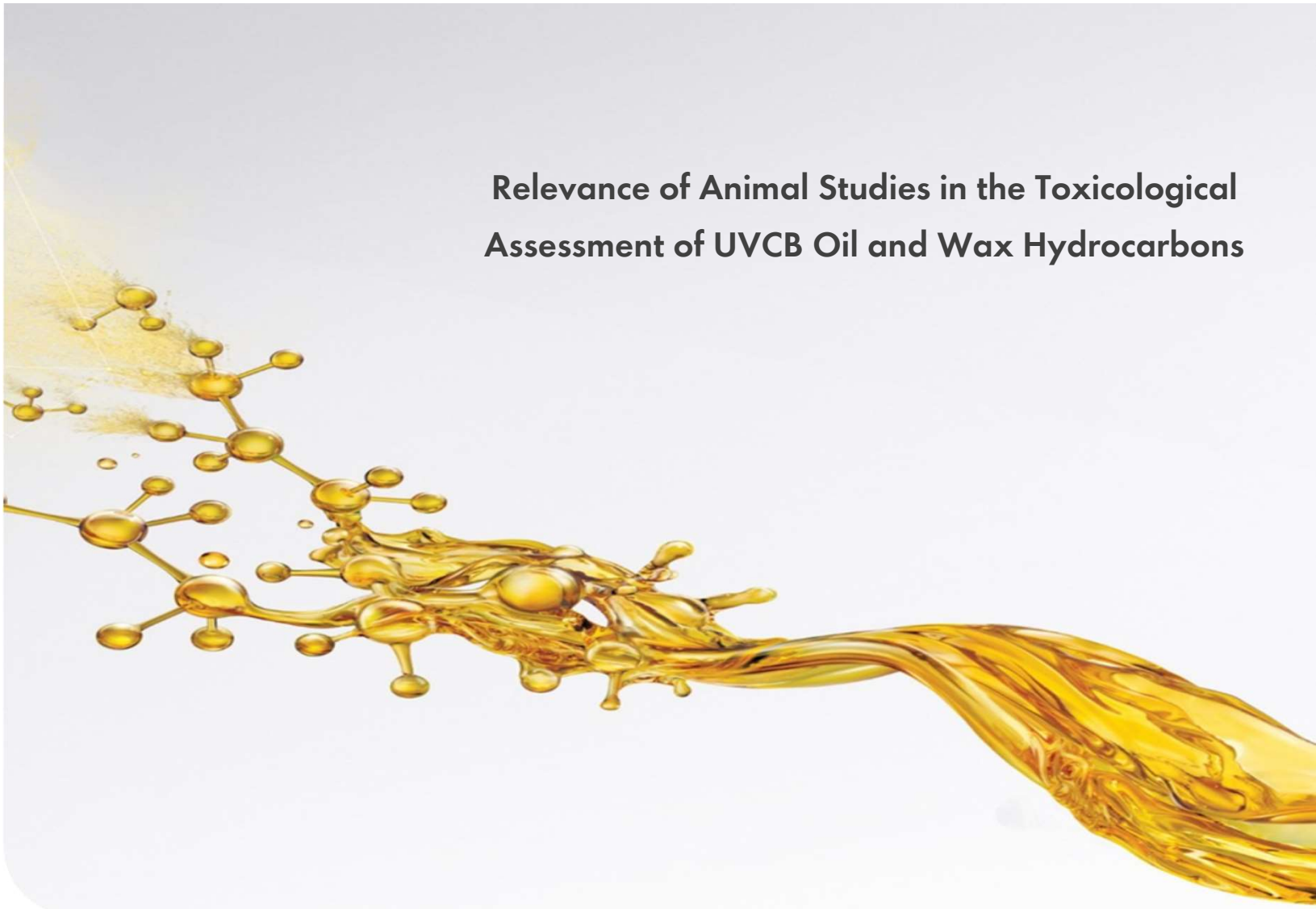
Relevance of Animal Studies in the Toxicological Assessment of UVCB Oil and Wax Hydrocarbons



Juan-Carlos Carrillo
Senior Toxicologist
Shell Product Stewardship

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The companies in which Shell plc directly and indirectly owns investments are separate legal entities. In this presentation "Shell", "Shell Group" and "Group" are sometimes used for convenience where references are made to Shell plc and its subsidiaries in general. Likewise, the words "we", "us" and "our" are also used to refer to Shell plc and its subsidiaries in general or to those who work for them. These terms are also used where no useful purpose is served by identifying the particular entity or entities. ''Subsidiaries'', "Shell subsidiaries" and "Shell companies" as used in this presentation refer to entities over which Shell plc either directly or indirectly has control. Entities and unincorporated arrangements over which Shell has joint control are generally referred to as "joint ventures" and "joint operations", respectively. "Joint ventures" and "joint operations" are collectively referred to as "joint arrangements". Entities over which Shell has significant influence but neither control nor joint control are referred to as "associates". The term "Shell interest" is used for convenience to indicate the direct and/or indirect ownership interest held by Shell in an entity or unincorporated joint arrangement, after exclusion of all third-party interest.

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Shell's operating plan, outlook and budgets are forecasted for a ten-year period and are updated every year. They reflect the current economic environment and what we can reasonably expect to see over the next ten years. Accordingly, they reflect our Scope 1, Scope 2 and Net Carbon Intensity (NCI) targets over the next ten years. However, Shell's operating plans cannot reflect our 2050 net-zero emissions target and 2035 NCI target, as these targets are currently outside our planning period. In the future, as society moves towards net-zero emissions, we expect Shell's operating plans to reflect this movement. However, if society is not net zero in 2050, as of today, there would be significant risk that Shell may not meet this target.

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This presentation may contain certain forward-looking non-GAAP measures such as cash capital expenditure and divestments. We are unable to provide a reconciliation of these forward-looking Non-GAAP measures to the most comparable GAAP financial measures because certain information needed to reconcile those Non-GAAP measures to the most comparable GAAP financial measures is dependent on future events some of which are outside the control of Shell, such as oil and gas prices, interest rates and exchange rates. Moreover, estimating such GAAP measures with the required precision necessary to provide a meaningful reconciliation is extremely difficult and could not be accomplished without unreasonable effort. Non-GAAP measures in respect of future periods which cannot be reconciled to the most comparable GAAP financial measure are calculated in a manner which is consistent with the accounting policies applied in Shell plc's consolidated financial statements.

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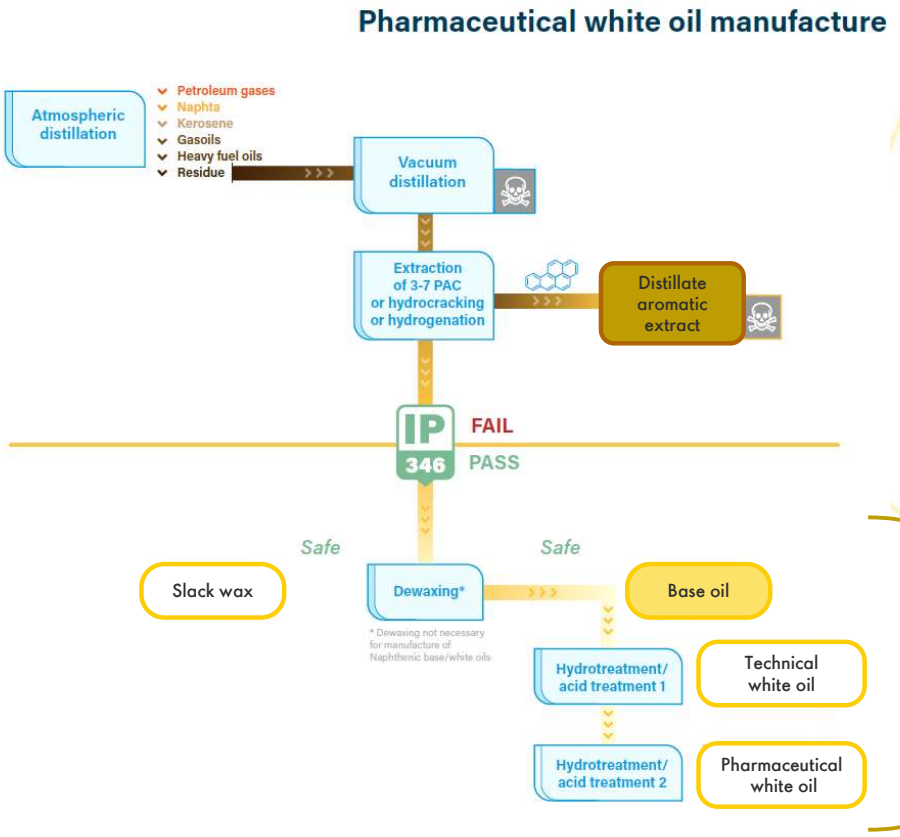
1

Where do we come from?

