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Health: CONCAWE activities and contributions over 50 years in *Toxicology*

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Role and remit of TSG

- **Role** : The Toxicology Subgroup serves as an expert resource on matters related to all toxicological aspects of petroleum substances, whether arising during refining or subsequent uses of petroleum products

  → **one of the engine rooms of CONCAWE**

- **Background**: A proper understanding of the nature and magnitude of the potential human health impacts are critical for the successful management of health risks associated with the manufacturing and use of petroleum products. Most aspects of these human health impacts, in particular health risk assessment, relate to the intrinsic toxicological properties of petroleum products and the toxicokinetics of their individual constituents.
- **Objective**: To provide guidance and advice on all toxicological aspects related to petroleum substances, whether arising during refining or subsequent uses of petroleum products, in relation to regulatory and product stewardship issues.

Scope of TSG (1)

1. Identification and characterisation of relevant toxic properties of petroleum substances with regard to occupational and environmental health aspects.
2. Provide advice, guidance and support to the CONCAWE Management Groups and Task Forces on toxicological matters.
3. Identification, initiation and supervision of necessary toxicological studies needed for regulatory compliance and credible product stewardship; ensure that the generated data are properly incorporated in legally required databases.

→ ***TSG has performed this role when the DSD, DPD and ESR were introduced in the EU***

→ ***Currently TSG deals with the REACH requirements***

Scope of TSG (2)

4. Identification, initiation and supervision of research activities addressing toxicological issues where it is advisable to improve the basis of existing scientific understandings.
5. Develop and implement technical approaches to toxicological issues to address critical questions and opportunities and to close critical gaps.
6. Dissemination of generated toxicological data and scientific/ professional opinion to support evidence-based regulations and legislation.
7. Stimulating of and contributing to scientific and policy discussions in the area of the regulatory assessment of worker and consumer health risks to ensure that the specific considerations affecting petroleum substances are duly considered and that CONCAWE is recognised a valued stakeholder.

Specific examples: neurotoxicity (1)

2. *Provide advice, guidance and support to the CONCAWE Management Groups and Task Forces on toxicological matters.*

- **Report 86/51: Effects of petroleum hydrocarbons on the nervous system**

1986: *Oldest report still on CONCAWE website…*

Prepared by P. Grasso, A. Blok & TSG: B. Simpson (chair), M. Butler, S. Dally, M. Pointet, N. Sarginson, O. Skaane, K. Trettin and A. Eyres (technical coordinator)

Main conclusions:

- peripheral neurotoxicity of *n*-hexane is a serious adverse health effect and exposure to *n*-hexane should be strictly controlled
- the central nervous system effects of hydrocarbons (toluene, white spirit) cannot be confirmed beyond doubt, but it is wise to strictly observe OELs

Specific examples (2)

- The TSG basically seeks experts to address emerging toxicological issues, they review the results, and report it to HMG (or other management groups).
- This continues to be an important task of TSG:

Report 89/56: Review of the toxicity of catalytically cracked clarified oil

Prepared by J. Freeman; TSG has roughly the same composition, B. Simpson is still chair, CONCAWE is still in The Hague

Report 91/52: Review of chemical and UV light induced melanomas in experimental animals in relation to human melanoma incidence

Prepared by A. Ingram; CONCAWE has moved to Brussels

Specific examples (3)

- **Report 99/60: The health effects of $PM_{2.5}$ (including ultrafine particles)**

  Prepared by CTL (P. Hext, K. Rogers & G. Paddle); reviewed by M. Evans, R. Priston, W. Tordoir); Jan Urbanus is Technical Coordinator

- **Report 00/53: An assessment of the reproductive toxicity of gasoline vapor**

  R. McKee, S. Dally, B. Dmytrasz, J. Gonnet, R. Hagemann, C. Mackerer, C. Nessel, R. Priston, A. Riley, J. Urbanus

Specific examples (4)

- **Report 8/04: European epidemiology studies of asphalt workers – a review of the cohort study and its results**

