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Proceedings of the Mineral Oil CRoss Industry IssueS (MOCRINIS) Workshop

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ABSTRACT

CONCAWE organised a 2-day Mineral Oil Cross Industry Issues (MOCRINIS) Workshop in Bologna, Italy in September 2013. The objective of the Workshop was to address topics that have arisen following the publication of results demonstrating the presence of saturated and aromatic hydrocarbons in some foods. The Workshop was attended by delegates from a range of industry sectors with an interest in the issue such as mineral oil producers, printing ink manufacturers, cardboard and paper packaging industries as well as regulators from the European Union (EU) and individual countries.

The topics of measurement and characterisation, exposure to and toxicity of hydrocarbons were discussed fully and openly and possible ways forward were identified. This report presents the proceedings of the MOCRINIS Workshop.

KEYWORDS

Mineral oil, hydrocarbons, MOSH, MOAH, hydrocarbon analysis, food safety, food packaging legislation, food additive legislation, food contact materials, food packaging, printing ink, toxicology, exposure assessment, risk assessment

INTERNET

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SUMMARY

Hydrocarbons found in food can originate from a variety of sources including: food-grade mineral oil, fuels and lubricants used in machinery to treat or harvest food crops, packaging made from recycled printed paper or may even be of natural origin. Evaluation and control of risks associated with exposure to hydrocarbons in food is therefore a complex issue, requiring input from several industry sectors and regulators. To begin to address this complex issue, CONCAWE organised a Workshop that was held over two days in Bologna, Italy which was attended by approximately 80 participants representing a wide range of interests from academia, several industry sectors and regulatory authorities.

There were presentations on mineral oil production, composition and use; toxicology; risk assessment; the regulatory framework in Europe and analytical methodology for hydrocarbons. In addition to the presentations in plenary session, three separate discussion groups were held dealing with toxicology and risk assessment, analytical methods and downstream users interests/concerns respectively. During the discussion sessions there was an open and in-depth discussion of a range of topics.

During the Workshop, it became apparent that there was confusion in the nomenclature, a need to further delineate the pharmacokinetic differences between human and the Fischer 344 rat, a need to update the available database on hydrocarbon exposure via food, and shortcomings in a consistent way of measuring/analysing hydrocarbons in food.

At the end of the Workshop a general outline for possible future work to address the outstanding topics and concerns were discussed. The path forward included the following general recommendations or questions that need to be addressed:

- Reduce uncertainty around exposure estimates to hydrocarbons that have been reported previously.
- Identify methods/approaches leading to a better understanding of the pharmacokinetic/toxicodynamic differences between the human and rat models.
- Improve understanding on the potential toxicity of the aromatic hydrocarbons detected in food.
- Investigate options to resolve the confusion in nomenclature of hydrocarbons/mineral oils.
- Improve available analytical methods for hydrocarbon measurement.
- Provide guidance on interpretation of chromatographic data.
- Identify suitable reference standards for the available analytical methods.

In addition it was recommended that a position paper should be prepared that clearly provides accurate information on the current status of topics surrounding hydrocarbons in food. It was also suggested that a steering group of stakeholders should be created to monitor progress. Finally, it was suggested that it would be useful to hold another Workshop to assess the progress that has been made in addressing the topics identified from MOCRINIS Workshop.

Note to the reader about terminology:

It became apparent during the Workshop that there was considerable confusion with the meaning of some vaguely-defined terms such as mineral oil and mineral oil hydrocarbons.

For some, the term mineral oil refers to either highly-refined base oils, including food-grade oils or lubricating base oils, while others use the term mineral oil to include several other petroleum products.

Every effort has been made to ensure that the terminology used by each of the presenters or those delegates who made comments is reported faithfully and has not been modified in this report.

Readers of this report should, therefore, be aware that some terminology may have different meanings for different individuals. As a guide, some terms are defined in the glossary to this report.

1. INTRODUCTION AND BACKGROUND

Food-grade mineral oils were evaluated by the Scientific Committee for Food and ADIs (Acceptable Daily Intakes) were established for their use as food additives (SCF, 1997). Subsequently the Joint FAO/WHO Expert Committee on Food Additives (JECFA) also set several ADIs for mineral oil (FAO/WHO, 2002). More recently the European Food Safety Authority Panel on Contaminants in the Food Chain (EFSA CONTAM panel) published their Scientific Opinion on "Mineral Oil Hydrocarbons in Food" (EFSA, 2012).

Hydrocarbons have been found in food (Biederman, Fiselier et al. (2009)) and their origin could have been from a variety of sources, one of which could be mineral oil. For example, one of the sources might be from cardboard food packaging that has been produced from recycled paper that had in turn been printed using ink containing mineral oil (Biederman and Grob, 2010). Hydrocarbons found in food might also have originated from fuels used in machinery used to treat or harvest food crops or might even be of vegetable origin. In their Scientific Opinion, the EFSA Contam Panel list many possible sources of hydrocarbons that have been found in food (EFSA, 2012).

It became apparent that to evaluate and develop risk reduction measures from exposure to hydrocarbons, input from several industry sectors would be required.

To address this complex issue it was decided to hold a **M**ineral **O**il **CR**oss **In**dustry **I**ssue**S** (**MOCRINIS**) Workshop where all the stakeholders could discuss the topics and agree on an appropriate way of addressing them.

The main purpose of the MOCRINIS Workshop was to achieve a common understanding on the complexity of this issue among stakeholders and to accomplish the following:

- Allow all stakeholders to express their view on the issue.
- Develop a clear understanding of mineral oils as Substances of Unknown or Variable Composition (UVCB substances) and their technical applications in relation to their analytical profile. Seek clarity in nomenclature of hydrocarbon substances.
- Understand sources of intentionally, not intentionally, or naturally occurring hydrocarbons that would lead to a similar analytical profile.
- Discuss validated and robust analytical methods for identifying hydrocarbons and the migration and fate of these complex substances.
- Understand the risk assessment of petroleum derived substances in food and non-food settings. In this context, discuss the latest scientific findings in regard to ADIs for specific mineral oils in food applications.
- Understand the regulatory framework for substances not intended for food use and their presence in food and food packaging.
- Review EFSA's recommendations on mineral oils.
- Agree and develop a plan on the way forward.

- Publish Workshop proceedings.

This report describes the proceedings of the MOCRINIS Workshop in the order that they occurred. Brief summaries are provided for each of the presentations that were given in the plenary sessions as well as relevant points that arose following the presentations and during panel discussions. The conclusions and recommendations from the three separate discussion groups are also presented in this report.

Finally, the overall general recommendations from the Workshop are summarised separately in section 12 of this report.

2. THE WORKSHOP

The MOCRINIS Workshop was held over 2 days (10-11 September, 2013) at the Sheraton Airport Hotel, Bologna, Italy and was attended by 77 participants representing a wide range of interests from academia, industry and regulatory authorities. A list of attendees and their affiliations is included in **Appendix 1**.

The first day of the Workshop was devoted to plenary sessions during which presentations were given on the five subject areas:

1. Mineral oil production, composition and use
2. Toxicology
3. Risk assessment
4. The regulatory framework in Europe
5. Analytical methodology.

Two panel discussions were held during which all attendees were encouraged to share their views/concerns.

Three different breakout discussion groups were held on the second day of the Workshop covering:

- Toxicology and risk assessment
- Analytical methods
- Downstream user interests/concerns.

The purpose of these breakout sessions was to encourage a more in depth discussion and to arrive at a set of conclusions on a possible way forward to resolve outstanding topics. Each of the discussion groups presented their conclusions/recommendations during a plenary session which followed.

Finally, the overall recommendations from the Workshop were identified, discussed and agreed, in general terms, in a plenary session.

The agenda for the Workshop is shown in **Appendix 2**.

3. THE PROCEEDINGS OF THE WORKSHOP

(Moderator – D. Danneels, European Wax Federation [EWF])

3.1. GOALS AND OUTLINE OF THE WORKSHOP

(J-C. Carrillo, Shell International)

Different kinds of oils are used in many applications, and involve uses which are supported in the REACH registrations of these substances. Although some mineral oils are not intended for direct food contact applications, it has been reported that their use in printing newspapers could result in the detection of hydrocarbons in food packaged in cardboard boxes produced from recycled newspaper. Thus "printing inks" are regarded as a potential indirect source of mineral oil in food.