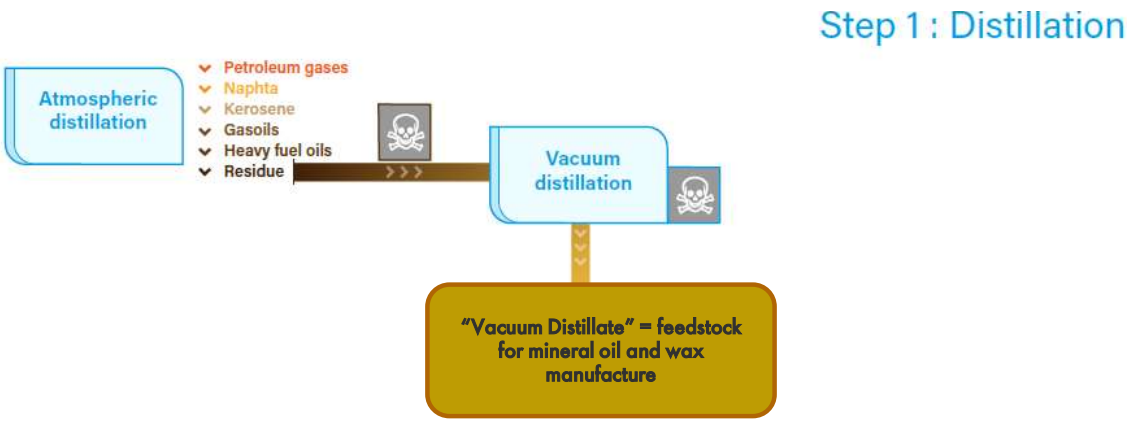
Some background

Manufacturing of UVCB substances – oil and wax – food contact

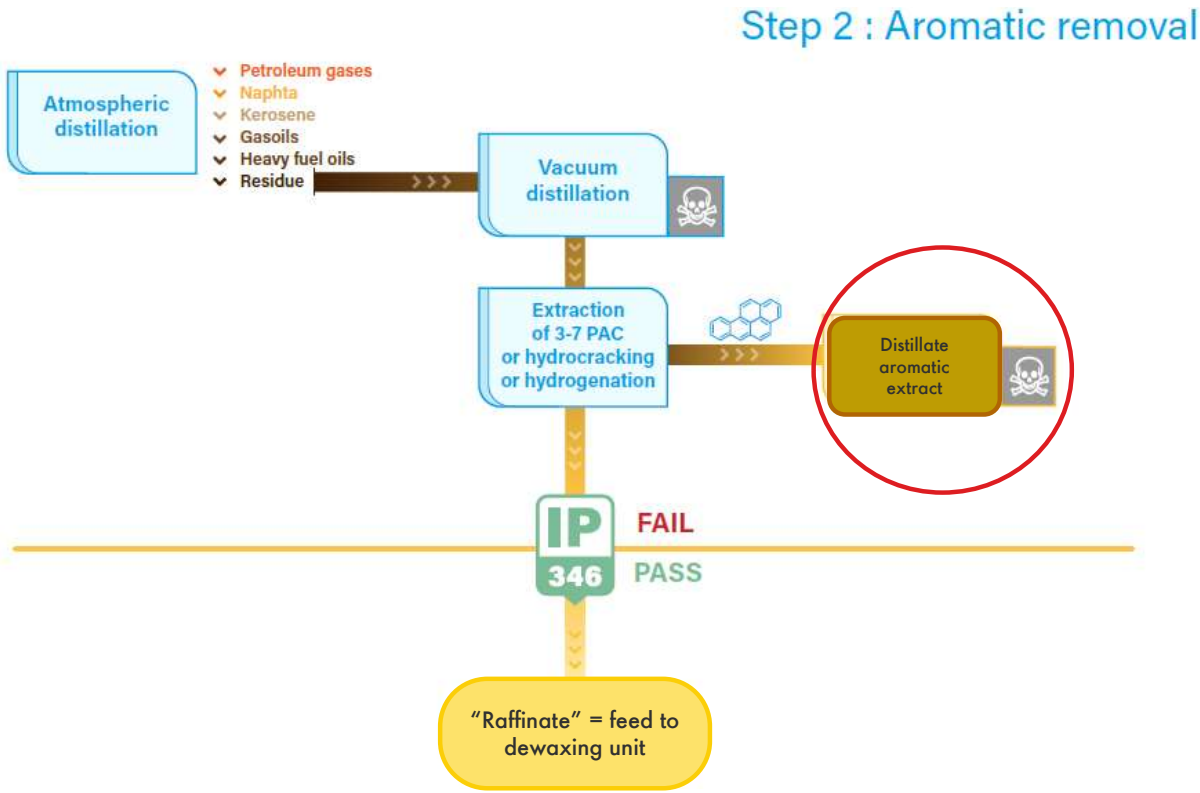


*Flowchart by CONCAWE

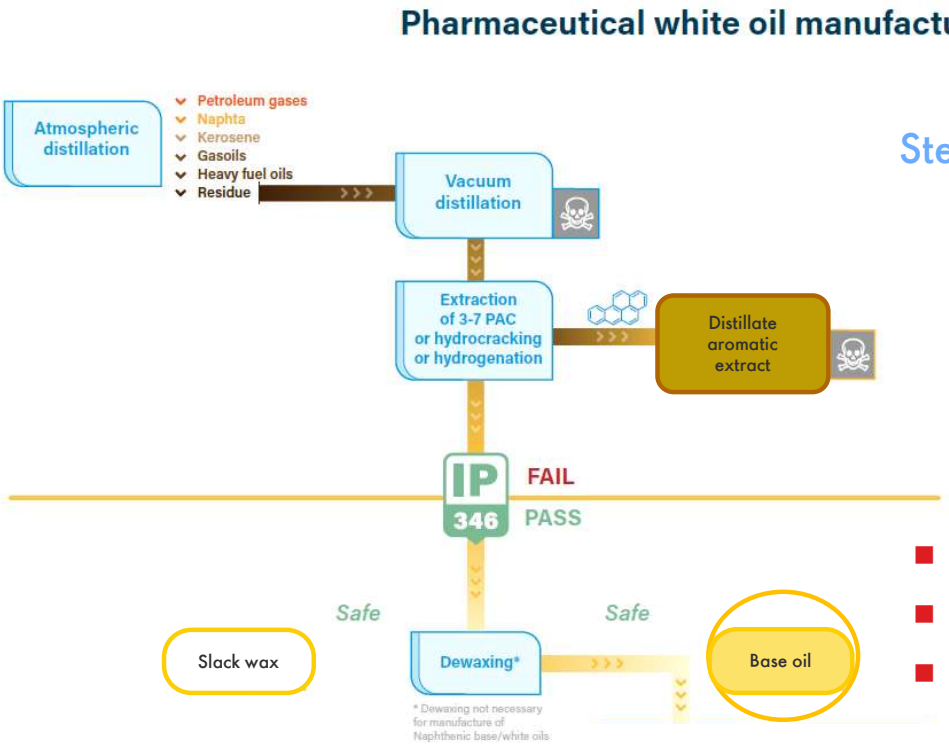
Manufacturing of UVCB substances – oil and wax



Manufacturing of UVCB substances – oil and wax



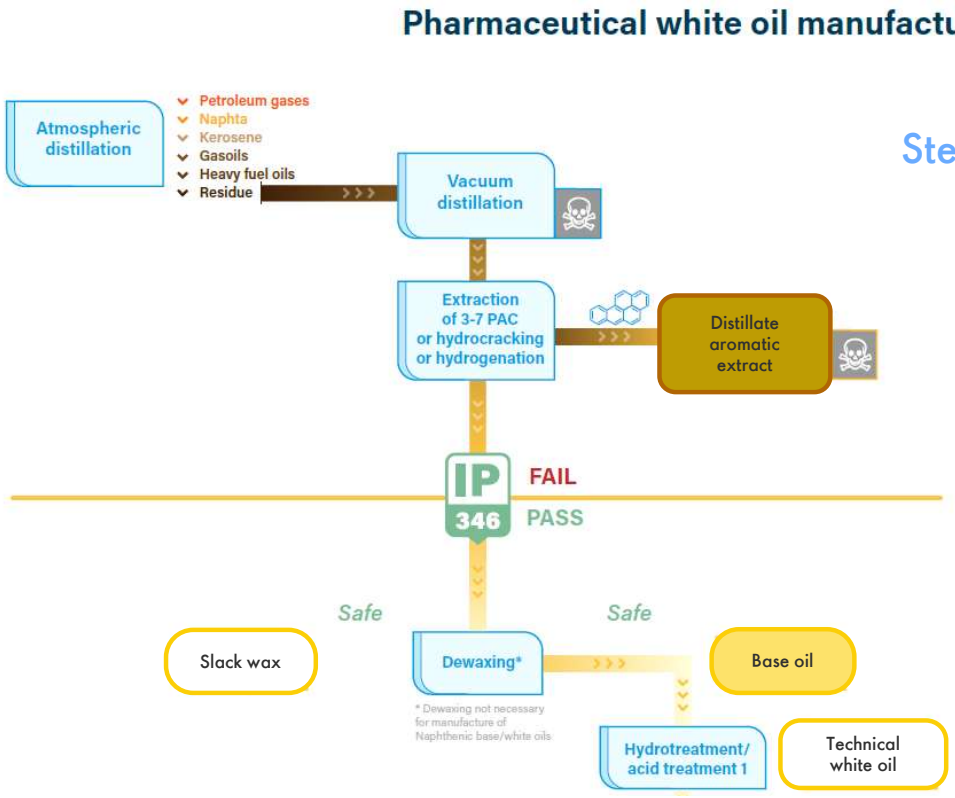
Manufacturing of UVCB substances – oil and wax



Step 3 : Dewaxing

- Motor oil
- Offset printing ink
- Lubricant oil

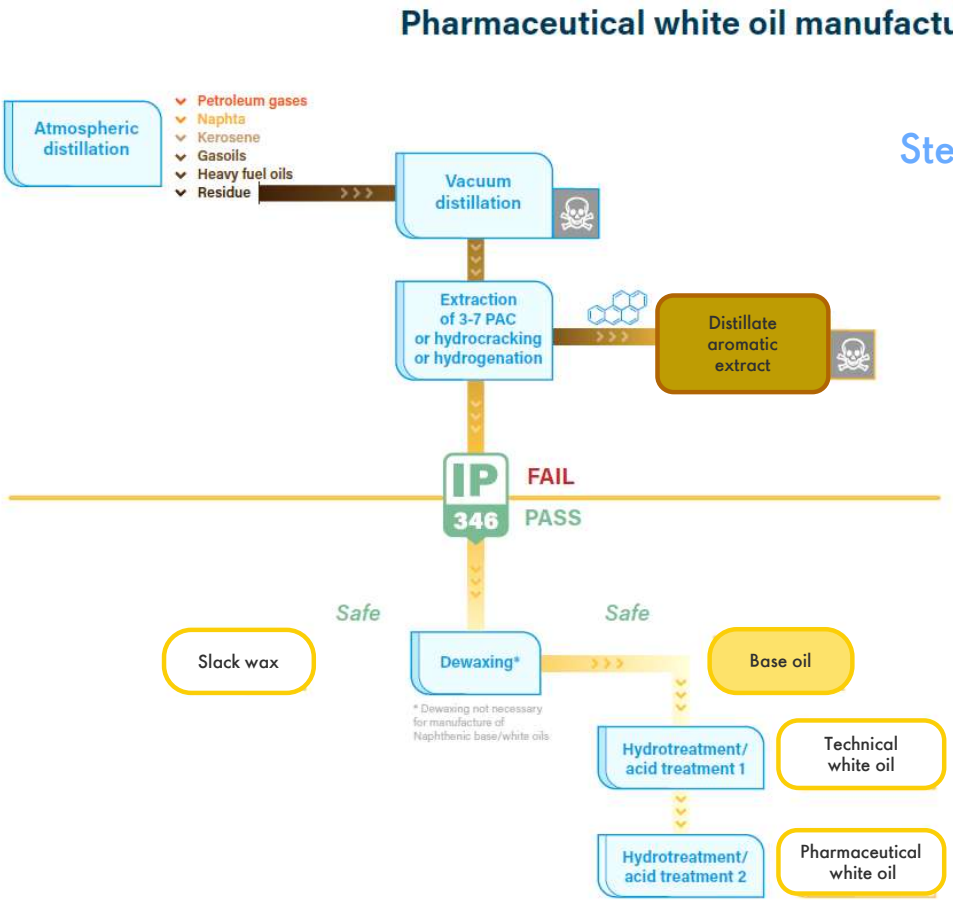
Manufacturing of UVCB substances – oil and wax