  Prepared by G. Swaen, reviewed by R. Ahlberg & A. Riley

- **Report 5/05: Factors potentially affecting the hearing of petroleum industry workers**

  Prepared by P. Hoet, M. Grosjean & C. Somaruga, reviewed by P. Boogaard & J. Urbanus

- **Report 5/10: Review of the dermal effects and uptake of petroleum hydrocarbons**

  Prepared by S. Kezic, J. Kruse, I, Jakasa, P. Boogaard, G. Minsavage

4. *Identification, initiation and supervision of research activities addressing toxicological issues where it is advisable to improve the basis of existing scientific understandings.*

- **Report 96/62: Overview of the CONCAWE middle distillate programme**

  Prepared by S. Dally, R. Hagemann, R. McKee, C. Nessel, R. Priston, A. Riley, B. Simpson (TC)

  This programme was set up to investigate the *mechanism* of the dermal tumourigenicity of middle distillates – an effect found in the early 1980's in mouse skin painting studies.

  This report is a summary of a series of five CONCAWE reports issued between 1991 and 1996.

CONCAWE middle distillates programme

Phase 1: Short-term screening studies on 10 different middle distillates: physico-chemical properties, PAH, mutagenicity, skin irritation → mutagenicity is related to PAH content; some middle distillates are strong irritants

Phase 2: Testing of 5 middle distillates in 90-day studies to find application scheme without causing dermal irritation, but, as shown by radio-active hydrocarbon tracers, delivering the same amount of material into the skin.

Phase 3: Testing of 3 middle distillates (straight-run kerosine and gas oil, and light cycle oil) in 2-year studies, diluted and undiluted → LCO causes skin tumours through a genotoxic mechanism (PAH); kerosine and gas oil may cause skin tumours, but through a non-genotoxic mechanism: *prevention of skin irritation prevents cancer*.

TOXICOLOGICAL SCIENCES 49, 48–55 (1999)

The Role of Dermal Irritation in the Skin Tumor Promoting Activity of Petroleum Middle Distillates

Craig S. Nessel, James J. Freeman, Richard C. Forgash, and Richard H. McKee[1]

Exxon Biomedical Sciences, Inc., East Millstone, New Jersey 08875–2350

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Petroleum middle distillates (PMDs), a class of hydrocarbons which boil between 350–700°F, are tumor promoters in mouse skin. The promotional activity is produced under conditions that also result in local changes, including chronic irritation and epidermal hyperplasia. The present study was conducted by comparing equal weekly doses of irritating and minimally or nonirritating test materials, to assess whether tumor promotion was a secondary response to these effects. Four PMDs, C10–C14 normal paraffins (NP), lightly refined paraffinic oil (LRPO), Jet Fuel A (JF), and steam-cracked gas oil (SCGO), were evaluated. Test materials were applied undiluted (2×/week) or as 28.6% (7×/week) or 50%

primarily or entirely produced from the distillation of crude oil at atmospheric pressure. These products are called "straight-run" middle distillates. Alternatively, it is possible to produce hydrocarbons of similar boiling range by processes that break down larger and more complex molecules by catalytic or thermal methods, generally referred to as "cracking". Products such as diesel fuel or residential heating oils may contain cracked stocks, and may have higher levels of aromatic components than straight-run materials of a similar boiling range.

The carcinogenic activity of some petroleum-derived materials is associated with the presence of biologically active 4–6

Specific examples: bitumen

3. *Identification, initiation and supervision of necessary toxicological studies needed for regulatory compliance and credible product stewardship; ensure that the generated data are properly incorporated in legally required databases.*

- Series of bitumen studies between 2001 and 2009:
- 2-Year carcinogenicity/chronic toxicity nose-only inhalation studies with field-generated bitumen fume with additional investigative studies (amongst others: toxicogenomics)
- A series of studies in German bitumen workers to investigate a range of (adverse) health effects respiratory such as irritation, genotoxicity, genetic disposition etc.
- Unique role of TSG to link both studies by ensuring that the same parameters are included in the animal and human studies

