated to be 0.47 mg/kg bw/day, of which class III mineral oils accounted for 0.21 – 0.25 mg/kg bw/day, and classes I and II 0.18 – 0.19 mg/kg bw/day (WHO 2002).

Mineral spirits are mainly used as solvents, and an oral intake is therefore purely accidental, while inhalatory exposure in various occupational situations is apparently the main route of exposure (Amoruso et al. 2008)

2. The metabolism of mineral oils and spirits

As inert substances the ingested mineral oils mostly are excreted intact in feces and to some degree in urine. However, some absorption form the small intestine has been observed (Stryker 1941). Using radiolabeled mineral oil, it was established that the amount absorbed in rat was appr. 1.5 % (Ebert et al. 1966).

After absorption the mineral oils are mainly distributed to the liver, spleen, mesenteric lymph nodes and fat pads (Low et al. 1992). Further hepatic metabolism may include oxidation and breakdown into smaller components that may enter the general lipid metabolism (Bollinger, 1970).

The metabolism and distribution of mineral spirits have been assessed after inhalatory exposure in experimental animals. The findings indicate a relatively rapid elimination from blood and brain, but prolonged high concentrations in fat tissues (Löf et al, 1999). No data appear to have been published on the oral kinetics or metabolism of mineral spirits.

3. Clinical and toxicological findings related to oral exposure

3.1. Human data

A. Mineral oils

Reports of mineral oil associated -adverse effects in humans are rare. Nochomovitz et al. (1975) described a patient case with “massive deposition” of mineral oil in the small intestine tissue, abdominal lymph nodes, liver, spleen and lungs after prolonged ingestion of liquid paraffin. Hepatic damage caused by deposits of mineral oil in the portal part of the liver of a patient suffering from a peptic ulcer was reported by Blewitt et al. (1977). In the latter case no obvious reason for the mineral oil deposits were identified, although the patient had consumed small amounts of liquid paraffin as a laxative for a limited period of time.

There are several reports of mineral oil deposits in human tissues (mainly liver and spleen) observed either in biopsies or recorded as post-mortem findings from individuals died of natural courses (Cruikshank and Thomas, 1984; Dincsoy et al. 1982; Liber and Rose. 1967; Wanless and Geddie, 1985.). In the study of Dincsoy et al. (1982) 44 cases of mineral oil associated lipogranuloma[1] out of 824 biopsy samples from non fatty livers were found, while in the study of Wanless et al (1982) the frequency of lipogranulomas was as high as 48 (liver) or 46% (spleen) in a material from 465 autopsies. The incidence was related to age and gender, being more frequent in older men. In most cases there was no clear indication of the source of the mineral oils or the nature of the exposure. Generally the findings have not been associated with any symptoms and have been considered as clinically inconsequential.

B. Mineral spirits

The toxicology mineral spirits and related human clinical findings (based mainly on data on the occupational exposure to solvents) have been extensively reviewed by Amoruso et al (2008). Mineral spirits are known to cause, especially by inhalatory exposure, effects on the central nervous system, such as dizziness, lightheadedness, lack of coordination, even narcosis. However, the question of irreversible long term effects remains open, since no unequivocal epidemiological data have been produced. The same applies to other long term effects, such as cancer. A confounding factor in most studies is that mineral spirits are seldom specifically addressed, but have been included in the total solvent exposure.

3.2. Animal findings

A. mineral oils

Several oral toxicity studies on different animal species have not indicated any toxicological concerns (see 3.2.A.ii below). However, certain studies performed with Fischer 344 rats have indicated inflammatory effects in the liver, mesenteric lymph nodes and, in some studies, also inflammation of the mitral valve. Mainly because of these findings the Acceptable Daily Intakes (ADIs) have been proposed for microcrystalline waxes and high viscosity paraffinic oils (0 – 20 mg/kg bw) , medium and low viscosity class I oils (0 - 10 mg/kg bw) and class II and III oils (0 – 0.01 mg/kg bw) by The Joint FAO/WHO Expert Committee on Food Additives (2002). The relevant studies are described in more detail below

i. Studies in Fischer 344 rats

Baldwin et al. (1992) reported a range of adverse effects in 90 day feeding studies with both oleum-treated and hydrogenated mineral oils (dose range from 10 up to 20 000 ppm in feed) in Fischer 344 rats. They included changes in haematology and clinical chemistry, associated with increased organ weights (mesenteric lymph nodes, liver, kidney and spleen). The histopathological findings, observable from the dose of 5000 ppm onward, were mainly lipogranulomata in lymph nodes and liver. The effects were more severe in female than in male rats.

These findings were confirmed by Smith et al. (1996) in a 90 –day feeding study (again with Fischer 344 rats, and 20 000 ppm as the top dose) that was performed with seven different oils and five paraffin waxes. While high molecular weight waxes and oils did not induce significant effects, lower molecular weight waxes and low to mid-viscosity oils were associated with similar adverse effects as already mentioned above, and again predominantly in females. Inflammation of the cardiac mitral valve in rats exposed to high doses of paraffin waxes was reported as a novel finding.