Step 4 : Hydrotreatment

FDA *21.CFR 178.* 3570 & 3620

Manufacturing of UVCB substances – oil and wax



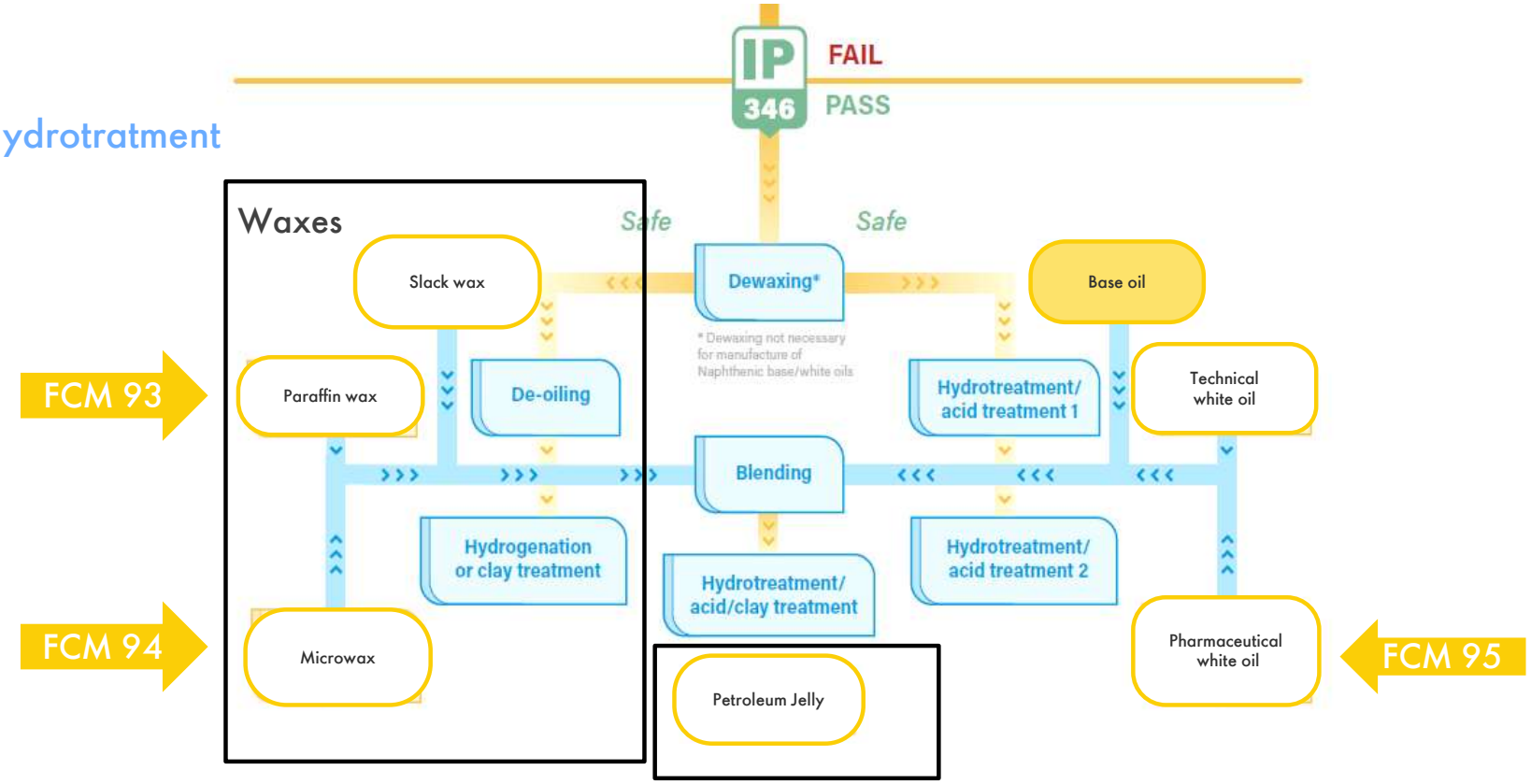
Step 5 : Hydrotreatment

FCM 95

FDA 21. CFR 172.878
EU Pharmacopeia

Manufacturing of UVCB substances – oil and wax

De-oiling & Hydrotratment



FCM – defined by physchem properties - not by product composition

COMMISSION REGULATION (EU) No 10/2011
of 14 January 2011
on plastic materials and articles intended to come into contact with food
(Text with EEA relevance)

- Viscosity at 100 °C
- MW
- Hydrocarbon content
  - >C25

(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)
FCM substance No	Ref. No	CAS No	Substance name	Use as additive or polymer production aid (yes/no)	Use as monomer or other starting substance or macromolecule obtained from microbial fermentation (yes/no)	FRF applicable (yes/no)	SML [mg/kg]	SML(T) [mg/kg] (Group restriction No)	Restrictions and specifications	Notes on verification of compliance
93	95858	—	waxes, paraffinic, refined, derived from petroleum based or synthetic hydrocarbon feedstocks, low viscosity	yes	no	no	0,05		Not to be used for articles in contact with fatty foods for which simulant D is laid down. Average molecular weight not less than 350 Da. Viscosity at 100 °C not less than 2,5 cSt ($2,5 \times 10^{-6}$ m^2/s). Content of hydrocarbons with Carbon number less than 25, not more than 40 % (w/w).	
94	95859	—	waxes, refined, derived from petroleum based or synthetic hydrocarbon feedstocks, high viscosity	yes	no	no			Average molecular weight not less than 500 Da. Viscosity at 100 °C not less than 11 cSt (11×10^{-6} m^2/s). Content of mineral hydrocarbons with Carbon number less than 25, not more than 5 % (w/w).	
95	95883	—	white mineral oils, paraffinic, derived from petroleum based hydrocarbon feedstocks	yes	no	no			Average molecular weight not less than 480 Da. Viscosity at 100 °C not less than 8,5 cSt ($8,5 \times 10^{-6}$ m^2/s). Content of mineral hydrocarbons with Carbon number less than 25, not more than 5 % (w/w).	

JECFA - food grade mineral oils

FCM specifications

Table 1 Classification of mineral oil hydrocarbons according to JECFA (2002).

Substance name	ADI (mg/ kg bw)	Viscosity at 100° C (mm^2/s)	Average relative molecular weight
High viscosity ☆	0-20	>11	>500
Medium/low viscosity (Class I) ★	0-10	8.5-11	480-500
Medium/low viscosity (Class II) ★	0-0.01	7.0-8.5	400-480
Medium/low viscosity (Class III) ★	0-0.01	3.0-7.0	300-400

☆ *Same ADI for high viscosity microwax*

★ *'no specified' ADI for medium/low viscosity wax*

- Viscosity
- MW
- ADI – "mineral hydrocarbons"
  - Driven by relationship between viscosity and toxicity effects…in the F344

2

Evaluation of pharmaceutical grade oils and waxes

Gradual loss of product composition distinction

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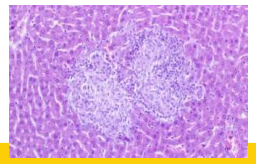
Volume 24, Number 2, 1996
Printed in U.S.A.

Ninety-Day Feeding Study in Fischer-344 Rats of Highly Refined Petroleum-Derived Food-Grade White Oils and Waxes*†‡

JACQUELINE H. SMITH,[1] ANTHONY K. MALLETT,[2] ROBERT A. J. PRISTON,[3] PAUL G. BRANTOM,[4] NAN R. WORRELL,[4,5] CHRISTINE SEXSMITH,[6] AND BARRY J. SIMPSON[7]



< 1995

- Food grade oils and waxes caused liver epithelioid granuloma in F344
- Highest effects by low melting point wax – LMPW
- No effects with high viscosity oils or waxes

1995 – SCF*

- Oils and waxes become "mineral hydrocarbons" **MHC**
- F344 rat liver granuloma used as common denominator
- SCF* specifications
  - Viscosity
  - Carbon number
  - Mw
- Basis for **FCM** – oils and waxes

**SCF - scientific committee for food*

2012 - EFSA

- MOSH is a catch all term
- No distinction for FCM
- **LMPW → most potent MOSH**
- No distinction of alkane sub-class: oils and waxes are MOSH

efsa
european Food Safety Authority
EFSA Journal 2012;10(6):27

SCIENTIFIC OPINION

Scientific Opinion on Mineral Oil Hydrocarbons in Food[1]

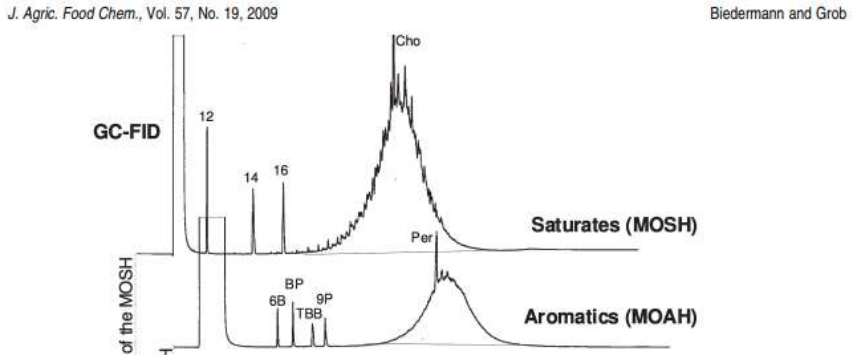
EFSA Panel on Contaminants in the Food Chain (CONTAM)[2, 3]