Recently, mineral oils have been described as consisting of two types of hydrocarbons: Mineral-Oil-Saturated-Hydrocarbons (MOSH) and Mineral-Oil-Aromatic-Hydrocarbons (MOAH) and that these two hydrocarbon fractions of mineral oil could present a health risk. As the abbreviations suggest, it is assumed that these hydrocarbons detected in food are from mineral oil and the main sources are recycled cardboard and printing inks. This assumption has been challenged from recent studies showing that hydrocarbons detected in chocolates from advent calendars do not originate from the printed cardboard calendar: the cardboard was from virgin fibres and the inks used were mineral oil free.

This issue is complex because of the overlap between REACH and food legislation. Additionally, analysis of hydrocarbon fractions in food cannot distinguish between the various sources of hydrocarbons with similar carbon number range. Thus the challenge lies in regulating complex hydrocarbon substances or fractions of hydrocarbons in food when their source is unknown.

The **M**ineral **O**il **Cr**oss **In**dustry **I**ssue**s** Workshop - MOCRINIS is intended as a platform to discuss the complexity of these topics and through a joint effort, find a way forward.

Why MOCRINIS?

<u>M</u>ineral <u>O</u>il: is it an issue of Mineral Oil or hydrocarbons in general or is it about products or fractions of hydrocarbons?

<u>Cr</u>oss <u>In</u>dustry: It is not only about printing inks; hydrocarbon complex substances are used in different downstream industries regulated by different legislations.

<u>I</u>ssue<u>S</u>: The issues are not easily resolved because of the complex nature of the substances and the overlapping hydrocarbon ranges of complex substances (and background hydrocarbons). There are differences in the toxicological interpretation of available studies and uncertainties in analytical procedures to ensure compliance. There is a need to identify the practical approaches that are required to resolve this complex issue.

4. SETTING THE SCENE ON MINERAL OIL

4.1. MINERAL OIL ORIGIN, PRODUCTION, COMPOSITION

(A. Hedelin, Nynas AB)

Petroleum products originate from crude oil which is a complex combination of hydrocarbons extracted from the ground. The compositions of petroleum products are linked to their refinery history. All petroleum products are refined to meet a pre-set performance specification.

To assist in the collection and assessment of toxicological information the petroleum substances have been arranged into 18 categories, ranging from short carbon-chained products like gasoline to longer-chained substances such as bitumen.

Mineral oil is an unspecific term which has numerous definitions. Being derived from crude oil, petroleum substances are by nature complex in composition. They include many petroleum products categories and can be used for several applications including fuel, heating and base oils. Fuels are less refined petroleum substances and are often only straight-run (distilled from crude oil without any further treatment) while base oils can be highly refined including by severe hydrotreatment. The refinery history defines the composition and hence the toxicity of the products. Base oils are categorised as either Lubricant Base Oils or Highly Refined Base Oils, where the toxicity is linked to degree of refining. IP346 is the analytical method used to distinguish between carcinogenic and non-carcinogenic base oils.

4.2. ANALYTICAL CHARACTERISATION OF MINERAL OIL

(S. Forbes, Shell Global Solutions)

Petroleum products are very complex mixtures of predominantly hydrocarbon components. The lighter products, such as gasoline, contain a few hundred individual components but heavier materials, such as lubricating oils, contain many millions of components. These components typically span a carbon number range from 4 to >50 and may contain single or combined chemical functionalities (paraffinic, naphthenic, aromatic). Although petroleum products are manufactured primarily to meet performance specifications for their use as fuels, lubricants, solvents etc., analytical techniques have been developed to provide detailed information on the chemical composition of these substances.

Information was shown to demonstrate the type of chemical compositional information that has been derived to characterise gasoline, conventional diesel fuel, diesel fuel derived from vegetable oil and lubricant base oil. The need for clear definitions of MOH, MOSH and MOAH as groups of specific hydrocarbon components was highlighted. The question was also raised as to how it would be possible to distinguish between hydrocarbons originating from a petroleum substance as opposed to those originating from vegetable oil.

4.3. MINERAL OILS IN PRINTING INKS

(E. Frank, Flint Group Germany GmbH, for EuPIA [European Printing Ink Association])

For many decades mineral oils have been typical raw materials for nearly all types of offset inks. These mineral oils have been and continue to be used, due to their physical properties, to adjust rheology, drying properties and other important characteristics of offset inks. Mineral oils classified as either Toxic, Carcinogenic, Mutagenic or Toxic to reproduction according to REACH/CLP are not used in printing inks. Normal offset inks are generally not classified at all according to DPD/CLP and are considered safe for their intended use. Mineral oil-free sheet-fed offset inks for food packaging (low migration) and other applications have been considered state-of-the-art for many years. Although it is feasible to use Mineral oil-free offset inks to print newspapers and magazines there has been no significant request for such inks up to now. It should be mentioned, that such mineral oil-free inks may show differing properties and are more expensive.

For the further development of mineral oil-free inks, the printing ink industry requires clear product definitions, with an indication of which types of hydrocarbons are acceptable in such inks and their applicable limits for migration into food.

4.4. MINERAL OILS IN CARTONS

(J. Cardon, European Carton Makers Association [ECMA])

Following the publication in 2010 of data showing high levels of MOSH (up to 80/mg/kg) migrating from cardboard cartons produced from recycled paper and also at lower levels from virgin cartons, ECMA (European Carton Makers Association) and the broader paper and board industry platforms evaluated ways of preventing such an occurrence and concluded that this might be achieved by either:

- Using only Mineral oil-free printing for all paper and board applications,
- Introducing a cleaning out step in the recycled pulping process,
- Making an appropriate selection of recovered paper flows, or
- Introducing barriers on the reverse side of the cardboard.

The two first options were considered as not achievable in the short term or not efficient enough. The so called optimised recycled board grades using less contaminated waste paper categories and barrier boards were commercialised.

At the converting carton manufacturing level, ECMA recommended its members to “use only low migration inks for food packaging” and “confirmed the safety of standard recycled cardboard for food packaging if combined with an appropriate functional barrier” adding that “a responsible, safe, direct contact application of recycled cardboard remains possible for specific food types in combination with a systematic risk assessment”. ECMA published its detailed GMP (Good Manufacturing Practice) in October 2011 which included recommendations for compliance and guidance on inks and varnishes.

For cartons made according to the ECMA GMP, the migration of hydrocarbons should remain very low.

From a broader paper and board supply chain perspective, ECMA raised questions at the Workshop regarding the composition of the hydrocarbons used for paper and board articles, whether it is possible to look into the subclasses of the MOAH fraction, to check the absence of a certain number of genotoxic carcinogens and whether it is possible to eliminate those substances if present.

At the policy level, ECMA questioned the proportionality of an overall very low limit for MOAH. Certain MOAH substances are relatively safe or have been assessed thoroughly.

The need was highlighted for all sources of hydrocarbons to be taken into account and that solutions should also be assessed from a recycling and EU recycling targets perspective. The outcome of the advent calendar issue in Germany in November 2012 confirmed that other non-packaging sources can also lead to hydrocarbon contamination in food.

Still with respect to legislation it was felt that there should be identical requirements for imported packs and that there is a need for harmonisation at the EU level.

To conclude, ECMA stressed the need for open adequate communication and a strict safety commitment in the supply chain.

4.5. MINERAL OILS, THE POINT OF VIEW OF THE PAPER INDUSTRY

(E. Cavallini, Confederation of European Paper Industries [CEPI aisbl])

The mineral oil issue is considered by all stakeholders, industry and regulators alike, as a complex issue with a high degree of uncertainty. Uncertainty surrounds definitions for mineral oil saturated hydrocarbons (MOSH), mineral oil aromatic hydrocarbons (MOAH), polyolefin oligomeric saturated hydrocarbons (POSH), etc., the analytical methods that have been used and also a concern that there is a lack of toxicological information. The EFSA CONTAM panel scientific opinion confirms that overall uncertainty is substantial.

As an example Cavallini informed delegates at the Workshop that a German consumer foundation (Stiftung Warentest) published test results demonstrating that mineral oil hydrocarbons were present in most chocolates in 24 advent calendars available in Germany. It was also reported that recycled cardboard packaging was the source of the mineral oil. Subsequently it was demonstrated that of the 24 advent calendars, 23 had been made from virgin fibres, and in 23 cases mineral-oil free inks had been used, the details of the analytical methods used were not known, that mineral oils were found in the large majority of samples and that the findings had been based on assumptions that the source of contamination was recycled board.

