GERMAN FEDERAL INSTITUTE FOR RISK ASSESSMENT

15 YEARS Science in the Service of Humanity

BfR Bundesinstitut für Risikobewertung

Gesundheitliche Risiken durch Mineralölkomponenten in kosmetischen Mitteln

Andreas Luch

Use of Mineral Oils and Waxes in Cosmetic Products

Functions of mineral oils and waxes in cosmetic products:

- antistatic agent
- emollient
- skin protection
- solvent
- viscosity control

Product groups:

- skin creams and lotions, body and face cleaning agents
- sunscreen, self-tanning lotions
- deodorant, anti-transpirants
- lip care products, make up, nail care products
- hair gel
- skin / eye salves
- adhesion cream for teeth
- petroleum jelly (vaseline), baby care oil

Concentrations: 1 - 99 %

Cosmetic Products on the Market (BfR, 2015): Dermal Exposure

- **Cosmetic products with declaration of mineral oil based ingredients** (N=18, e.g., moisturizer, skin care cream, hand cream, foot cream, after sun lotion, body milk, child care products, hair styling products):
  - **MOSH contents: 1.9 – 76%**
  - **MOAH contents: 0.0069% (69 ppm) – 4.5%**
  - MOSH to MOAH ratio: 9:1 – 680:1
  - Declaration of petrolatum as main ingredient correlates with high MOAH contents

    (e.g. “vaseline”: 1.7 – 5%, 4 samples)

- **Cosmetic products without declaration of mineral oil based ingredients** (N=10)
  - **MOAH contents: 0.0004% (4 ppm) – 0.04% (400 ppm)**

Lip Care Products on the Market (BfR, 2016): + Oral Exposure

- **German market** (N=27, 19 based on mineral oil ingredients, 8 with cera alba as ingredient)**:**
  - **MOSH contents: 8.2% – 73.9%**
    Average: 40.4%,
    Median: 27.2%
  - **MOAH contents: > 0.5 % (12 samples), max: 3.9%**
  - MOSH to MOAH ratio: 16:1 – 209:1
  - Samples that do fulfill all criteria according to Cosmetics Europe recommendation #14: 21% (= 4)

Dermal Absorption of MOSH: Exposure

***In vivo* (guinea pig, hairless mouse) and *in vitro* (porcine skin) studies**

- model compounds: ^{14}C-hexadecane (C16), ^{3}H-docosane (C22)
- majority absorbed in *Stratum corneum*; < 1% reaches dermis
- not detectable in blood or receptor fluid

Cave: Exposure max. 48 h and no repeated exposure in vivo

(Rossmiller and Hoekstra 1966; Brown et al. 1995)

Human volunteer studies

- paraffin oil and petrolatum (Raman spectroscopy)
- penetration only into *Stratum corneum*

Cave: Short exposure times (30 and 90 min) and limited sensitivity of the method

(Stamatas et al. 2008; Patzelt et al. 2012)

Dermal exposure: No evidence of systemic bioavailability !

Dermal Absorption of MOSH: Toxicology

Repeated exposure in C3H mice, Fischer 344 rats, New Zealand White rabbits

- white mineral oils
- exposure: life time (mice), 91 days (rats), 20 days (rabbits)
- **no histolopathological/hematological alterations in any organ**
- F344 rats (91d; light oil): gain in liver and kidney weight (12-16%) → oral ingestion of oil?

Cave: Study limitations (e.g., classification of the oil applied)