European Food Safety Authority (EFSA), Parma, Italy

his scientific output, published on 28 August 2013, replaces the earlier version published on 6 Ju

It started with a few papers…MOSH/MOAH

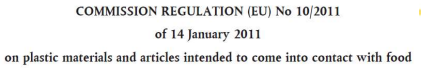
- The 'iconic' terms are coined
- Two fractions by HLPC-GC-FID
  - **MOSH** – mineral oil *saturated* hydrocarbons
  - MOAH – mineral oil *aromatic* hydrocarbons



EFSA steps in…

- A chromatography approach for risk evaluation:
- MOSH → <u>all alkanes in oils and waxes</u> → **liver granuloma**
  - Wax most potent MOSH
  - NOAEL = 19 mg/kg bw/day

- NOAEL = 1200 mg/kg bw/day
- AF = 100
- ADI = 12 mg/kg bw/day
- Viscosity = 8.5 – 11 ≥ cSt at 100 °C
- Supportive of FCM 95



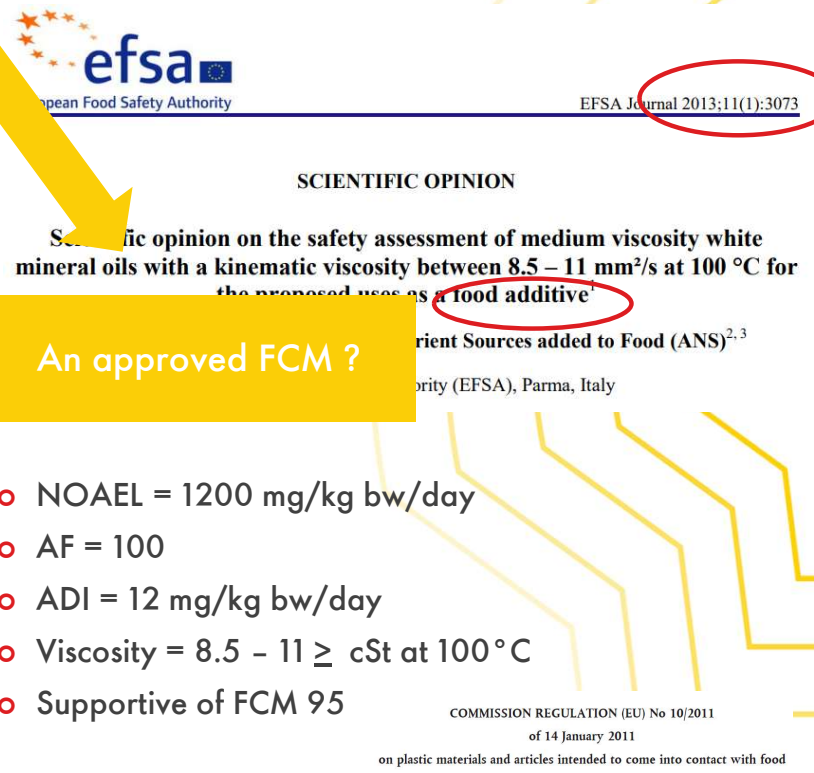
EFSA steps in…

Mineral oil analysis by MOSH


efsa
European Food Safety Authority
EFSA Journal 2012 2704
SCIENTIFIC OPINION
Scientific Opinion on Mineral Oil Hydrocarbons in Food[1]
EFSA Panel on Contaminants in t
European Food Safety Autho
This scientific output, published on 28 August 2013. on 6 June 2012*.

A contaminant?

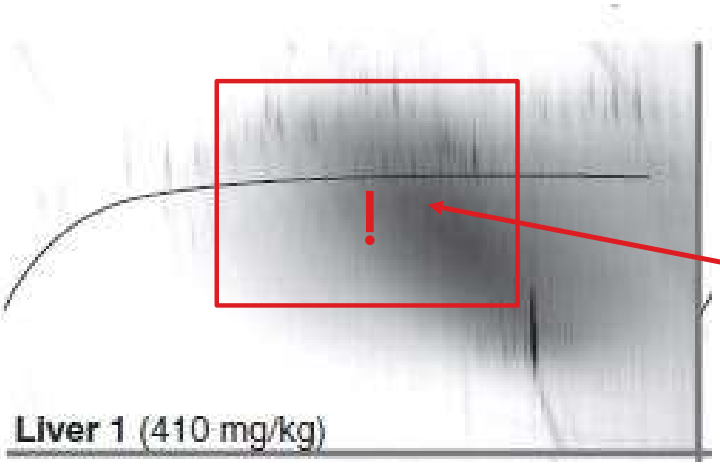
- A chromatography approach for risk evaluation:
- MOSH → <u>all alkanes in oils and waxes</u> → **liver granuloma**
  - Wax most potent MOSH
  - NOAEL = 19 mg/kg bw/day


efsa
pean Food Safety Authority
EFSA Journal 2013;11(1):3073
SCIENTIFIC OPINION
ic opinion on the safety assessment of medium viscosity white mineral oils with a kinematic viscosity between 8.5 – 11 mm²/s at 100 °C for the proposed uses as a food additive[1]
rient Sources added to Food (ANS)[2, 3]
rity (EFSA), Parma, Italy
COMMISSION REGULATION (EU) No 10/2011
of 14 January 2011
on plastic materials and articles intended to come into contact with food

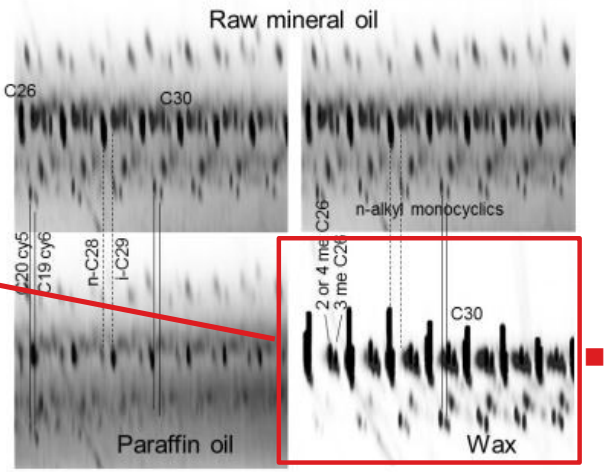
An approved FCM ?

- NOAEL = 1200 mg/kg bw/day
- AF = 100
- ADI = 12 mg/kg bw/day
- Viscosity = 8.5 – 11 ≥ cSt at 100 °C
- Supportive of FCM 95

Alkane sub-class differentiation turning point



Source: Barp et al., 2014 and Bidermann et al. 2014.



Source: Cravedi et al. 2017

- MOSH Analysis

- MOSH analysis in human livers
- Virtually no n-alkanes!
- Only a grey cloud

- What is in the liver is not in the wax →
  - what is the wax is not in the liver
- Should wax (the most potent MOSH) and oil be assessed as:
  - mineral hydrocarbons (MHC) ?
  - MOSH ?