Finally a chronic (two year) oral toxicity study in Fischer 344 rats using both high viscosity and medium viscosity mineral oils was performed by Trimmer et al. (2004). The top dose of the oils was 1200 mg/kg/day. No treatment related mortalities occurred during the study, nor were there any indications of neoplastic lesions, or effects on clinical health, on hematology or on clinical chemistry. Despite higher mesenteric lymph node weights associated with increased filtration of histiocytes and mineral hydrocarbon deposits in the liver (which turned out to be reversible) the No Observable Adverse Effect Level (NOAEL) was considered to be the top dose of the study (1200 mg/kg/day).

ii. Comparison of the Fisher 344 rat results with data obtained from other animal and human studies

The discrepancy with the effects observed in Fischer 344 rats and the either non-existent or relatively insignificant effects of mineral oils in other species and strains was pointed out in the review of Miller et al. (1996). The authors cite several studies performed with either paraffinic or naphthenic oils in beagle dogs, Sprague-Dawley rats and Long-Evans rats, in which no significant microscopic anomalies in liver, kidneys, spleen or mesenteric lymph nodes were detected and no mineral oil deposits in the tissues were observed (Shubik et al, 1962; Smith et al, 1995; McKee et al., 1987; Firriolo et al. 1995). The authors also point out that the lipogranulomas of the liver observed in human autopsies (see 3.1. A above) are considered clinically insignificant, while those observed in Fischer 344 rats can be associated with inflammatory and necrotic lesions. The authors further suggest that the observed effects reflect rat strain specific differences in the responses to mineral oils.

In the 1995 study by Firriolo et al. the low viscosity oils that show the most obvious signs of adverse effects in Fisher 344 rats, were studied both in Fisher 344 and Sprague-Dawley rats in equal doses for 92 days. In Fisher 344 rats the familiar effects, such as increased liver, mesenteric lymph node and spleen weights associated with granulomatous lesions (in liver and lymph nodes). These findings were absent in Sprague-Dawley rats, although there was a dose-dependent accumulation of MHC (mineral hydrocarbon material) in the liver and mesenteric lymph nodes. However, the MHC content in these organs was only half of that observed in Fischer 344 rats.

Finally, the lymph nodal and hepatic lesions observed in rats orally exposed to mineral oils were further assessed in a special pathology workshop held in 2001 at the Fraunhofer Institute of Toxicology (Hannover, Germany) (Carlton et al. 2001). According to the final conclusion of the workshop: “The available data suggest that the granumalotous lesions experimentally induced by MHC-feeding, particularly in the liver of F344 rats, are exaggerated toxicological responses peculiar to rats.”

B. Mineral spirits

In the studies reviewed by Amoruso et al. (2008) the acute oral toxicity of mineral spirits is very low, the LD_{50} in rats being consistently > 5.0 g /kg in various experiments. A single 90 day feeding study in rats fed with a mixture of $C_{10} – C_{13}$ mixed alkanes with a low (0.5 %) aromatics content has been reported (EMBSI 1991). The dose range was from 500 up to 5000 mg/kg. While no mortalities were observed, there was a decrease in the male body weight, increase in the male liver weight, decreased weight of adrenals in both sexes, and finally hyaline droplets and other changes in the male kidney. The last finding, indicative of α_{2u}-globuilin-mediated male rat nephropathy, is also a common finding in repeated dose inhalatory toxicity studies and is considered a male rat specific phenomenon not relevant to humans. On the whole, the authors conclude that mineral spirits do not appear to produce toxicologically relevant systemic effects, although the consequences of long term (inhalatory) exposure for the central nervous system are not known, yet.

4. Conclusions

Both mineral oils and mineral spirits have a low acute oral toxicity, and no signs of carcinogenicity have been detected in long term studies. In animal experiments rats exposed to low and medium viscosity mineral oils and low-melting point waxes have shown granulamatous lesions in the liver and mesenteric lymph nodes. While liver granulomas associated with mineral oils have been relatively frequently observed in human autopsies performed on people died of natural causes, these lesions appear to differ histopathologically from those seen in rats and have not been considered clinically significant. Moreover, the effects have been shown to be highly dependent on the rat strain, Fischer 344 showing most obvious responses, while in other rat strains (Sprague-Dawley, Long Evans) or other species (beagle dogs) the effects have been either absent or only marginal.

The present ADI values put forward by WHO in 2002 (0 – 0.01 mg/kg bw/day for medium and low viscosity class II and class III oils) are mainly based on results obtained from the experiments with Fischer 344 rats, and the estimated present daily oral intake of these oils is already > 20 times higher than the proposed values.

The ADIs of 2002 for mineral oils obviously need a re-evaluation taking into consideration the accumulated data on the apparently anomalous response of Fischer 344 rats.

No oral ADIs for mineral spirits have been proposed, nor is an oral exposure via food contact materials likely. Were the mineral spirits present in packaging materials, the main risk would probably be the inhalatory occupational exposure of persons handling these types of products

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