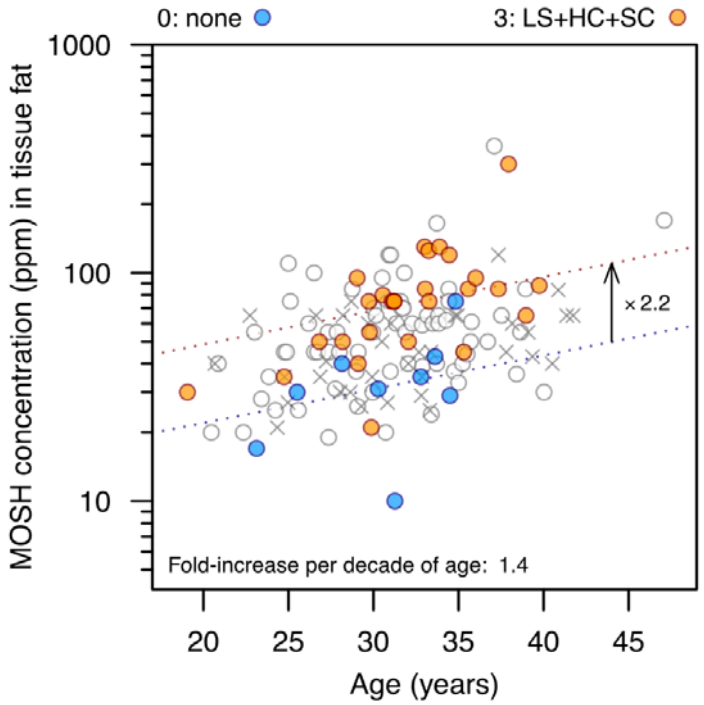
(Nash et al. 1996)

Dermal exposure: No evidence of local and systemic toxicity !

MOSH in Cosmetics and Human Body Burden: Experimental

Measurement of MOSH in subcutaneous fat tissue of 142 women and survey regarding use of cosmetics (questionnaire)

- Correlation to:
  1. Age
  2. BMI
  3. Kind of Cosmetic Product:
     a) Sun lotion during pregnancy (SC)
     b) Hand cream (HC)
     c) Lipstick (LS)



→ **2.2-fold higher MOSH concentration for this group of users** (LS+HC+SC) compared to women that used non of these three products (none)

Likely: Oral uptake responsible !

(Concin et al. 2011; BfR, unpublished data)

Oral Absorption of MOSH: Exposure Calculation

Exposure to MOSH via lip care products and lipsticks (worst case)

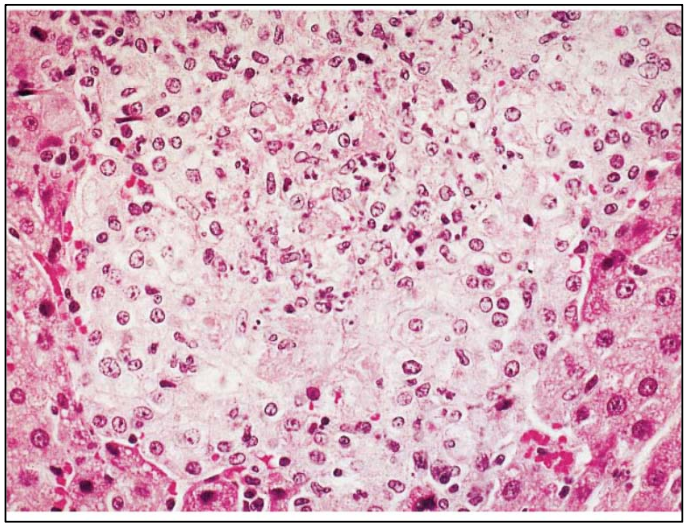
Daily amount of lip care products:	57 mg/person per day (SCCS)
MOSH content:	8.2 – 74 % (BfR data)
Oral intake (100%):	4.7 – 42 mg/person/day
Body weight 60 kg:	0.08 – 0.7 mg/kg bw per day

Estimated daily dietary intake of MOSH: 0.03 to 0.3 mg/kg bw per day (EFSA 2012)

Significant contribution of lip care products to the body burden of MOSH !