Rethinking MOSH assessment – alkane subclasses

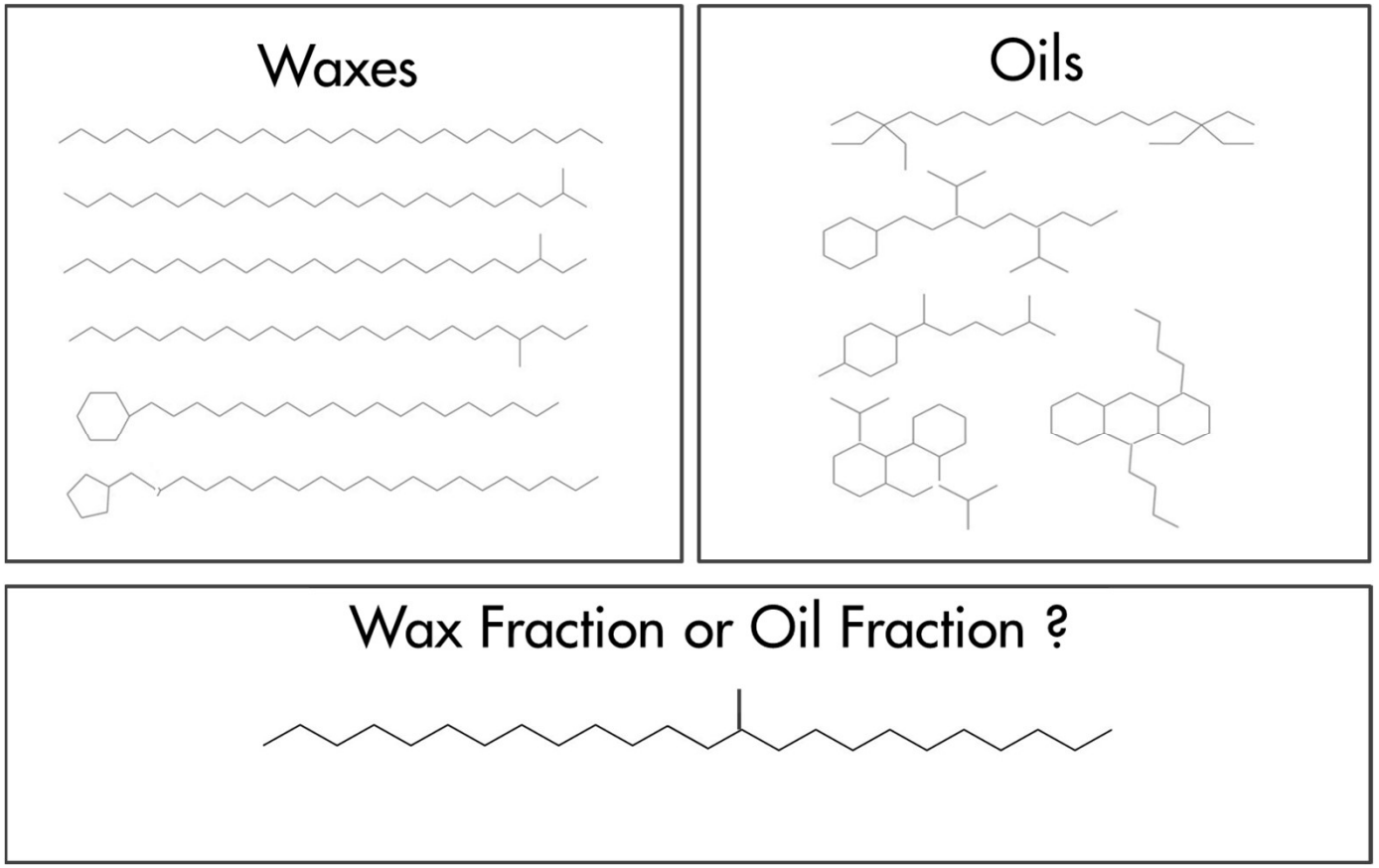
oils

- Highly branched and cyclo alkanes
- liquid

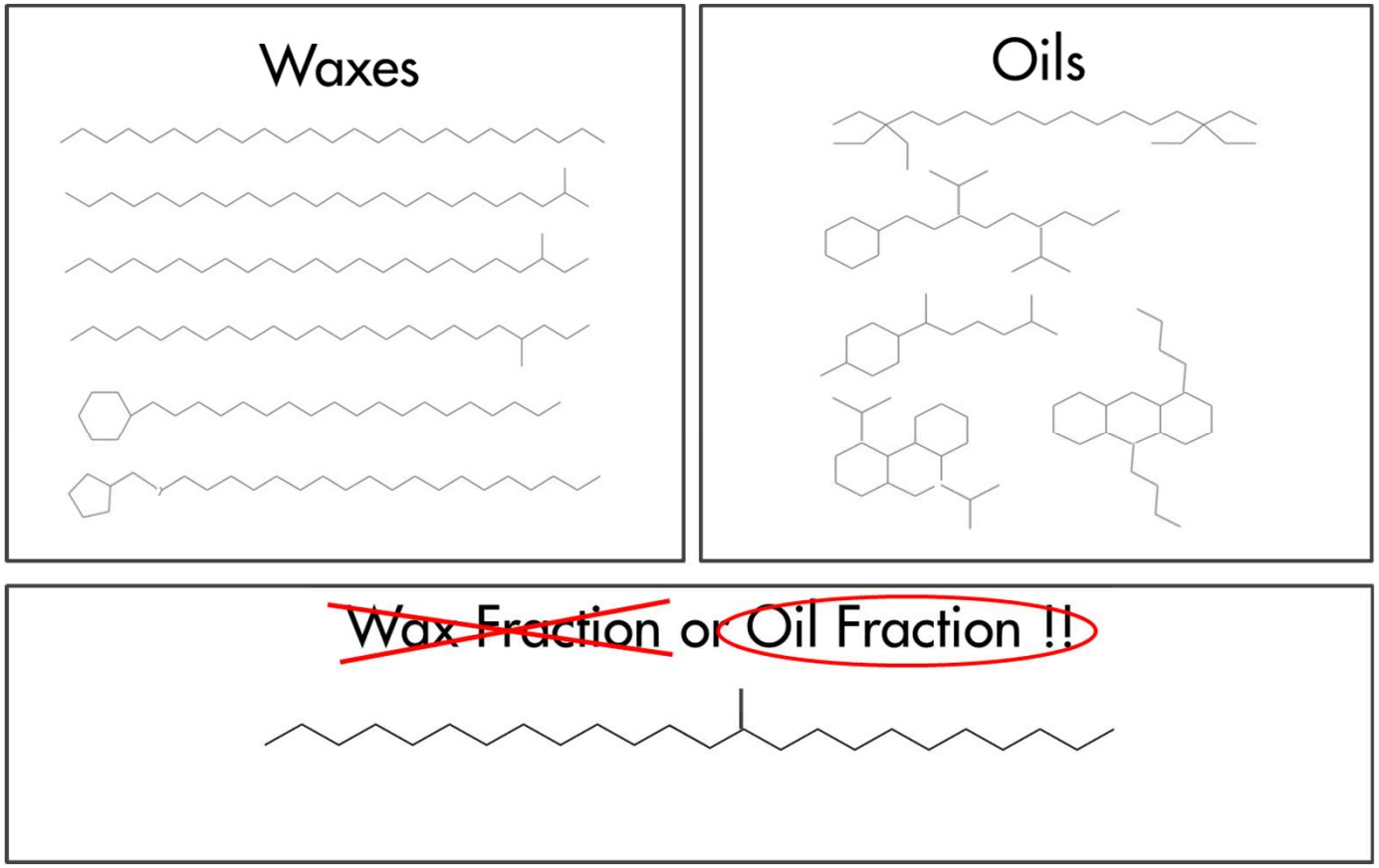
waxes

- n-alkanes and linear C- backbone
- solid

Molecular structures waxes and oils



Molecular structures waxes and oils



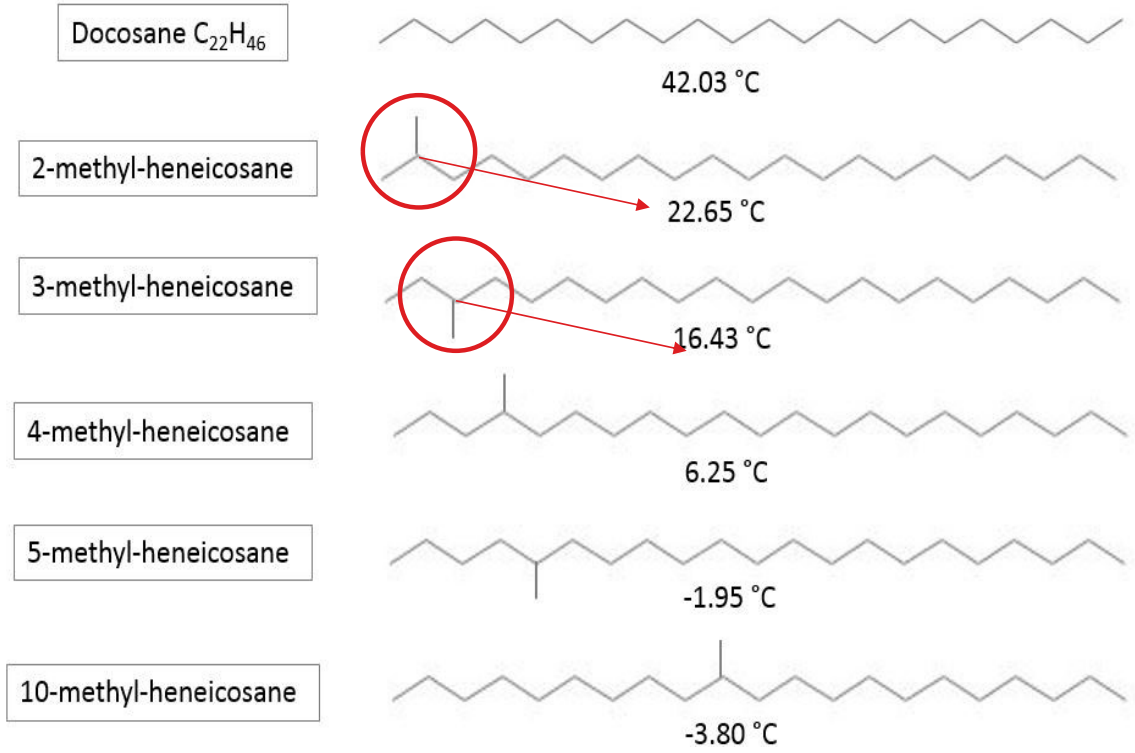
UVCB –'ness of Waxes

How unknown and variable?

Table 3. Possible alkane isomers by carbon number.

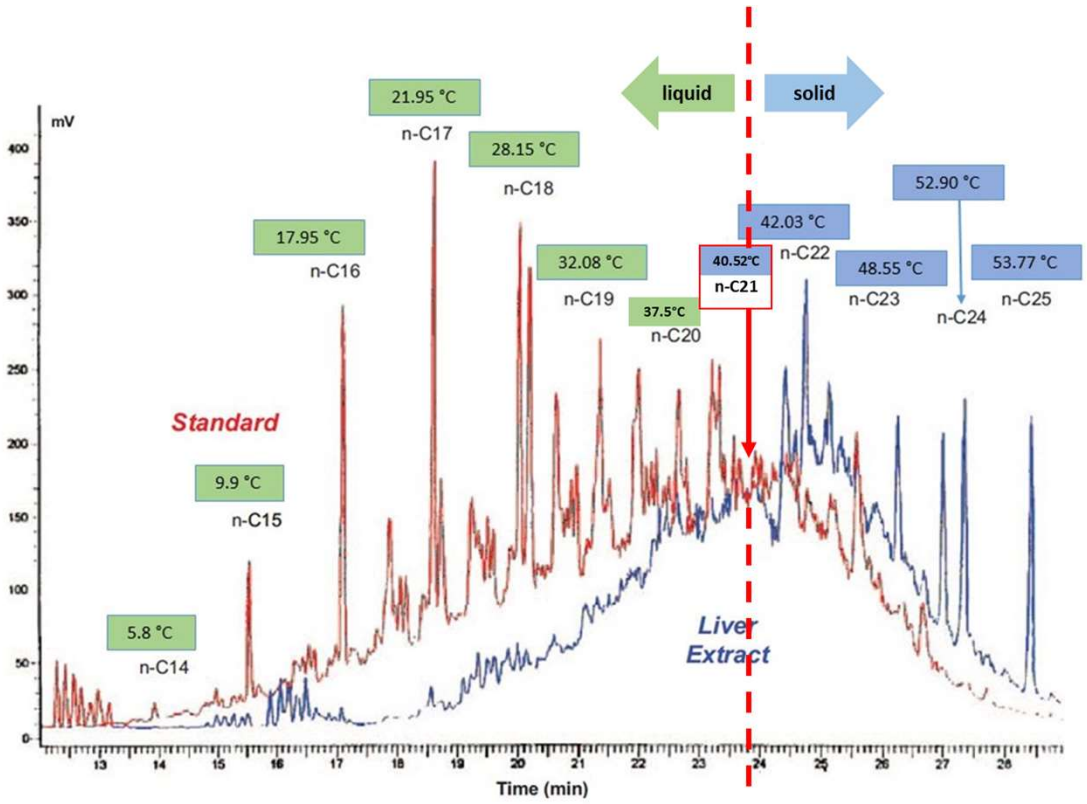
number of carbons	Isomers alkanes C_nH_{2n+2} (cycloalkanes not counted)	Mono-Methylalkanes potentially present in wax	Cyclohexyl alkanes potentially present in wax	Total Mono-Methyl and Cyclohexylalkanes
5	18			
20	366,319			
25	36,797,588			
30	4,111,846,763			
40	62,481,801,147,341			
50	1,117,743,651,746,953,270			