The lack of a scientific basis for the conclusion relating to the occurrence of hydrocarbons in chocolate has led to uncertainty which in turn may lead to hasty and wrong conclusions especially if it is influenced by prejudice.

In summary, the point of view of the European paper industry is that there is a strong need to investigate the topics on a scientific basis as the only possible way to make progress and to avoid prejudice, as well as to cooperate transparently along the supply chain.

4.6. MINERAL OILS AND FOOD. A PARTNERSHIP FOR THE FUTURE?

(A. Adam, FRAGOL GmbH & Co. KG)

Mineral oil hydrocarbons may enter the food chain from either their intentional use (e.g. mould release agents), via incidental food contact (e.g. from food production equipment) or by migration from other materials such as food packaging. Globally, the most commonly-used guidelines are those of the FDA which permits the use of mineral oils in many foods with restrictions on the maximum permitted amount for each use. In addition to the permitted uses, contamination within the food supply chain may also occur from the use of mineral oils for corrosion protection, leakage, equipment design or as a consequence of human error.

The lubricant producing industry and the food producing industry receive mixed messages when operating in the international field.

In many markets outside the EU the use of mineral oils are accepted and regulated whereas inside the EU the finding of hydrocarbons in some foods has led to widespread negative reaction in the media and this has given rise to questions regarding their use in food.

This has led to concern and confusion that needs resolution for the industry to operate globally. There is a need to alter the course of discussions around mineral hydrocarbons from an emotional to a factual, balanced consideration.

4.7. DISCUSSION SESSION

Some confusion has arisen because the EFSA CONTAM panel opinion had referred to technical grade mineral oil and had also commented that composition was unknown. During the discussion this was clarified; the term technical grade oil was referring to anything other than food grade mineral oils and the lack of toxicological information was related to the hydrocarbons found in food, not to the food-grade mineral oils or technical grade oils themselves on which there is a substantial oral and dermal toxicity database respectively.

In trying to distinguish between the different sources of hydrocarbons, a question was raised as to the possibility of identifying a chemical marker that could be used to help identify the source. However, it was generally agreed that this would not be possible because the same hydrocarbon molecules are present in different products. It would be difficult to make a distinction between hydrocarbons originating from food or non-food grade oils, as well as those which are naturally-occurring hydrocarbons.

Members of the Workshop were informed that the hydrocarbons reported to have been found in chocolate possibly could have entered the food chain from the use of jute sacks that were used to store cocoa beans. It is a common practice globally to soften the jute sacs by treating them with mineral oil despite existing regulatory opinion on this practice. Other delegates agreed that there may be several possible sources of hydrocarbons that were found in chocolate.

5. TOXICOLOGY OF MINERAL OILS

5.1. MAMMALIAN TOXICOLOGY AND TOXICOKINETICS OF MINERAL OIL

(P. Boogaard, Shell International)

Crude oils are carcinogenic due to the presence of benzene and polycyclic aromatic hydrocarbons (PAH). Simple refining by distillation doesn't alter the molecules it merely separates them into different boiling fractions. Less refined base oils that contain PAHs may be carcinogenic to the skin. Base oils which have undergone more severe refining, resulting in removal of most PAHs, are not dermal carcinogens.

The industry has conducted mouse skin painting studies on many petroleum substances but because these studies are costly and time consuming other techniques have been developed to distinguish between carcinogenic and non-carcinogenic petroleum substances. For lubricant base oils an analytical procedure (IP346) and a modified Ames assay have been developed and by using one or both of these techniques, the industry has been able to ensure that all base oils placed on the market are non-carcinogenic.

White oils are highly-refined base oils (HRBO) and contain no aromatic components. Historically, oral studies on these oils were carried out in Long Evans rats and in beagle dogs and no treatment-related effects were found apart from a mild laxative effect in the study with beagle dogs. Special staining techniques (Oil Red O) were used in the microscopic examination of tissues taken from the animals in the studies and no evidence was found of accumulation of mineral hydrocarbons. Overall, the results confirmed the previously-held view that white oils are non-hazardous.

Recently 90-day repeat-dose oral studies of a range of white oils and highly refined waxes have been carried out in Fischer 344 rats. Two main effects were observed. These were histiocytosis of mesenteric lymph nodes and the occurrence of inflammatory hepatic microgranulomas. The mesenteric lymph node changes were regarded by EFSA as most probably a non-adverse effect, whereas the liver lesions are regarded as a critical effect.

In an attempt to evaluate the relevance of the findings in the F344 rat for humans, single dose pharmacokinetic studies were conducted in F344 and Sprague-Dawley (SD) rats and in humans. The results demonstrated that the F344 was more sensitive than the SD rat and humans appear to be less sensitive. It was also demonstrated that blood concentrations can be correlated to liver concentrations of hydrocarbon and can therefore be used as an internal marker for mineral hydrocarbons. In the study with humans, no hydrocarbons were detected in blood after the administration of mineral oil as a single dose of 1 mg/kg.

5.2. OVERVIEW OF METABOLIC DIFFERENCES

(J.-P. Cravedi, French National Institute for Agricultural Research [INRA])

Mineral oils may accumulate to a significant extent in animals and humans and substantial differences in the toxicity of these hydrocarbons have been reported between rat strains. The metabolism of lipophilic compounds such as mineral oils is a dominant factor in determining the extent to which these chemicals may accumulate in various tissues. Metabolism involves enzyme-mediated reactions able to convert a substrate (in this case n-, branched- and cyclo-alkanes) to polar, readily excretable molecules. These enzymatic transformations are generally a multistep process. For instance for alkanes, the hydrocarbon may undergo a reaction of oxidation, catalysed by cytochrome P450, and resulting in the formation of an alcohol group; this first sequence is usually followed by additional oxidation and hydrolysis steps but can alternatively be a preliminary step prior to conjugation to an endogenous compound such as glucuronic acid, amino acids or sulphate, before ultimate elimination as a conjugate metabolite. The presentation gave an overview of the in vivo and in vitro metabolic pathways of n-, branched- and cyclo-alkanes.

In addition to the description of the biotransformation routes of the different classes of alkanes, a focus was given on the metabolic rates of these compounds. These rates were investigated in liver microsomes obtained from 3 rat strains (Wistar, Sprague Dawley and Fischer) and from humans using pure radiolabelled compounds (C^{14} heptadecane, H^3-pristane, and H^3-dodecylcyclohexane) incubated individually at different concentrations. After incubation with the subcellular fractions, the hydrocarbons and corresponding metabolites were extracted, then separated and quantified by radio-HPLC. Hydroxylation rate was evaluated from the sum of the different metabolites. In these experimental conditions, no metabolism was observed for the representative branched- and cyclo-alkanes pristane and dodecylcyclohexane. In contrast, the representative n-alkane heptadecane was biotransformed at a significant extent in both rat and humans. Average metabolic rates (expressed as pmol/hr/mg prot) observed at 60 µM (the highest concentration tested) for heptadecane in rats and humans were: for Wistar strain 95 ± 28 and 134 ± 49, for males and females, respectively; for Sprague Dawley 78 ± 32 and 148 ± 47, for males and females, respectively; for Fischer 101 ± 20 and 76 ± 38, for males and females, respectively, and for humans 159 ± 46 and 180 ± 10, for males and females, respectively.

Major conclusions from this experiment on model compounds were that for females, heptadecane is metabolized at a higher rate in humans compared to Fischer and also in Sprague Dawley compared to Fischer, whereas in males, no significant differences were detected between rat strains or between rats and humans.

Part of *the data in this presentation were obtained thanks to* a *contract between INRA and EFSA (NPIEFSAICONTAMI2011103), however, the conclusions do not necessarily reflect the position* of *EFSA, its Scientific Panels or Committee or any* of *any body* of *the European Union.*

5.3. MINERAL OIL HYDROCARBONS (MOH) AND HUMAN PATHOLOGY

(K. Fleming, Royal College of Pathologists)

Until relatively recently, investigations into possible toxicity of Mineral Oil Hydrocarbons (MOHs), which are widely present in many foods, had not shown any evidence of harm. However in 1992 the finding of dose–dependent granulomas in the liver of Fischer 344 rats caused this conclusion to be questioned. Later experiments confirmed these findings, further raising the question of potential human toxicity.

In this regard, it has been known for years that MOHs accumulate in up to 40-50% of human livers and that they are associated with minimal macrophage granulomas (called lipogranulomas), but, crucially, there has been no evidence of any clinical significance.