However: ADI (JECFA): 10 and 20 mg/kg bw/day (…)

Critical Toxicological Effect of MOSH



F344 rat liver after 90-day oral dosing
of low viscosity mineral oils

(Carlton *et al.*, 2001)

- **Inflammatory / epitheloid cell granuloma formation in liver of female Fischer 344 rats after oral administration. Its occurence depends on oil viscosity and MOSH contents in the liver**

Oral Absorption of MOSH: Liver Retention and Micrograniuloma

- Incidence and severity of micrograniuloma in female Fischer 344 liver
- 90-day feeding study (2000 mg/kg bw/day)

Group	Viscosity; 100°C [mm²/s]	Average C-number	MOSH in liver [mg/g]	Granuloma „incidence/severity score“
control 1/2/3			0.15/0.28/ 0.35	0/5/0
P15H	**3.5**	**18-30**	**2.86**	**80**
P70H	8.6	27-43	0.98	0
P100H	11.0	28-45	0.59	0
LMPW2	**3.3**	**19-42**	**16.9**	**305**
HSW	13.7	20-74	0.54	0
HMPW	15.4	22-80	0.17	5

(Smith et al. 1996)

Severe granuloma formation found with low viscosity oils and low melting point (paraffin) waxes only !

MOSH: Species and Strain Differences of Liver Effects

Strain	Dose	P15H (Firiollo et al. 1995)	LMPW (Griffis et al. 2010)	Granuloma
	mg/kg bw/day	mg MOH/ g liver	mg MOH/ g liver	
F344	160	5.6	13.3	+
	1600	8.2	19.8	+
SD	160	1.7	< LOQ	ø
	1600	4.1	< LOQ	ø

(Woldhuis & Danneels, EWF 2017)

- Higher MOSH levels in liver of Fischer 344 rats compared to SD rats

  (Miller et al. 1996; Halladay et al. 2002; Boogaard et al. 2012)

- Microgranulomas only in F344 rats, not in other strains (Sprague Dawley, Long Evans) or beagle dogs

  (Shubik et al. 1962; Firriolo et al. 1995; Smith et al. 1995; Carlton et al. 1985)

- **Humans: Lipogranulomas only!**

Relevance of Fischer 344 findings for humans health ?

MOSH: Retention in Liver and Granuloma Formation (F344 only)

Group	MOSH in liver [mg/kg]	Granuloma
Broad MOSH mixture	> 3200 (- 5500)	+
Low viscosity oil	> 9200 (- 14600)	+
High viscosity oil	3800	**ø**
High viscosity oil + LMPW	≥ 4800	+

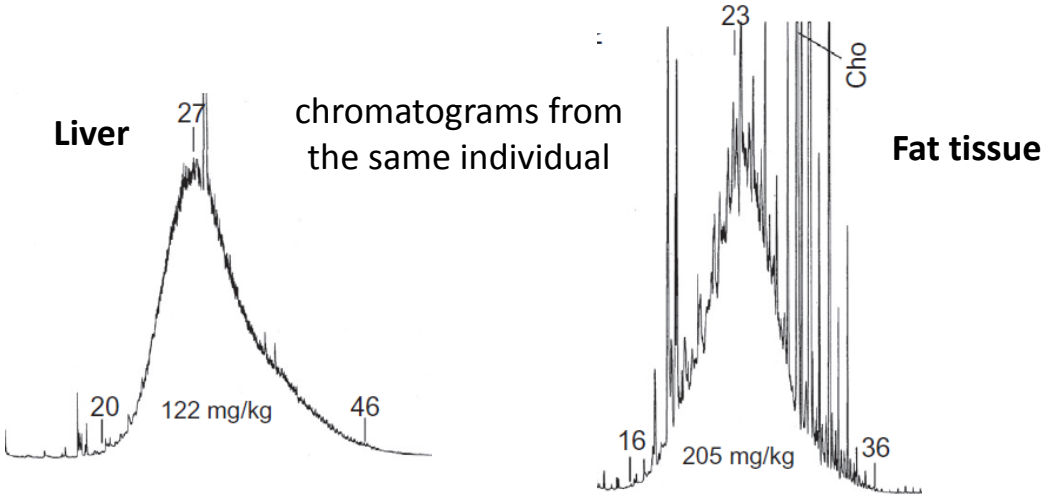
(Cravedi et al. 2017)