Influence of the methyl substituent on the carbon backbone melting point



"uninterrupted linear alkane backbone of at least 20 carbon atoms"

Preferential retention of n-alkanes in F-344 livers by melting point



McKee et al., 2012

F-344 has limited metabolic capacity

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			
	1600			

(Woldhuis & Danneels, EWF 2017)

F-344 has limited metabolic capacity

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	4	ø
	1600	4.1	10	ø

(Woldhuis & Danneels, EWF 2017)

F-344 fed low melting point wax (LMPW) form wax crystals

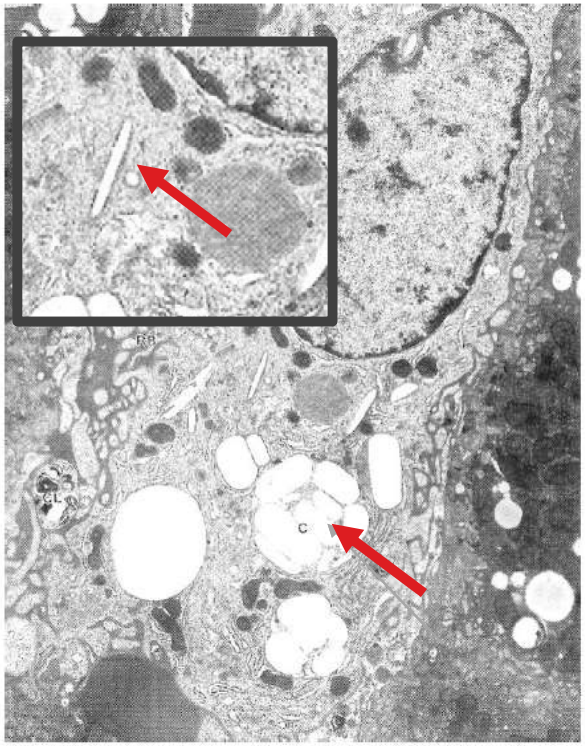
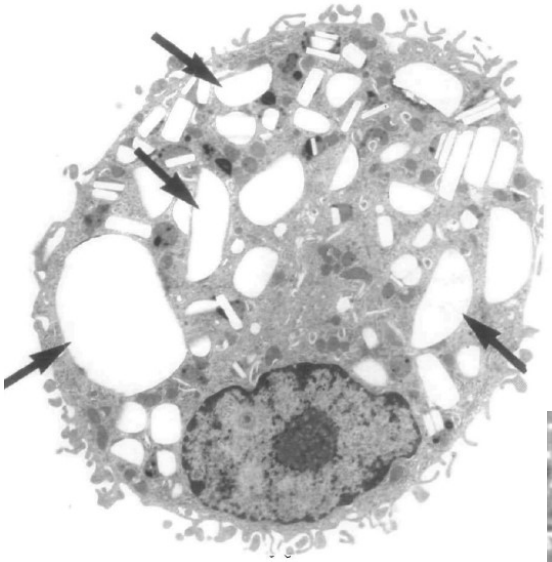
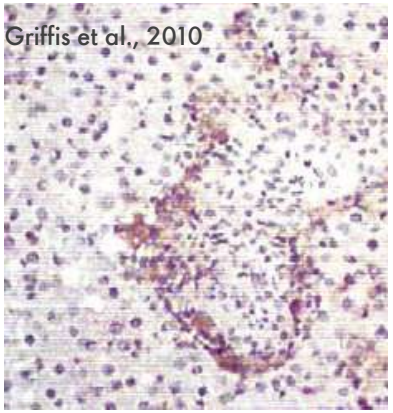


Fig. 2. Liver (EM; 10,880×) from an F-344 rat after 90 days at 2% LMPW. Kupffer cell with accumulation of lysosomal crystalloid structures and signs of activation. E, endothelial cell; LY, lysosome; RB, ruffled border; CL, concentric lamellar bodies; and C, crystalloid structure.

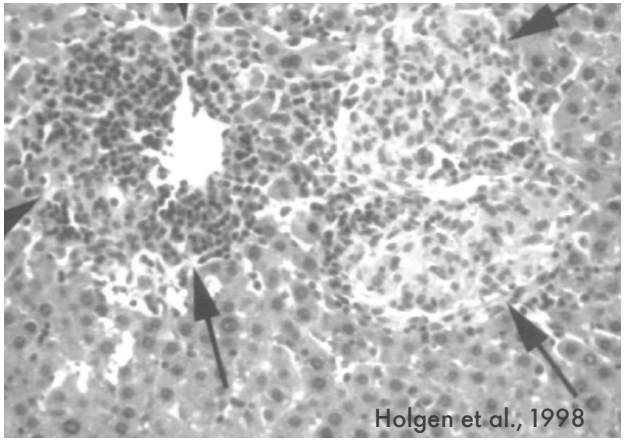
Griffis et al., 2010



Holgen et al., 1998



Griffis et al., 2010



Holgen et al., 1998

What we know so far – smaller KC population

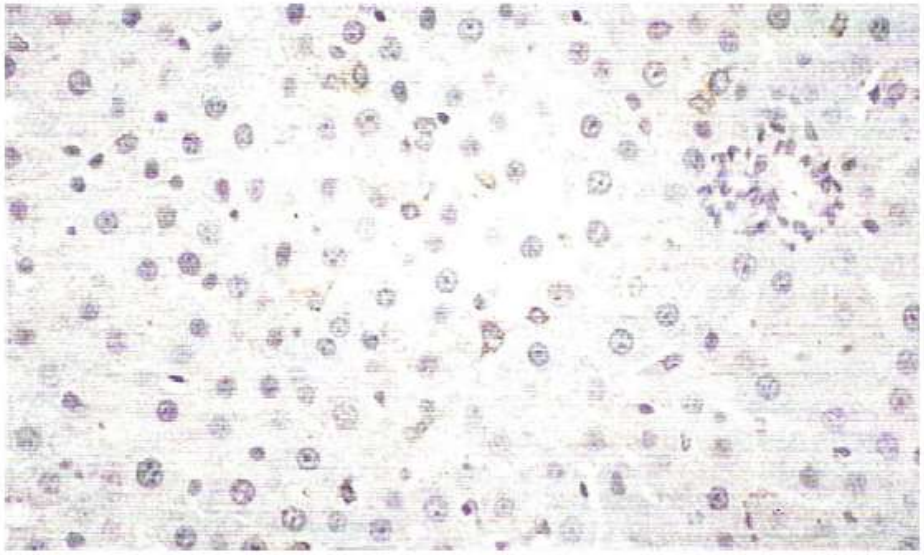


Fig. 4. Liver (stained for ED2, silver enhanced, 400×) from F-344 control rat. Note the smaller relative number of ED2-positive (Kupffer) cells in hepatic sinusoids of this control F-344 versus an untreated S–D rat (Fig. 5).

- F344 control

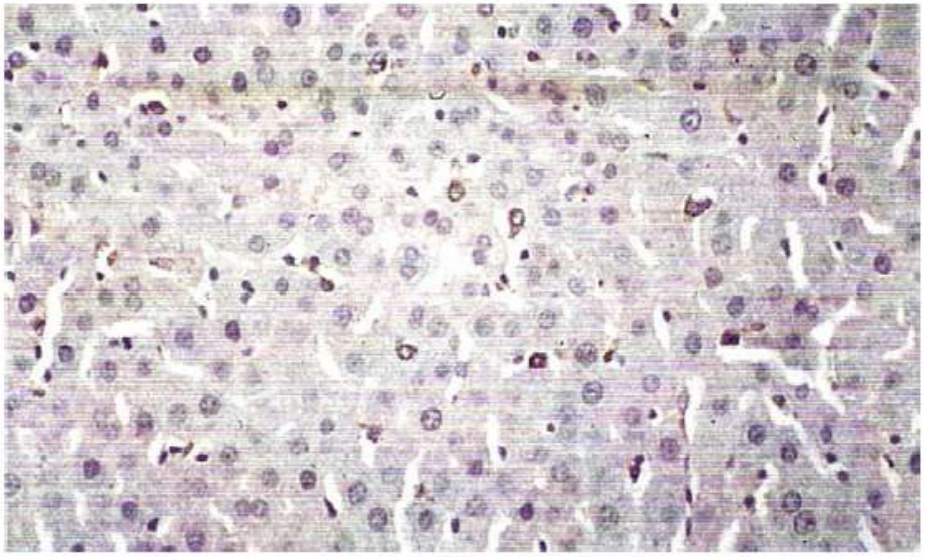


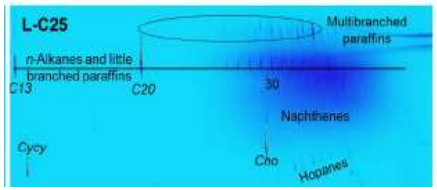
Fig. 5. Liver (stained for ED2, silver enhanced, 400×) from S–D control rat. Note greater relative number of ED2-positive (Kupffer) cells in hepatic sinusoids versus F-344 control rat (Fig. 4).