However, as these innocuous mineral oil granulomas are morphologically dissimilar to the most severe F344 granulomas, two questions arise. First, are any lesions, which are morphologically similar to the severe F344 lesions, ever found in human livers? Second, if so, is there any evidence that they are related to MOH accumulation?

To attempt to answer these questions, four further questions are addressed. How often do granulomas occur in human liver, what types are they, what are the causes, and what is the outcome?

The literature shows that, excluding lipogranulomas, granulomas occur in around 5-10% of all liver biopsies which range in type from histiocytic to large necrotising lesions. There are around 100 causes of liver granulomas such as tuberculosis or sarcoidosis and the outcome depends on the cause.

However, crucially in around 10-25% of liver granulomas their cause is unknown. This then raises the question of whether some/all of these unexplained granulomas could be atypical reactions to MOHs?

There is no evidence that this is the case. Moreover, even if it was the case, all the evidence is that such cases are not progressive and that the prognosis is excellent.

However, if one were to assume a worst-case scenario, to get an idea of the potential scale of the problem, it is guesstimated that there might be between 80-400 such cases a year in the UK and around 640-3200/year in the EU. Even if one assumed that as many as 5% showed clinically significant progression – and all the evidence is that patients with unexplained granulomas were MOH-related, the numbers are small (say 1200/year in the EU). All/most cases are non-progressive and it is guesstimated that, at worst, 12 do not have progressive liver disease - then this would mean between 32-160 cases/year in the EU population of 500 million.

In conclusion, given the lack of any clinical significance in the known MOH-lesions in human livers, the absence of any evidence linking MOHs to F344-like granulomas in human liver, and the minimal numbers involved in even the worse-case scenario, the conclusion is that MOHs do not pose a significant public health hazard to humans.

5.4. DISCUSSION

It was acknowledged that liver microgranulomas in humans might have occurred as a result of past exposures to mineral hydrocarbons and that there is a need to know if the situation has changed due to any change in current exposure patterns.

However, the group was informed that there is no good evidence that liver granulomas currently observed in human liver samples are related to exposure to mineral oils.

One question was whether the population in which the liver biopsies were reported on are representative of the normal population. In response to this question it was stated that those patients who have had liver biopsies are a subset of the general population because they are suspected to have some kind of liver disorder.

It was questioned whether the blood or liver hydrocarbon levels had been determined in those patients who have had liver biopsies. It was believed that hydrocarbon levels had not been determined. However, in the early days, some estimates had been made for those patients with lipogranulomas and that it might be of interest in the future to determine hydrocarbon levels in those patients who have unexplained liver microgranulomas.

A comment was made that although there seems to be dermal carcinogenicity data on lubricating base oils and highly refined base oils and oral toxicity data on food grade mineral oils there doesn't appear to be any oral repeated-dose toxicological data on lubricating base oils. This is considered to be especially important since these might be the materials entering the food chain.

To address this concern, the group was informed that the saturated molecules present in food-grade oils are the same as those present in lubricating base oils. The only difference between the two types of oils is that there are no aromatic hydrocarbons in the white oils because they have been removed through additional refining processes required in order to meet the more stringent analytical specifications set for white oils. Further, the technical oils are not intended for oral ingestion and no oral studies have been conducted on them. Since no systemic effects have been observed in the dermal studies, there has not been an identified need to carry out further oral toxicity studies on technical oils.

Workshop delegates were informed that in the food industry there is much more awareness that ingress of oil into food should be avoided. As a consequence and also because of the control of points at which hydrocarbons could possibly enter the food chain it is expected that exposures from food are likely to be less in the future.

6. RISK ASSESSMENT

6.1. MINERAL OIL HYDROCARBONS IN FOOD, SCIENTIFIC OPINION OF THE SCIENTIFIC PANEL ON CONTAMINANTS IN THE FOOD CHAIN (CONTAM)

(M. Binaglia, EFSA)

Following a request received from the European Commission, the EFSA Panel on Contaminants in the Food Chain (CONTAM Panel) assessed the risks for human health related to the presence of mineral oil hydrocarbons (MOH) in food. A wide range of MOH are present in food, both as a result of contamination and from intended uses during food production.

The CONTAM Panel identified the main sources for the presence of MOH in food, including food packaging, additives, processing aids and lubricants. Depending on the source, MOH containing virtually only saturated hydrocarbons (MOSH), or 10-35% of aromatic hydrocarbons (MOAH) can be found in food. However, the characterisation of the occurrence in several foods is limited by the presence of MOH from different sources and by the analytical limitations for these complex mixtures. The available occurrence dataset allowed for the estimation of the exposure levels for MOSH only. Exposure levels up to 0.3 mg/kg b.w. per day were estimated for background concentrations of MOSH, reaching up to 6.4 mg/kg b.w. per day if specific applications are considered.

The CONTAM Panel considered the formation of liver microgranulomas in a sensitive species as the key effect for the hazard characterisation of MOSH. The lowest NOAELs for liver microgranuloma observed in different MOSH grades were used as Reference Points for the risk characterisation following a margin of exposure (MOE) approach. For the different exposure scenarios, MOEs ranging from 59 to 680 were calculated, leading the CONTAM Panel to conclude that there is a potential concern associated with the dietary exposure to MOSH. No quantitative risk assessment was performed for MOAH. However, in view of the possible genotoxicity and carcinogenicity of some MOAH, the CONTAM Panel considered the exposure to MOAH through food to be of potential concern.

6.2. INTERPRETATION OF EXPOSURE DATA AND PATH FORWARD

(D. Tennant, Food Chemical Risk Analysis)

An explanation was given of how exposure data were generated in scenarios ranging from the simple in which exposure is estimated from a single eating occasion to more complex when intake is estimated from multiple food sources.

Dietary exposure analysis is a relatively new discipline and the approach used varies by sector. For example contaminants experts use occurrence to mean distribution of possible concentrations across all foods whereas additives experts use occurrence to mean the proportion of the supply that contains the additive. Exposure estimates for food contact materials is based on migration coefficients. For processing aids there is not an established approach. Taken overall it is clear that combining exposure data from different sources presents a challenge if outputs are to be realistic.

The potential sources of exposure to mineral oil hydrocarbons are wide-ranging and include a variety of food contact materials, contaminants as well as food additives, processing aids and other sources. There are large uncertainties in exposure data and some of these relate to the occurrence of hydrocarbons in food and include the use of incomplete data, use of data from old studies, use of data generated predominantly from one geographical location, etc. The following questions were raised with respect to the available data on mineral oil hydrocarbons:

- Are data obtained up to 20 years ago relevant to current food industry practices?
- Can targeted samples taken for compliance testing be relied upon?
- Are available data representative of practices across the EU?
- Are there sufficient data points for some food categories?

There are also uncertainties in exposure data relating to food consumption and exposure scenarios particularly in the identification of the major sources of exposure.

The following proposals were made for further investigations and a path forward:

- Consult with food industry experts to identify current practice in relation to:
    - Bakery release agents
    - Bakery dough dividers
    - Grain de-dusting
    - Confectionary release agents
- Base monitoring plans and revised exposure estimates on current practices
- Identify MOH class (molecular mass, carbon number, etc.) in surveys
- Identify source of packaging migrant exposure data covering all applications and taking usage patterns into account possibly using the FACET system
- Investigate models for estimating total vegetable and animal fat consumption
- Consider options for generating appropriate models of long-term chronic/cumulative exposure.

7. PANEL DISCUSSION

Panel members: P. Boogaard, J.-P Cravedi, D. Tennant, D. Benford and K. Fleming

The following comments were raised and/or discussed:

- A question was raised about the timescale of exposure, and if it was possible to be modelled in a realistic way.

- It was acknowledged that there is a need to obtain more precise exposure data and also identify any trends in exposure patterns.

- It was stressed that what humans are exposed to in food is not what the rats were exposed to in the toxicity studies on food-grade mineral oils and therefore, there is a need to identify and characterise the hydrocarbons to which humans are exposed. In addition it was suggested that there is a need to assess hydrocarbon body burden.

- There was a short discussion on the time it takes for microgranulomas to develop, and although it was known that in rats the timescale is short (possibly 1-2 days), there is no indication of progression of such a lesion over time in humans.