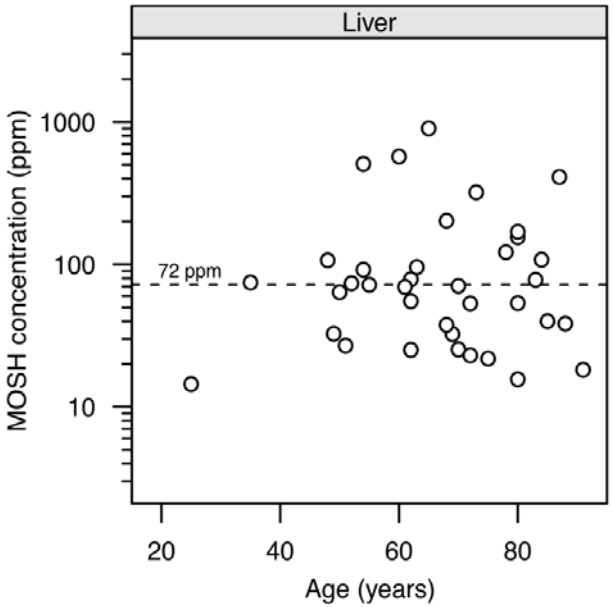
Granuloma incidence does not correlate to overall MOSH content (retention of certain structures, e.g. n-alkanes?)

No granuloma formation with high viscosity mineral oil !

MOSH: Accumulation in human liver and fat tissue

Tissues from 37 autopsy patients (25 – 91 yrs)



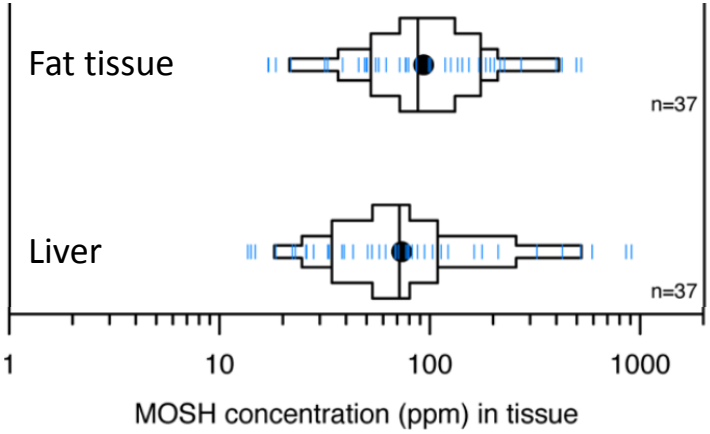


Liver tissue:

- C18-C45: max. C25/27; no retention < C20
- no n-alkanes
- highly isomerized and polycyclic compounds
- virtually no granulomas
- no age-dependent increase

Fat tissue:

- C16-C35: max. C23/24
- n-alkanes of plant origin
- MOSH levels quite similar to liver (steady state?)



(Barp et al. 2014; Biedermann et al. 2015; BfR, unpublished)

MOSH in Cosmetics: Summary

Dermal route: No evidence for systemic bioavailability

- Currently no evidence for systemic bioavailability

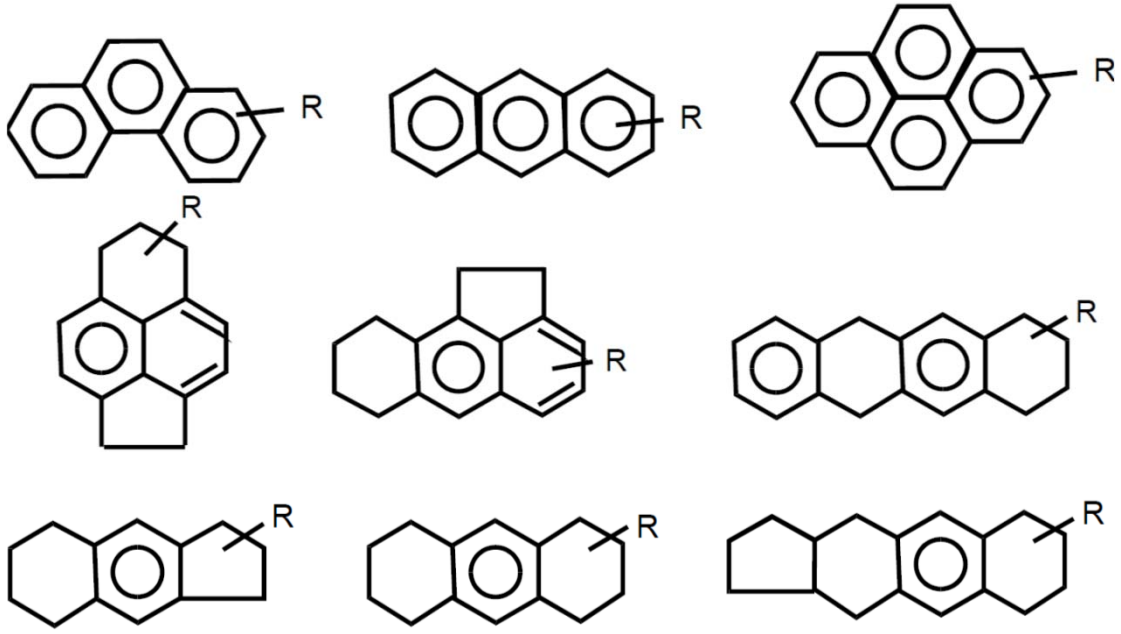
Oral route: Adverse effects (epitheloid cell granuloma) in female Fischer 344 rats only