- SD control

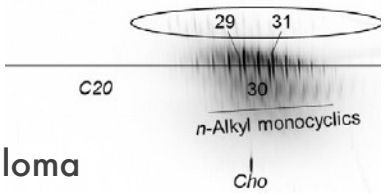
Griffis et al., 2010

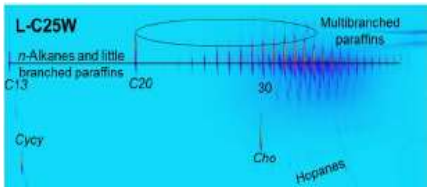
The "*we would have never done it this way*"- experiment

- <u>F-344 fed sub-fractions</u>:
  - High viscosity oil only (**L-C25**)
    - *~no n-alkanes*
  - L-C25 + paraffin wax
    - *high n-alkane*
- Dose levels:
  - 400, 1000, 4000 ppm

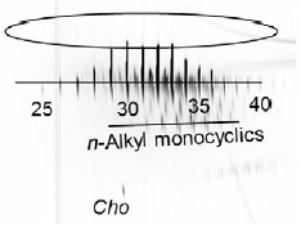


→ No liver granuloma
→ *retention of n-alkanes from feed*





→ Liver granuloma at all dose levels
→ *Heavy retention of n-alkanes*



- By the way: controls also accumulated biogenic n-alkanes

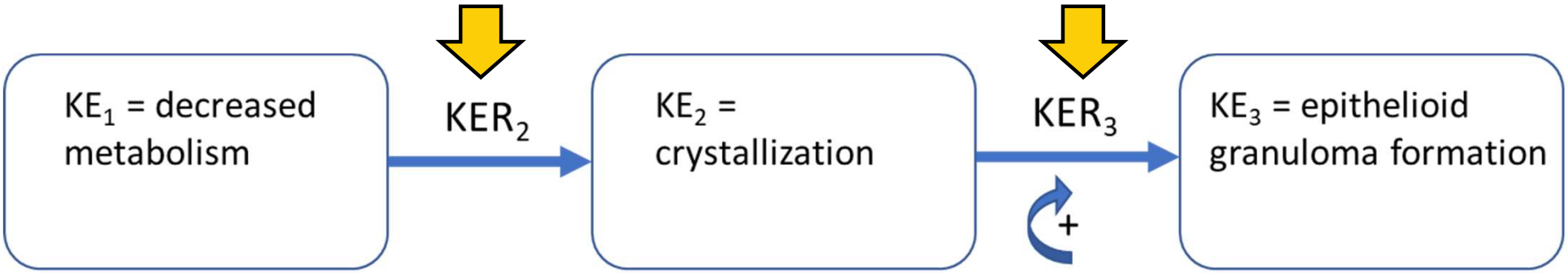
EFSA Supporting publication 2017: EN-1090, p80

L. Barp et al. / Science of the Total Environment 583 (2017) 319–333

… accumulation of biogenic n-alkanes

Mode of action using an AOP

- Dose and time dependant accumulation
- increased phagocytic activity with positive feedback

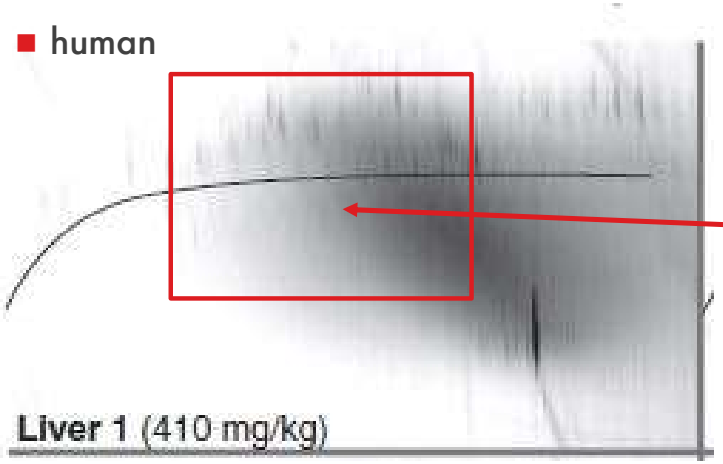


- Stressor agent → n-alkanes
- Appearance of foreign body
- Activation of KC
- To isolate/clear crystals
- in F-344 this is adverse

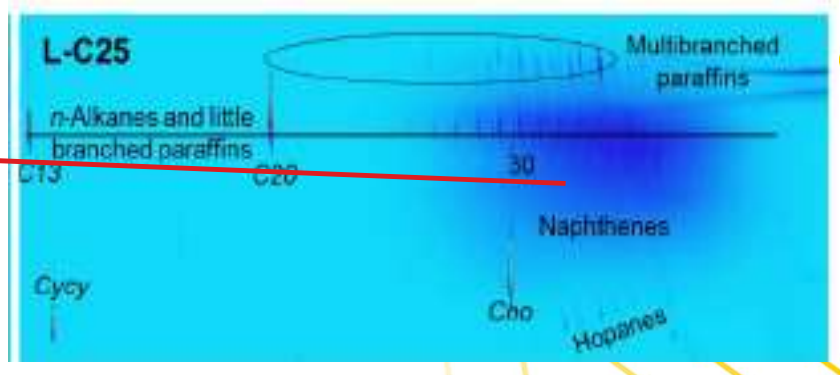
Carrillo, J. C., Danneels, D., & Woldhuis, J. (2021). Critical Reviews in Toxicology

High viscosity oil and human relevance

- human



- F344



Source: Barp et al., 2014 and Bidermann et al. 2014.

- MOSH is mostly related to naphthenics
- MOSH is retained at a critical range across species
- Critical range is within high viscosity oil MW (FCM 95)

3

Summary and Outlook

EFSA assessment 2023

SCIENTIFIC OPINION

efsa JOURNAL

ADOPTED: 12 July 2023

doi: 10.2903/j.efsa.2023.8215

Update of the risk assessment of mineral oil hydrocarbons in food

EFSA Panel on Contaminants in the Food Chain (CONTAM),
Dieter Schrenk, Margherita Bignami, Laurent Bodin, Jesús del Mazo, Bettina Grasl-Kraupp, Christer Hogstrand, Laurentius (Ron) Hoogenboom, Jean-Charles Leblanc, Carlo Stefano Nebbia, Elsa Nielsen, Evangelia Ntzani, Annette Petersen, Salomon Sand, Tanja Schwerdtle, Christiane Vleminckx, Heather Wallace, Jan Alexander, Christophe Goldbeck, Konrad Grob, Jose Ángel Gómez Ruiz, Olaf Mosbach-Schulz, Marco Binaglia and James Kevin Chipman

- F344 n-alkane induced hepatic granuloma are not relevant for humans
- Oil MOSH $_{\text{no n-alkanes}}$ NOAEL = 236 mg/kg bw
- MOSH hepatic retention
  - highest > C25
  - limited < C25
- MOSH retention pattern similar across species

- Wax (not MOSH) NOAEL = 9 g/kg bw

MOSH and food grade mineral oils (FCM 95)

Table 1 Classification of mineral oil hydrocarbons according to JECFA (2002).

Substance name	ADI (mg/ kg bw)	Viscosity at 100° C (mm^2/s)	Average relative molecular weight
High viscosity[1]	0-20	>11	>500
Medium/low viscosity (Class I)[2]	0-10	8.5-11	480-500
Medium/low viscosity (Class II)[3]	0-0.01	7.0-8.5	400-480
Medium/low viscosity (Class III)[4]	0-0.01	3.0-7.0	300-400

2023

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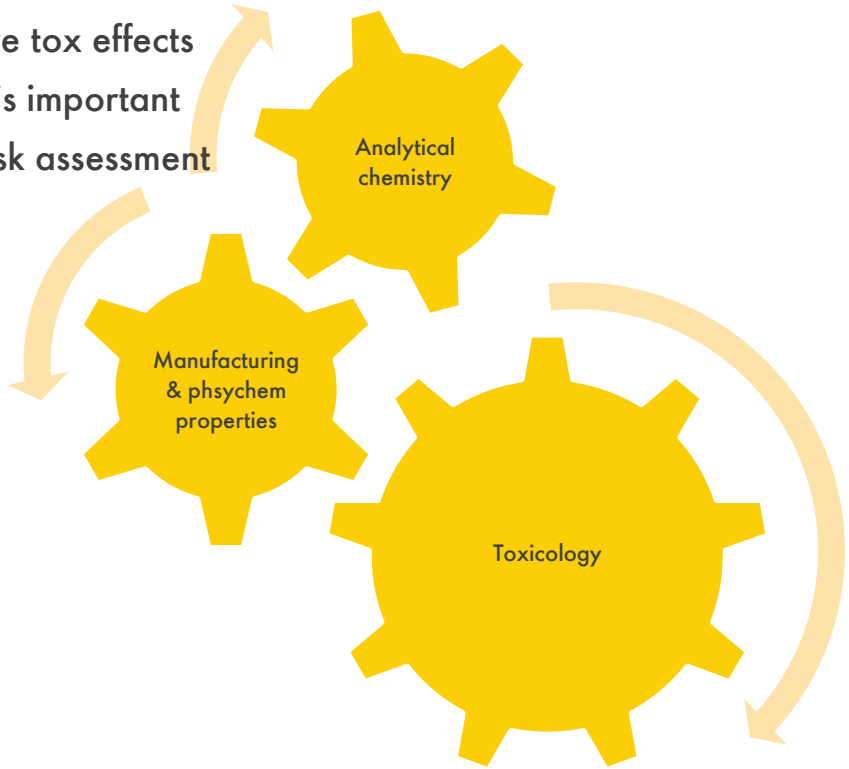
- Liver granuloma no longer relevant → re-evaluation of data by endpoint and sub-class
- Oils and waxes should be (re)assessed separately
- Waxes are not MOSH
- MOSH analysis should only refer to what is of relevance → accumulation
- High viscosity and Class I oils→ <u>safe</u> but potential higher accumulation
- Class II and III oils → re-evaluated for new ADI

4

Take home message

UVCB - assessment

- UCVB is not mixture
- UCVB composition differences drive tox effects
- Distinction of hydrocarbon blocks is important
- Define a marker of exposure for risk assessment
  - Oils “naphthenic” fraction



acknowledgements

- Lenny Kamelia - Shell
- Olaf Kral - Shell
- Danlei Wang – Wageningen University
- Dirk Danneels – EWF

Q&A

BACKUP

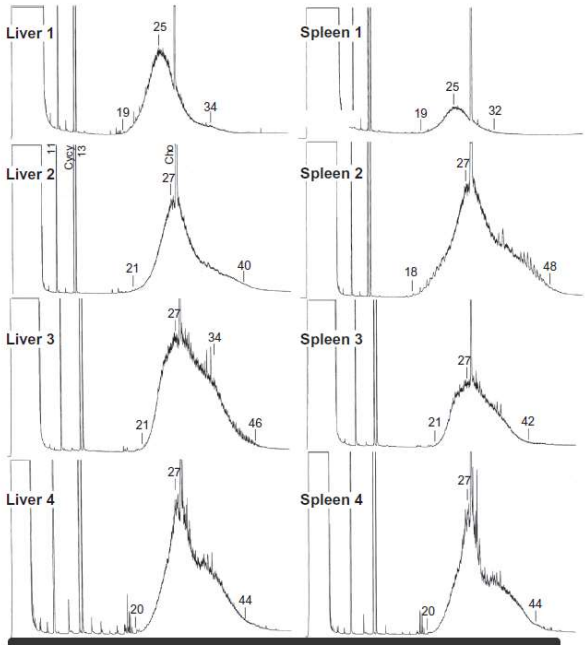
Interpretation of MOSH and MOAH fractions

The MOAH fraction

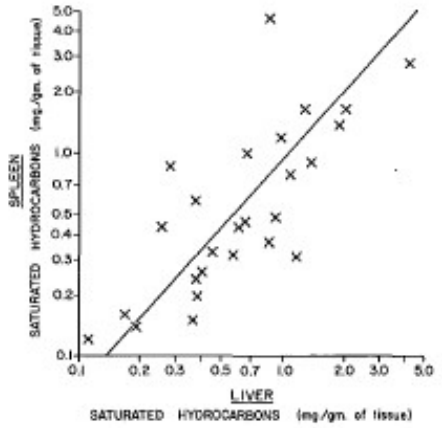
A new look at mineral oils – compositional considerations

What is relevant for humans?