- Although estimation of exposure was important, the need for exposure data was probably unnecessary if a significant hazard had not been identified. Furthermore, since there was no indication of a health problem in humans and that microgranulomas only occur in F344 rats there would be a preference to focus attention on human health effects, rather than on exposure.

- From a regulatory approach, there was a need to look for evidence of safety rather than evidence of harm. Also, both JECFA and EFSA had stated that liver granulomas are of concern and furthermore hydrocarbons have been observed around the liver granulomas found in humans.

- A question was asked that if there is no evidence of harm, why we should be concerned. In response it was stated that current evidence of no-harm relates to exposures that have occurred over decades and if human exposure to hydrocarbons has increased, evidence of no harm now is insufficient.

- During the discussion, workers in the newspaper printing industry were identified as a group of individuals who are likely to have been exposed to high levels of mineral oil and there is no evidence of health effects among this population.

- The need for more information on the apparent differences between the F344 rat, the SD rat and humans was highlighted. The only pharmacokinetic study in humans had been a single dose study and a repeated-dose study was needed to evaluate the potential of hydrocarbons to accumulate in humans.

- There seemed to be some confusion as to whether mineral oils contain aromatic hydrocarbons. It was explained that the mineral oils approved for food use are free of aromatic hydrocarbons, but other products derived from crude oil such as fuels and some lubricating base oils may contain aromatic hydrocarbons

- It was stated that the use of recycled fibre and the use of lubricants, etc., is increasing.

8. REGULATORY FRAMEWORK

8.1. COMPARISON OF VARIOUS EUROPEAN FOOD REGULATIONS

(R. Semail, Keller and Heckman LLP)

An overview was given of the rules applicable to mineral oils in food contact legislation, food additive legislation and pesticides legislation. An EU Framework regulation provides the general provisions and principles for food contact materials (FCM). The regulation is to ensure the effective functioning of the internal market and provides the basis for securing a high level of protection of human health and the interests of consumers. In addition individual EU Member States have implemented specific food contact legislation and examples were given of the types of limits etc., set for hydrocarbons in The Netherlands, Spain, Germany, France and Belgium. The EU Regulation on Food additives lays down the rules on additives used in food and has the same objectives as those for FCM, but additionally takes into account, where appropriate, the protection of the environment. The Regulation requires the creation of a positive list of food additives. The requirements for National legislation in France for mineral oils were summarised. Plant protection products are also covered by an EU Regulation which requires that active substances must be approved at EU level.

For each of the three regulations identified above, the European Food Safety Agency (EFSA) is responsible for carrying out the evaluation. EFSA requires information to be provided on chemical properties and intended application, information on levels of exposure to food and information on toxicological properties. For the pesticide regulation, there is an additional requirement to provide information on the effects on workers, the environment and non-target plants and animals. It was noted that:

- There was a large disparity of the mineral oils that were subject to legislation and restrictions, both at EU and national level.
- The names used in different (and sometimes within the same) sets of legislation are not consistent.
- For mineral oil hydrocarbons the limits are mainly set for<C16 fractions.
- Most limits set in the food contact and food additive legislation are for MOSH only.

Generic restrictions exist for mineral oil hydrocarbons without size restriction, but they address the (poly) aromatics present in the hydrocarbon substance.

8.2. UNDERSTANDING THE REQUIREMENTS OF EU FOOD CONTACT REGULATIONS (NON-PLASTIC MATERIAL)

(A. Schäfer, DG SANCO, European Commission) [NB Summary prepared by B. Simpson]

Food contact materials (FCM) are covered by Framework regulation (EC) 1935/2004 and are defined as materials:

- Already in contact with food
- Intended to come into contact with food
- Reasonably expected to come into contact with food

Contact can arise through food packaging, from food processing machinery and/or from kitchenware or tableware.

The regulation which is applicable to all FCM is designed: to ensure that they do not endanger human health, do not change the composition of the food in an unacceptable way, do not mislead the consumer, are manufactured according to GMP, ensure traceability and also cover labelling requirements. The regulation on GMP (2023/2006) which applies at all manufacturing stages except the starting materials requires that a quality assurance system is in place and that there is adequate documentation and quality control.

For materials for which the EU has not adopted scientific measures national legislation exists that addresses specific materials.

Future developments and challenges include how to address non-harmonised materials. For instance how should materials be prioritised, how to identify what needs to be regulated and how it should be regulated. In addressing these topics there needs to be consideration of the administrative burden for authorities and industry and also identify the economic impact regulation might have.

A roadmap was described for a way forward, the overall objective of which is to ensure that safe FCM are placed on the EU market and to improve the functioning of the internal market. In preparing the roadmap problems were defined relating to the safety of materials on the market and on the incomplete functioning of the internal market. With respect to materials on the market, the following problems were identified: limitations on national risk assessment, limitations on enforceability, limitations on enforcement and limitations on GMP and risk assessment at the industry level. The parties affected included member states, FCM manufacturing industry, food industry using FCM, importers, manufacturers in third countries, risk assessment bodies and testing institutes.

The options that seem to be available include:

- No action at EU level, leaving Member States to set up specific requirements at national level.
- Establish lists of substances, materials or processes used together with migration limits.
- Establish negative lists of substance not to be used in FCM.
- Set out obligations and criteria for risk assessment of substances and/or materials.
- Set out obligations and criteria for information exchange throughout the manufacturing chain.
- Set out detailed material specific rules on GMP.
- Combinations of the above.

The impact of the various options needs to be assessed.

8.3. DISCUSSION

There were no questions or further discussion following the two presentations in this session.

9. ANALYTICAL METHODS FOR MINERAL OILS

9.1. THE COMPOSITION AND ANALYSES OF OIL FRACTIONS PRESENT IN FOOD

(J. Beens, Consultant, University of Amsterdam and Free University of Amsterdam)

In view of the different behaviour of the different types of hydrocarbons present in oil fractions in the human body, it is necessary to get as much information from these fractions as possible. This is particularly true for (poly)aromatic species, i.e. parent compounds apart from (highly) branched compounds.

The analyses of oil fractions (middle distillates) in this respect can be performed in 3 different ways:

1. Off-line (pre-separation) by HPLC of saturates (MOSH) and aromatics (MOAH) on a NH_2 silica column by collection of the two fractions, followed by GC analyses of the fractions for quantitation. Manual method.

2. HPLC coupled on-line to GC for the (pre) separation of MOSH, mono-aromatics, di-aromatics and tri-aromatics, and quantitation and speciation of some aromatic compounds of all the fractions on the GC. Can be automated.

3. On-line coupling of HPLC to comprehensive two-dimensional GC (GCxGC), for the (pre) separation of MOSH and MOAH, followed by quantitation and a thorough speciation of compounds in these two fractions. Can be automated.

Obviously, the 3rd method provides more information than the other two and is not more labour intensive. However, not all laboratories are equipped or familiar with the GCxGC methodology. Some information was given to explain the working of GCxGC and its advantages.

9.2. LATEST DEVELOPMENTS ON MOSH/MOAH METHODS

(P. Stolper, The Graphic Technology Research Association [FOGRA])

Currently, there are two methods published by Bundesinstitut für Risikobewertung (BfR) for the determination of MOSH / MOAH (mineral oil saturated hydrocarbons / mineral oil aromatic hydrocarbons) compounds in paper, board and foodstuff. These are online-coupling of LC-GC (determined as reference method) and group separation of MOSH and MOAH prior to GC analysis (so called manual method) according to BfR. In both cases the detection after GC separation is done by flame ionisation detection.

However, the methods have limitations, for example when analysing virgin fibre-based paper according to the manual method, a certain amount of MOSH and MOAH will be detected. This was shown by Fogra during a round-robin study in 2012 in which different samples were distributed to various laboratories, including virgin fibre-based paper, recycled paper and print products with mineral oil free ink and mineral oil containing ink.

The limitations of the methods were analysed at each major step and discussed in detail for the manual method.

Sample preparation and extraction steps are fairly robust and the effect of random errors is small. The subsequent solid phase extraction (SPE) step that is necessary to obtain the MOSH and MOAH fractions can show poor repeatability of test results, as the SPE material - silica gel with 0.3% silver nitrate - is not commercially available and has to be prepared for each new SPE column. One result of this research showed that the quality of the silica gel is important for the fractionations of the extract in MOSH and MOAH. It is also possible, that components not originating from the mineral oil, elute within these two fractions, for example DIPN (Diisopropylnaphthalene) or olefin compounds, and lead to false test results.