Specific examples: IP346 methodology

5. *Develop and implement technical approaches to toxicological issues to address critical questions and opportunities and to close critical gaps.*

- **Report 94/51: The use of the DMSO extract by the IP346 method as an indicator of the carcinogenicity of lubricant base oils and distillate aromatic extracts**
- Issue: the level of PAH in base oils determines whether or not they can act as dermal carcinogens, but not all PAH are carcinogenic: only certain 4- to 7-ring PAH
- IP346 methodology (DMSO extraction) as indicator for carcinogenicity was developed at Shell in the late 1970's.
- IP346 and B[a]P were correlated to 100+ long-term cancer studies to establish a critical level to differentiate between potentially carcinogenic and non-carcinogenic base oils
- IP346 proved useful, was presented to the EU authorities (ECB, Ispra) and incorporated into EU legislation for base oils

Mutagenicity/carcinogenicity of RAEs

The IP346 method works very well for base oils and distillate aromatic extracts, but not for residual aromatic extracts

- **Report 12/12: Use of the modified Ames' test as an indicator of the carcinogenicity of residual aromatic extracts**
- Modified Ames' test was developed by Mobil in the 1980's to differentiate between carcinogenic and non-carcinogenic base oils (MI of 1 as cut off).
- Test programme, round-robin test for validation of modified Ames' test, correlations between mod Ames' test and mouse skin painting studies set up and run by TSG without any 'external support' (MI of 0.4 as cut off).

Specific examples: White oils

6. *Dissemination of generated toxicological data and scientific/ professional opinion to support evidence-based regulations and legislation.*

- **Report 1/04: Chronic toxicity studies on white oils**

  There are a couple of long-standing issue with white oils: they do not cause any adverse health effects in dogs or SD rats, but when low-viscosity white oils were tested in F344 rats, liver micro-granuloma's were seen as well as accumulation of mineral hydrocarbons in several organs.

  At the request of the Scientific Committee for Food (SCF), two commercially important white oils were tested in 2-year chronic toxicity/ carcinogenicity studies, with recovery, in the most sensitive species (F344 rats) to establish the No-Observed Adverse Effect Level (NOAEL) which allows to derive an Acceptable Daily Intake (ADI).

Publication White Oils

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Results of Chronic Dietary Toxicity Studies of High Viscosity (P70H and P100H) White Mineral Oils in Fischer 344 Rats

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ABSTRACT

Two-year dietary studies were conducted to determine the chronic toxicity and its reversibility, and the carcinogenicity of P70(H) and P100(H) white mineral oils in Fischer-344 rats (F-344). The studies were identical in design and followed the Organization for Economic Cooperation and Development, Guidelines for Testing Chemicals, Guideline 453, 1981. Additional endpoints evaluated were: (1) extent of mineral hydrocarbon deposition in liver, kidneys, mesenteric lymph nodes, and spleen of female rats at 3, 6, 12, 18 and 24 months, and (2) reversibility of effects following cessation of exposure. Dietary concentration were 60, 120, 240, and 1,200 mg/kg/day, adjusted periodically to account for bodyweight changes. Study results were consistent with preceding subchronic studies. No treatment-related mortality, neoplastic lesions, or changes in clinical health, hematology, serum chemistry, or urine chemistry were evident in any group administered either white oil. Statistically significant higher food consumption was noted in the 1,200 mg/kg group males and females exposed to either white oil and statistically significant higher body weights were noted in the 1,200-mg/kg males during the latter portion of the P100(H) study. Higher mesenteric lymph node weights were accompanied by increased severity of infiltrating histiocytes. This occurred to a greater extent with the P70(H) than the P100(H) oil. No other histopathology of significance was observed. Mineral hydrocarbons were detected in the liver following exposure to either oil. Maximal concentrations of mineral hydrocarbons in the liver were similar with both oils but occurred more rapidly with the P70(H) oil. Liver mineral hydrocarbon content returned to near-background levels during the reversibility phase. In conclusion, lifetime exposer of F344 rats to P70(H) and P100(H) white oils resulted in only minimal findings and with no consequence to clinical health