- Data from 1970 and 2014 are in agreement:
  - n-alkanes are transient
  - MOSH retention in liver and spleen similar
- MOSH preferential retention: highly branched and poly-ring cycloalkanes (naphthenics)
- Critical retention range → high viscosity oils FCM



Barp et al., 2014 Food Chem. Tox

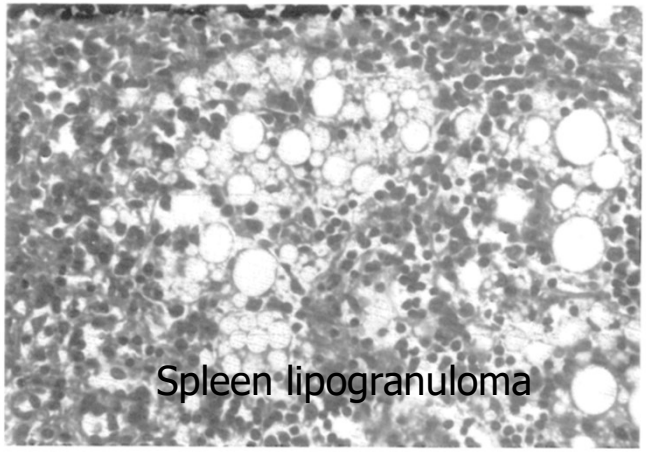


Analyses of Mass Spectrometric Data on Saturated Hydrocarbons from Two Cases Compared to Similar Analyses of Mineral Oils

Saturated Hydrocarbon Types	Composition (percent) #34135 (liver)	#34226 (spleen)	Mineral Oils*
Alkanes (normal & branched)	27.9	39.3	12.7 - 48.1
Cycloalkanes			
Non-condensed	25.7	18.8	21.3 - 26.0
Condensed			
2 rings	25.3	16.2	14.1 - 21.1
3 rings	11.4	11.5	7.4 - 18.3
4 rings	7.1	11.3	5.0 - 15.0
5 rings	2.6	2.9	2.0 - 8.4
6 rings	0.0	0.0	0.0 - 3.2

Boitnott et al., 1970. Hopkins Med. J.

An excess of naphthenics leads to lipogranuloma



- Referred to as "follicular lipidosis" or lipogranuloma (Cruickshank; 1984. Fleming 2017)
- A vacuolated, separate, oil deposit associated with macrophages
- Not the same F-344 type reaction or inflammation
- Lipogranuloma has no pathological consequence (Fleming 2017, 1998; Carlton et al., 2001.)

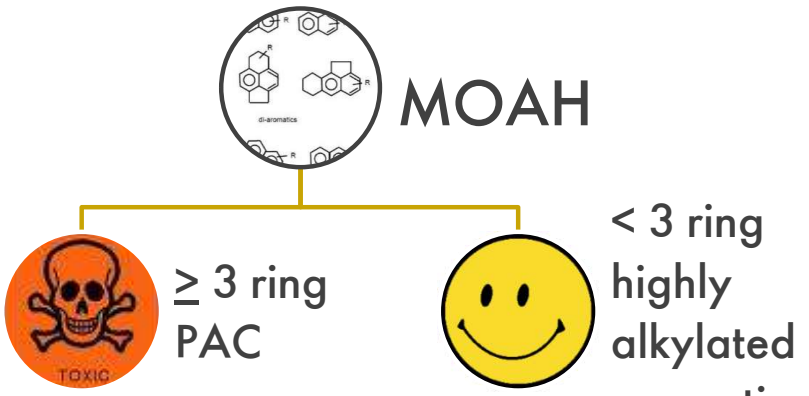
Cruickshank; 1984. Human Path.

Lipogranuloma incidence in spleen (likely in liver) has geographical variation (1983)

Highest: USA, UK, France, Australia, S. Africa

Nil: Greece, Mexico, Argentina, East Africa, Japan, India

Two types of MOAH

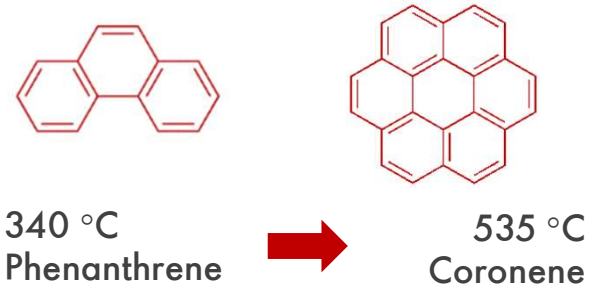


Substance or fraction	Live animals after 40 weeks	Re-treatment of live animals with a tumour promotor
Carcinogenic oil	Tumours in all animals	-
Fraction I (PAC "free")	No tumours	No tumours
Fraction II (2 and 3 rings)	No tumours	No tumours
Fraction III (> 3 rings)	No tumours	Tumours in all animals
Fraction I+II+III	Tumours in all animals	-

Agarwal et al., Arch Toxicol 62, 406–410, 1988

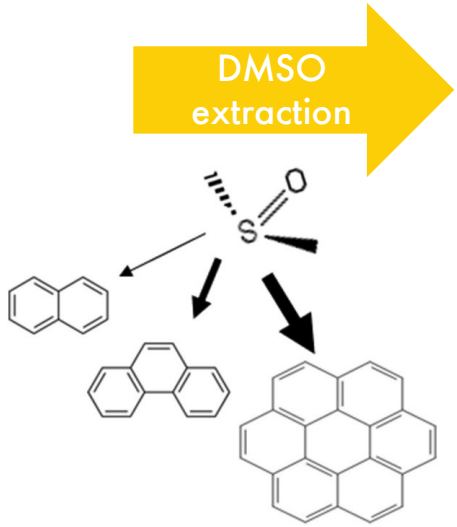
MOAH and aromatic ring numbers in mineral oil carcinogenicity

3-7 ring PAC



- Mineral Oil Production Boiling Range > 300°C
- The PAC in mineral oil are 3-7 rings because of 340-565°C boiling range
- MOAH, 1 and 2 ring must be highly alkylated to be found > 300°C
- Through PAC boiling points (and ring numbers) we can link manufacture to toxicity

How to distinguish MOAH types?



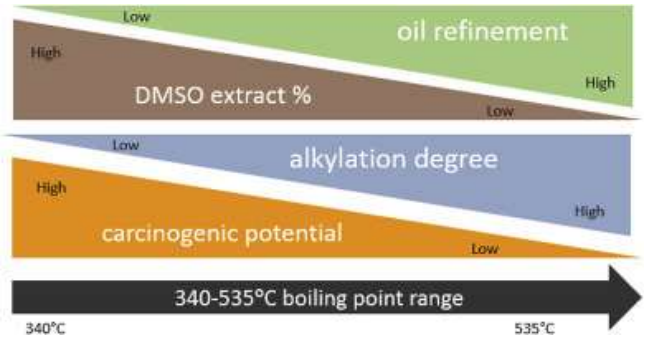
Regulatory tests are based on DMSO extraction

- DMSO selective extracts potential carcinogens

- IP346 – mandated in the EU
  - DMSO extract correlated to mouse skin painting data
  - < 3% DMSO extract → safe level
- Pharmacopeia tests
  - USP
  - EU
- Current MOAH tests measure "total aromatics" – 1,2 ring with 3-7 ring PAC → meaningless

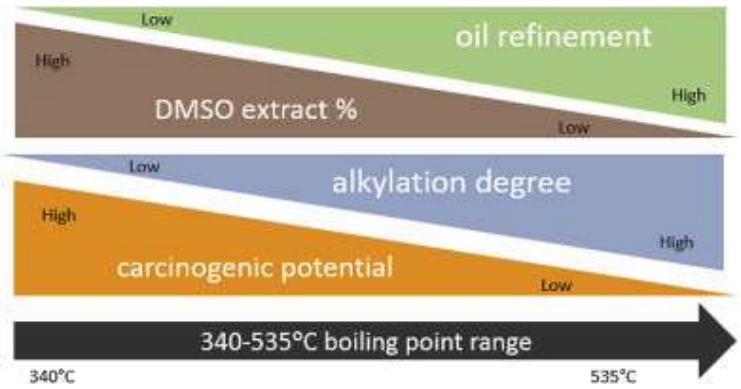
Long alkyl chain substitution decreases carcinogenic potential

- Experiments with 2,3 and 5 ring PAH
- Alkyl substitution shifts the oxidative metabolism from the aromatic ring to the alkyl side chain
- Long alkylation decreases carcinogenic potential of MOAH
- MOAH in refined oils is mostly 1 and 2 rings
- These can only be present at 300 °C if they are highly alkylated → Alkylation rises the bp



MOAH

- "MOAH" is contextual and in isolation has no meaning
- 1 and 2 ring MOAH is of low concern
- Focus on 3-7 ring PAC



Carrillo, J. C., et al., 2019; Reg Tox and Pharma, 106, 316-333.
Carrillo, J. C., et al., 2022; Reg Tox and Pharma, 132, 105193.