The concentration step following the SPE separation can discriminate low-boiling components and lead to an overestimation of the high-boiling components.

One of the most difficult problems appeared to be the way of integrating the GC-chromatograms, which is necessary for the quantification of the contaminants. This topic was discussed in the course of the latest round-robin study by the Berlin Kirchhoff Institute in which 17 laboratories from Germany and Switzerland participated. According to the report dated July 2013, 332 mg/kg (standard deviation 23%) of MOSH and 96 mg/kg (standard deviation 20%) of MOAH was found in recycled board. The question concerning the handling of single peaks was discussed, as some laboratories subtracted all single peaks, some did not and others only subtracted some peaks that did not originate from mineral oil. In the course of this round-robin study a position paper was prepared which included proposals for integration, possible clean-up steps and a statement, that a standard deviation of ±25% with an uncertainty of measurement of 50% is proposed and probably feasible.

An alternative method was introduced by the FABES research group (FABES Forschungs-GmbH for Analytic and Evaluation of Diffusion Processes) using mass spectroscopy to obtain structural information about the analytes and in this way determines the amount of MOAH. This method, which was originally set up for testing recycled board only, has been modified in a still ongoing research project of Fogra and FABES in order to get results comparable to those obtained by the BfR methods. In the two above mentioned round-robin studies of Fogra and the Kirchhoff Institute, the modified FABES method was also tested and the results were close to the results obtained by the other participants but showed slightly increased amounts of MOSH and real MOAH. An advantage of this method lies in the fact that it gains and uses structural information about the components for the quantification of "real" MOAH and that it does not need a LC-GC on line system.

At the present time, the BfR has not accepted this method.

9.3. SAFETY OF RECYCLED PAPERBOARD: MINERAL OIL CONTENT DETERMINATION IN FOOD, MIGRATION TO FOOD AND CLEAN-UP STRATEGIES

(I. Braschi, University of Bologna)

Direct determination of mineral oil (hydrocarbons) content in printed and/or recycled paperboard can be useful to avoid the difficult prediction of its long-term migration into food. Since the design of studies to determine migration for these contaminants in food packaging is still controversial, reliable analytical tools are required. In contrast to the partial evaluation of hydrocarbon isomers performed by GC-MS analysis, on-line coupled normal phase HPLC-GC-FID is able to measure the whole mineral oil content. Evaporation experiments show that hydrocarbons eluting up to about n-C24 are sufficiently volatile for relevant migration to occur into dry food (Lorenzini et al, 2010). The extraction of the paperboard was optimized to recover both the mineral oil saturated hydrocarbons (MOSH) and the aromatic components (MOAH), and also to discriminate against those of high molecular mass which tend to disturb the GC-FID analysis. The influence of time, storage conditions, food packaging structure and temperature on the migration of mineral oil to commercial products packed in recycled paperboard was monitored up to their shelf life end (ea. 1 year) (Lorenzini et al, 2013). Their migration to food whose packs were kept in transport boxes was the highest, followed by shelved and free-standing packs. Interestingly, the transfer to dry food is mediated by the "sponge effect" of polyolefin barriers which is due to their chemical affinity to hydrocarbons. After a "lag time" previously-retained hydrocarbons are released from the polyolefin barrier into the food (Lorenzini et al, 2013). Interestingly, migration tests at increased temperatures not only accelerated migration, but also widened the migration of hydrocarbons to include higher molecular masses, thus highlighting difficulties in interpretation of data from accelerated simulation (Lorenzini et al, 2013). A study aimed at cleaning-up paper polluted with hydrocarbons by means of innovative and environmentally friendly recyclable additives able to retain hydrocarbons during the productive process is currently underway.

10. PANEL DISCUSSION

Panel members: J. Beens, S. Forbes and P. Stolper.

The following topics were discussed:

- When asked about the results of "washing out" studies, Braschi stressed that the results shown were preliminary results, but it was possible to separate out 70% of the residual hydrocarbons from the most polluted Italian newspaper material available.

- When asked why there is a need for a new method when the existing BfR method was considered to be the gold standard Stolper replied that the method he had developed was an improvement on the BfR method since it had a much lower standard deviation. It is important to know, therefore, if the new method would be acceptable to the German authorities.

- It was explained that the current methods of analysis of hydrocarbons are costly and time-consuming and that there is a need for a simple screening technique for saturated and aromatic hydrocarbons. Samples found to contain hydrocarbons can then be characterised and quantified using sophisticated techniques. Screening methods are needed for testing large numbers of food surveillance samples and for quality assurance purposes for downstream users. Other delegates agreed with this view but recognised that, at the present time, they were not aware of how this might be accomplished.

- Given the lack of granularity in current analytical techniques and accepting that food contamination may be from several sources, a question was raised whether it was correct to assume the contamination was mineral oil. It was suggested that since it was not possible to distinguish between intentional and unintentional use, the materials should simply be described as hydrocarbons. Others confirmed that at the present time it was not possible to distinguish between hydrocarbons from different sources.

- It was concluded that because the source of hydrocarbons in food may not necessarily be mineral oil it would be preferable to call the hydrocarbons either saturated or aromatic hydrocarbons rather than MOSH or MOAH.

- From a pragmatic point of view, it was suggested that the term "mineral oil" should not be used, because of the confusion that has arisen, furthermore, chromatograms do not identify "mineral oil".

- It was generally recognised that there is a need for an agreement on definitions and nomenclature and that these should be related to method of analysis.

- It was asked whether bioaccumulation could arise from olive oil or sunflower oil. This question arose as a consequence of a presentation earlier in the Workshop. For clarification it was stated that in the earlier presentation the reference had been to hydrogenated vegetable oils and not to virgin vegetable oils.

- This being so, it was pointed out that hydrogenated vegetable oil is not the same as natural vegetable oil. If the molecules have many branched alkanes, they will not be metabolised in the same way as unbranched alkanes.

- It was stated there is a perceived issue relating to the presence and source of hydrocarbons in food and the size of the problem (if there is one) is not known.

- It was recognised that there is a need to better understand and identify all the possible sources hydrocarbons that might end up in food.

11. REPORTS AND CONCLUSIONS FROM DISCUSSION GROUPS

11.1. TOXICOLOGY AND RISK ASSESSMENT DISCUSSION GROUP

(J.-C. Carrillo)

The discussion group identified three broad areas of interest that needed attention; these were: accumulation, toxicity/hazard identification and exposure.

Accumulation

There needs to be a better understanding of the presence and sources of hydrocarbons detected in human liver biopsies and their relationship, if any, with the presence of microgranuloma.

The EFSA opinion cites old studies that relate accumulation to commercially-available white oils. Although older autopsy findings show accumulation, the source(s) of hydrocarbon is not known.

The relationship between the presence of (saturated) hydrocarbon in liver biopsies and microgranuloma was discussed. It is not clear if there is indeed any relationship, neither is it known whether any hydrocarbon is present in the microgranuloma. It was suggested that it may be possible to carry out laser capture dissection to determine whether there were any hydrocarbons in the microgranulomas. Even if hydrocarbon could be detected in the microgranuloma it would not necessarily be sufficient to demonstrate causality. The situation is complicated further because if hydrocarbon was found to be present in the liver but not in the granuloma, it would not necessarily mean that no relationship existed. It follows that the relationship between the presence of hydrocarbons in human liver and microgranuloma needs further investigation.

Toxicity/hazard identification

There was a consensus that hydrocarbons are present in human liver. The source of the hydrocarbons and whether they represent a hazard for humans is not known. In order to determine any potential hazard there is a need to demonstrate a causal relationship between presence of hydrocarbon in the liver and microgranuloma formation.

There still remains the issue of the relevance of the F344 rat model to risk assessment in humans, since to-date no studies have been conducted that would enable the F344 rat model to be considered irrelevant for humans. Although a single dose pharmacokinetic study in rats and humans had been carried out, it was not considered adequate and it might be helpful to conduct a comparative repeat-dose pharmacokinetic study in humans and in F344 rats in which dosing is continued until a steady state is achieved. This type of study would greatly assist in assessing the relevance of the F344 rat.

Some delegates believed that no systemic effects had been demonstrated in the subchronic toxicity studies that would warrant further testing, while other delegates disagreed with this view.