Low viscosity white oils

- JECFA (FAO/WHO Joint Expert Committee on Food Additives) requested more specific studies including comparative toxicokinetcis in rat strains and humans (2002).
- Several studies were done in different rat strains, which all pointed to the F344 rat being extraordinary sensitive to low-viscosity white oils
- In addition, an expert workshop was organised where histo-pathologists assessed the effects of white oils in animals and humans were discussed (Carlton et al., 2001)
- However, human studies were not conducted since the analytical technology to measure mineral hydrocarbons in human blood was not sensitive enough
- Methodology was developed and the required studies were conducted (rat studies in 2009, human studies in 2010)
- The results were published in 2011

Toxicokinetics White Oils

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Regulatory Toxicology and Pharmacology

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Comparative toxicokinetics of low-viscosity mineral oil in Fischer 344 rats, Sprague–Dawley rats, and humans – Implications for an Acceptable Daily Intake (ADI)

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ABSTRACT

Oral repeated-dose studies with low-viscosity mineral oils showed distinct species and strain differences, which are hypothesized to be due to differences in bioavailability, with Fischer 344 rats being more susceptible than Sprague–Dawley rats or dogs.

Sensitive analytical methodology was developed for accurate measurement of low levels of mineral hydrocarbons and applied in single-dose toxicokinetics studies in rats and humans. Fischer 344 rats showed a 4-fold higher $AUC_{0-\infty}$ and consistently higher blood and liver concentrations were found than Sprague–Dawley rats. Hepatic mineral hydrocarbon concentration tracked the blood concentration in both strains, indicating that blood concentrations can serve as functional surrogate measure for hepatic concentrations. In human volunteers receiving 1 mg/kg body weight of low-viscosity white oil, all blood

Specific examples: DNEL guidance

7. *Stimulating of and contributing to scientific and policy discussions in the area of the regulatory assessment of worker and consumer health risks to ensure that the specific considerations affecting petroleum substances are duly considered and that CONCAWE is recognised a valued stakeholder.*

- During the preparations for the REACH legislation, it was recognised that the guidance for the Derived No-Effect Levels (DNELs), which determine the theoretical highest level of a substance humans can be exposed to without foreseeable adverse health effects, was very conservative due to 'default assessment factors', which imply there is no specific knowledge.
- TSG developed the concept of 'informed assessment factors' and a dedicated approach for petroleum substances.

DNEL approach for REACH

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A consistent and transparent approach for calculation of Derived No-Effect Levels (DNELs) for petroleum substances

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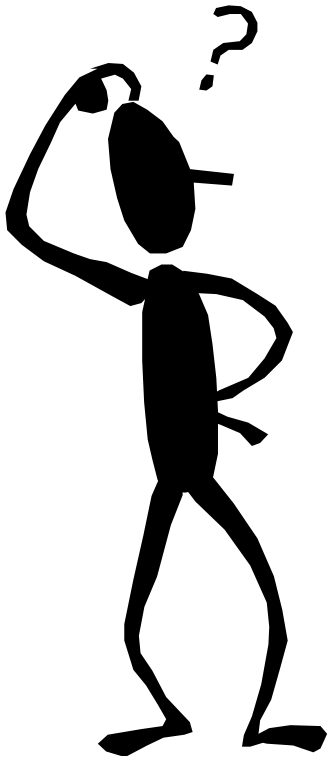
Conclusion

- The TSG is a very small group of highly dedicated professionals, which over the years have supported not only the HMG, but also a wide variety of other Management Groups and Coordination Groups and their respective task forces.
- Over the years TSG has evolved, moving from a primarily reviewing role and a rather responsive attitude (e.g. in reaction to new legislation or societal concerns) to a more proactive role, initiating research and steering legislation.
- It is foreseen that TSG will further develop, embracing new technologies in toxicology (e.g. next talk by Alan Boobis) to meet new challenges and maintain its position as one of CONCAWE's engine rooms…

Thank you for your attention



Any questions ?