- Relevance for humans unclear
- Observed with low viscosity mineral oils or low melting point waxes only
- Molecular cause and mechanism of inflammatory granuloma formation in F344 rats unclear
  (no correlation to overall MOSH contents; retention of certain compounds such as n-alkanes?)

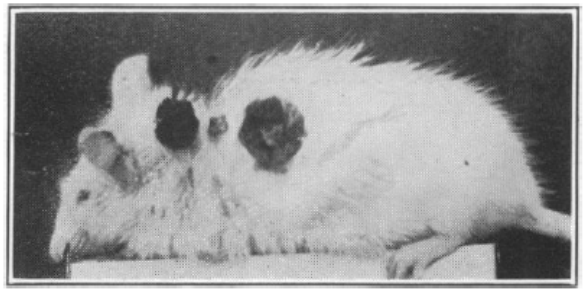
Reasonable Conclusion: Oral and lip care products should only contain mineral hydrocarbons for which an Acceptable Daily Intake (ADI) level has been derived based on toxicological data (accord. Cosmetics Europe Recommendation ♯14)

ADI [mg/kg bw]	JECFA (2012)	EFSA (2013)
Microcrystalline wax	20	
High viscosity mineral oil (P100H)	20	12
Medium viscosity mineral oil (P70H)	10	

Critical Toxicological Effect of MOAH ?



(EFSA, 2012)



(Leitch, 1922)

Assumption based on structural similarity to polycyclic aromatic hydrocarbons (PAHs) with proven carcinogenicity?

Toxicological evaluation of food grade mineral oils and waxes

Toxicological assessment:

- *in vitro* and *in vivo* mutagenicity studies
- 90-day oral toxicity studies (F344)
- 2-year oral chronic toxicity/carcinogenicity studies (F344, medium/high viscosity oils, up to 1200 mg/kg KG/day)
- 2-year oral chronic toxicity/carcinogenicity studies (SD, paraffin waxes, up to 5800 mg/kg KG/day)

→ **No safety concerns regarding genotoxicity**

→ **No carcinogenicity observed**

MOAH contents in medium and high viscosity white mineral oils and microcrystalline wax as food additives (limited data):

- **MOAH contents in white mineral oils (food grade; pharmaceutical)**
  supposed to be 100 – 600 ppm, structures unclear...
- **MOAH conents in mircrocrystalline wax (E905)**
  up to 5% MOAH > C35; highly alkylated mono- and diaromatic hydrocarbons

Cosmetic Product Regulation (EC) No 1223/2009

Annex II (list of substances prohibited in cosmetic products)
~100 entries of petroleum derived products (residual oils, lubricating oils, destillates, extracts, gas oils, slack wax, petrolatum) with different restrictions:

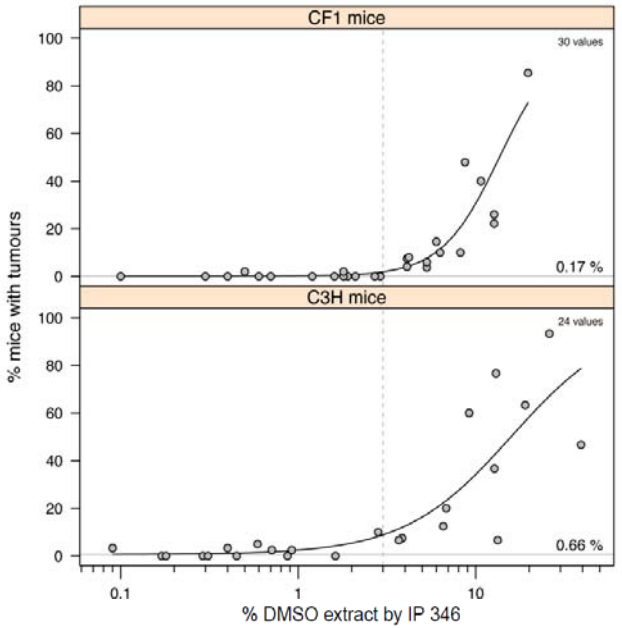
776	Distillates (petroleum), hydrotreated heavy naphthenic, if they contain > 3 % w/w DMSO extract	64742-52-5	265-155-0

→ Refers to the **IP346** method as indicated in the CLP regulation (1272/2008 EC) for determination of polycyclic aromatics in certain mineral oil raffinates.
→ Destillates < 3% DMSO extract by IP346 are not classified as a carcinogens and can be used.

904	Petrolatum, except if the full refining history is known and it can be shown that the substance from which it is produced is not a carcinogen	8009-03-8	232-373-2

→ Raw materials can be used that are not carcinogenic.
→ Proven through **IP346** or **UV** (pharmacopoeia)

IP346 Method – Dermal Carcinogenicity?



Method for the prediction of dermal carcinogenicity:

Correlation between carcinogenicity and the amount of substances that can be extracted with DMSO due to polarity

- Uncertainties: not all MOAH will be extracted – impact on carcinogenicity unclear; extraction of 3-7 ring PAHs; affected by alkylation and hydrogenation

CONCAWE Report no 94/51 (1994) → Basis for inclusion in CLP Regulation

- Data base of 104 mouse skin painting studies (1971 and 1986) and DMSO extract measurements by IP 346

CONCAWE Report no 6/16 (2016)

- Systemic literature search – 29 new carcinogenicity studies published since 1994 that were correlated with IP 346 data (Σ 133 carc. studies)

Critical examination and analysis of IP346 and dermal carcinogenic potential of mineral oils (**threshold: 3% w/w DMSO extract**)

MOAH in Cosmetics: Summary

General:

- No evaluation of mineral oils and waxes based on MOAH contents possible
  - due to complexity and the variable composition of MOAH fractions
  - no existing test method for the prediction of carcinogenicity based on MOAH contents

Dermal route:

- IP346 method shows good predicitivity of carcinogenic potential
  - CAVE: Not all MOAH compounds are being extracted
  - Contents of PAHs that are classified as carcinogens are unknown

→ **Further refinement of raw material improves Margin of Exposure (MoE)**

Oral route:

- Use of mineral hydrocarbons for which an ADI has been identified (EFSA, JECFA)
- No carcinogenic potential of food grade mineral oils and microcrystalline wax
  - although MOAH are still present and detectable (up to 5% for microcrystalline wax, E905)
  - MOAH comprise mainly highly alkylated mono- and dicyclic aromatic hydrocarbons
  - CAVE: Currently only limited data on MOAH content and compound structure

Mineral Oils in Cosmetics: Final Considerations

Clinical Dermatology: Ø

Epidemiology: Ø

GERMAN FEDERAL INSTITUTE FOR RISK ASSESSMENT

15 YEARS Science in the Service of Humanity

BfR Bundesinstitut für Risikobewertung

Thank you for your attention !

Andreas Luch

German Federal Institute for Risk Assessment (BfR)

Department of Chemical and Product Safety

Max-Dohrn-Strasse 8-10 ● 10589 Berlin, GERMANY