EFSA was unable to conduct a risk assessment of the aromatic hydrocarbons found in food because there are no chronic toxicity data on aromatic oils (lubricating base oils) other than dermal carcinogenicity data. There was a discussion on whether data from dermal carcinogenicity studies could be used to indicate systemic toxicity. Some delegates felt that this could be possible, since the reactive metabolites formed by carcinogenic constituents (PAHs) would cause tumours at the site of contact. Other delegates disagreed and felt that chronic oral studies were needed to assess long-term systemic toxicity.

It was recognised that not all aromatic hydrocarbons are carcinogenic and that there is a need to characterise the aromatic hydrocarbons that have been found in food in order to determine if there is any possibility of a carcinogenic hazard.

The need to conduct further oral studies was debated extensively and although it would be possible to conduct oral studies on aromatic oils or fuels, this was not considered worthwhile at the present time because of the uncertainty of the nature or source(s) of the hydrocarbons that have been found in food. It was suggested that once the hydrocarbons present in food had been characterised it would enable the selection of a suitable material for further study.

An alternative, preferable, approach might be to determine the chemical composition of the aromatic hydrocarbons found in food (the so-called “aromatic hump”). This might help to identify their possible source and also would enable a suitable test material to be selected for further animal toxicity studies.

Exposure

The question was raised as to whether there has been an increasing exposure to hydrocarbons over time and although there has been some suggestions that this might be the case there are no data to confirm this. Indeed in some areas it is believed that exposures to hydrocarbons have decreased over time. For example, in the past standard offset inks containing mineral oil were used to print on packaging made from paper and board, whereas for several years now, specially formulated low-migration inks have been used that are formulated without mineral oil. In the newspaper industry, poorly refined mineral oils may have been used 50 years ago but since then inks have been reformulated using mineral oils of lower aromaticity.

It was recognised there is a large measure of uncertainty around previously reported exposure estimates. There is a need therefore, to update the exposure data by conducting new exposure surveys.

The discussion group also identified a need to improve the nomenclature that has been used to describe the hydrocarbons to which humans are exposed.

11.2. ANALYTICAL METHODS DISCUSSION GROUP

(S. Forbes)

There were 17 participants in the analytical discussion group and about 30% of the participants had direct experience with the BfR MOSH/MOAH methodology, whilst others had been involved with contracting out such analyses.

The group considered that there was a lack of a robust, validated analytical method and that interpretation of chromatographic data is highly subjective. A need was identified for readily accessible methods. Concern was expressed about the complexity of some methodologies and they could not be used for screening purposes. A need for a consensus reference standard was highlighted, because it appears that different laboratories use a variety of materials as reference standards.

Before developing further methodology, there needs to be a clear definition of what needs to be measured. For example there is a need for methods capable of being used to measure specific hydrocarbon groups (saturates: C10-C16-C25-C35; aromatics <C25, C26-C35).

Recommendations from the discussion group were:

- There is a need for improvement of the BfR method
- Better guidance is required for interpretation of chromatographic data
- There is a need fora consensus reference standard (agreement with EFSA is needed)

The discussion group also raised the following questions:

- Is the issue Pan-European or wider?
- If wider, should CEN (European Committee for Standardisation) methodology be developed?
- Should sources of hydrocarbons in food and packaging be identified (EFSA recommendation)?

11.3. DOWNSTREAM USERS DISCUSSION GROUP

(A. Adam)

The discussion group identified the need for an inventory of intentional and unintentional sources of hydrocarbons and also recognized the need to prioritise them in order of importance.

It was felt that there is a need for a toxicological profile of the hydrocarbons to which humans are exposed. It was asked whether it is possible to extrapolate data from dermal exposure toxicity studies to oral exposure. Alternatively is there sufficient information already available so that industry can adjust its practices accordingly.

There was confusion about analytical testing. It was questioned whether the existing specifications are strict enough for all perceived intended food applications.

In view of the existing confusion over the safety of mineral hydrocarbons in food a need was identified for a clear message that could be communicated to customers.

12. RECOMMENDATIONS FROM MOCRINIS WORKSHOP

(B. Simpson, Consultant)

The participants, at a plenary session, agreed on the following general recommendations as a possible way forward to address the outstanding topics that required further discussion:

- **Identify methods/approaches leading to a better understanding of the pharmacokinetic/toxicodynamic differences between the rat and human models.**

  There still remains uncertainty about the relevance of results from studies using the F344 rat model for human health risk assessment. The previous pharmacokinetic study that was carried out in humans was a single dose study and is considered insufficient to address the questions relating to uptake and possible accumulation of Mineral oil hydrocarbons in the human livers.

  There is a need, therefore, to identify further approaches that may be used to address this issue. One possible approach would be to conduct another pharmacokinetic study in humans and in rats, but the study should be continued for a reasonable time period or until a steady-state plateau of hydrocarbon in the blood is reached.

  There is also a need to consider the possible relationship between hepatic hydrocarbon content and its relationship with the occurrence of microgranuloma. One possible way to address this would be to determine hydrocarbon concentrations in available blood and/or liver biopsy samples as well as other liver samples where possible and determine whether there is a relationship between the occurrence of microgranuloma and the presence of hydrocarbons, however the source of exposure would be difficult to identify. Alternative approaches to address this issue should also be considered.

- **Reduce uncertainty around exposure estimates to hydrocarbons that have been reported previously.**

  The current databases are at least 20 years old and requires updating. Hydrocarbons may enter the body via oral, dermal or inhalation routes of exposure from a variety of sources. There is a need to gain a better understanding of all the potential sources of exposure and any update should take exposure into account and also determine the contribution from food consumption.

- **Improve understanding on the potential toxicity of the aromatic hydrocarbon fraction detected in food.**

  Rather than conduct new toxicity studies on a range of petroleum products containing differing levels of aromatic hydrocarbons it would be preferable to target the studies to a test material which is representative of the materials to which humans are orally exposed. To achieve this it was suggested that the hydrocarbons found in food should be further investigated and characterised. This would allow the selection of a suitable test material for further toxicity study and allow a meaningful human health risk assessment.

- **Investigate options to resolve the confusion in nomenclature of hydrocarbons/mineral oils.**

  Throughout the Workshop there had been confusion over the terms MOSH and MOAH since they these terms imply that the hydrocarbons arise only from mineral oil when in fact they could arise equally from other sources, such as, vegetable origin. A suitable alternative nomenclature to MOSH and MOAH should be sought and clear analytical definitions provided to ensure there was no further confusion and ambiguity. The nomenclature ultimately agreed should be linked to the measurement method that has been used to identify the hydrocarbons.

- **Improve the available analytical methods available for hydrocarbon measurement.**

  There was general agreement that the available analytical methods could be improved and examples of how this might be achieved had been provided during the Workshop.

- **Provide guidance on interpretation of chromatographic data.**

  Interpretation of chromatographic data is subjective and gives rise to unnecessary variability in results. It was recognised that guidance would be useful in this area to help minimise variability from this source.

- **Identify suitable reference standards for the available analytical methods.**

  Currently, different laboratories use different reference standards for their analytical methods and this introduces another source of variability. It would be extremely helpful if suitable consensus reference standards could be identified and used by all laboratories working on the hydrocarbon issue. This would help ensure that the results from different laboratories could be directly compared.

- **Prepare a position paper which can be used to inform interested parties on the current state of the hydrocarbon issue.**

  At the present time there is confusion that has been caused by a variety of reasons including imprecise reporting of information, expression of prejudices, etc. To address and resolve the confusion, and to ensure that all stakeholders understand the current state of the issue, including the general public, it would be helpful if a statement of facts is prepared with an indication of the type of work planned or in progress. The statement should not be used to state opinions and bias but should be only factual.

- **Set up a stakeholder steering group.**

  To address all the recommendations and carry out the necessary work is an ambitious and large programme. Since there are a number of stakeholders it seems appropriate to create a steering group who would be responsible for ensuring that the issues are being addressed appropriately and to ensure progress is made with resolving outstanding hydrocarbon issues.

- **Hold MOCRINIS 2 as a follow-up from this MOCRINIS Workshop.**

  Consensus showed that to ensure that progress has been made and also to update all stakeholders of the progress and new information, there is a need to hold a second MOCRINIS meeting.

13. GLOSSARY

ADI	Acceptable Daily Intake
b.w.	body weight
BfR	Bundesinstitut für Risikobewertung
CEN	European Committee for standardisation
CEPI	Confederation of European Paper Industries
CLP	Regulation on classification, labelling and packaging of substances and mixtures
CONCAWE	The Oil companies European Association for Environmental, Health and Safety in refining and distribution
CONTAM	Scientific Panel on Contaminants in the Food Chain
DPD	EU Dangerous Preparations Directive
EC	European Commission
ECMA	European Carton Makers Association
EFSA	European Food Safety Authority
EU	European Union
EuPIA	European Printing Ink Association
EWF	European Wax Federation
FABES method	FABES Forschungs-GmbH for Analytic and Evaluation of Diffusion Processes
FACET	Flavourings Additives and Food Contact Materials Exposure Task
FAO	Food and Agriculture Organisation of the United Nations
FCM	Food Contact Material
FDA	Food and Drug Administration
FOGRA	The Graphic Technology Research Association Forschungsgesellschaft Druck e.V.
GC	Gas chromatography
GC-FID	Gas Chromatography - Flame Ionisation Detection
GC-MS	Gas chromatography - Mass Spectometry
GCxGC	Two-dimensional Gas Chromatography
GMP	Good Manufacturing Practices
HPLC	High Pressure (Performance) Liquid Chromatography
HRBO	Highly refined base oil
INRA	French National Institute for Agricultural Research
JECFA	Joint FAO/WHO Expert Committee on Food Additives
LC-GC	Liquid chromatography - Gas Chromatography
MOAH	Mineral Oil Aromatic Hydrocarbons
MOCRINIS	Mineral Oil Cross Industry Issues
MOE	Margin of Exposure
MOH	Mineral Oil Hydrocarbons
MOSH	Mineral Oil Saturated Hydrocarbons
NOAEL	No observed adverse effect level

PAH	Polycyclic aromatic hydrocarbons
POSH	Polyolefin Oligomeric Saturated Hydrocarbons
REACH	Registration, Evaluation, Authorisation of Chemicals
SD	Sprague-Dawley rat
SCF	Scientific Committee for Food
SPE	Solid phase extraction
UVCB	Substances of Unknown or Variable Composition, Complex reaction products or Biological Materials
WHO	World Health Organisation

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APPENDIX 1. LIST OF PARTICIPANTS

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Adam	Andre	Fragol GmbH+Co.KG	DE
Aronhime	Marc	Hewlett-Packard Indigo Division	IL
Astudillo	Maria Luisa	Repsol Lubricants and specialties	ES
Beens	Jan	Consultant	NL
Belson	Jeffrey	Hewlett-Packard Indigo Division	IL
Benford	Diane	Food Standards Agency	GB
Besler	Alissa	Henkel AG & Co. KGaA	DE
Binaglia	Marco	EFSA	IT
Bonuomo	Maurizio	Food Drink Europe	BE
Boogaard	Peter	Shell International bv	NL
Boon	Andy	Sun Chemical	GB
Braschi	Ilaria	University of Bologna	IT
Briggs	Jonathan	Food Standards Agency	GB
Broughton	Robert	Amcor Flexibles	GB
Brüschweiler	Beat	Federal Office of Public Health	CH
Byrd	Nick	Campden Bri	GB
Capendale	John	Paramelt BV	NL
Cardon	Jan	ECMA European Carton Makers Association	BE
Carrillo	Juan-Carlos	Shell International	NL
Casado	Maria	FEFCO	BE
Cavallini	Eugenio	CEPI aisbl	BE
Cravedi	Jean-Pierre	INRA	FR
Danneels	Dirk	European Wax Federation	BE
De Regibus	Paolo	Perfetti Van Melle Italia Srl	IT
Eijhusen	Gijs	ADM	NL
Fleming	Kenneth	K Fleming Consultancy Ltd	GB
Forbes	Stuart	Shell Global Solutions	GB
Frank	Erich	Flint Group Germany GmbH	DE
Ganster	Beate	Constantia Teich GmbH	AT
Goldbeck	Christophe	CVUA-MEL	DE

Last Name	First Name	Company	Country
Gonzalez	Azucena	SAICA	ES
Goyak	Katy	ExxonMobil Biomedical Sciences, Inc.	US
Grabitz	Andreas	Eurofins CPT	DE
Handelsman	Jacob	American Forest & Paper Association	US
Happonen	Nina	Metsä Board Corporation	FI
Hedelin	Anna	Nynas AB	SE
Kanert	Martin	EuPIA	BE
Kral	Olaf	Shell Deutschland Oil GmbH	DE
Kretschmer	Olaf	Sasol Wax GmbH	DE
Lindstrom	Eva	SCA	SE
Mainka	Monika	SGS Institut Fresenius GmbH	DE
Mannaerts	Anja	CONCAWE	BE
Matissek	Reinhard	Food Chemistry Institute (LCI) of the Association of the German Confetionery Industries	DE
Mauro	Elisa	TOTAL Lubrifiants	FR
Moret	Sabrina	University Udine	IT
Müller	Gesine	Harlan Laboratories Ltd	CH
Niemeck	Guenther	OMV AG	AT
Onsea	Sue	Mars	BE
Orsini	Lorenzo	SIT group	SM
Pardoen	Hans	Paramelt BV	NL
Petereit	Norbert	Sasol Wax GmbH	DE
Pezzi	Marcello	DS Smith Packaging Ltd	GB
Ramunni	Massimo	ASSOCARTA	IT
Riffard	Serge	ExxonMobil	FR
Ringman-Beck	Jori	CEPI	BE
Rohde	Arlean	CONCAWE	BE
Ronit	Kogan	Ievanon and kogan	IL
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Sackers	Emmerich	Solvay Acetow	DE
Sandrock	Rainer	Reno De Medici Arnsberg GmbH	DE

Last Name	First Name	Company	Country
Sangenís Magrasó	José María	LECO Instruments	ES
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Weber	Patrick	SGS Germany GmbH	DE
Woldhuis	Jan	Paramelt BV	NL

APPENDIX 2. WORKSHOP PROGRAMME

MOCRINIS Workshop
Bologna, Italy
10-11 September, 2013

Day 1: Tuesday 10 September 2013

1. Opening Session
Moderator: Dirk Danneels, European Wax Federation

09:00 **Welcome and opening comments**
Juan-Carlos Carrillo, Shell

09:15 **Goals and outline of the Workshop**
Juan-Carlos Carrillo, Shell

2. Setting the Scene on "Mineral Oil"
Moderator: Dirk Danneels, European Wax Federation

Mineral oils are petroleum substances obtained from crude oil. Mineral oils are complex substances of hydrocarbon components with carbon number ranging from C15 to C50 and consist of saturated (normal, branched, naphthenic) and aromatic hydrocarbons. The chemical composition is set by manufacturing processes to satisfy a range of performance, physical and toxicological properties.

09:30 **Mineral Oil – Origin, Production and Composition**
Anna Hedelin, Nynas

09:45 **Analytical Characterisation of Mineral Oils**
Stuart Forbes, Shell

09:55 **Mineral Oils in Printing Inks**
Erich Frank, Flint Group

10:05 **Mineral Oils in Cartons**
Jan Cardon, European Carton Makers Association

10:15 **Mineral Oils: The Point of View of the Paper Industry**
Eugenio Cavallini, Confederation of European Paper Industries

10:25 **Mineral Oils and Food. A Partnership for the Future?**
Andre Adam, FRAGOL

10:40 **Discussion**

10:50 **Coffee Break**

3. Toxicology of Mineral Oils

Moderator: Dirk Danneels, European Wax Federation

The known hazard information will be summarized both for mineral oils with non-food technical applications and for highly refined mineral oils with food contact applications. The hazard of concern for mineral oils with non-food applications is dermal carcinogenic potential, which is related to aromatic hydrocarbon content and evaluated with short-term predictive assays. Mineral oils used in food contact applications consist primarily of saturated hydrocarbons, and the hazard of concern is liver granuloma development that has been observed in a single rat strain. Differences in bioavailability and metabolic profiles across species will be reviewed in order to assess the human relevance of these liver granulomas.

11:15 **Mammalian Toxicology and Toxicokinetics of Mineral Oil**
Peter Boogaard, Shell

11:35 **Overview of Metabolic Differences**
Jean-Pierre Cravedi, French National Institute for Agricultural Research

11:55 **Mineral Oil Hydrocarbons (MOH)and Human Pathology**
Kenneth Fleming, Royal College of Pathologists

12:15 **Discussion/Questions & Answers**

12:30 **Lunch**

4. Risk Assessment

Moderator: Dirk Danneels, European Wax Federation

Risk assessments on mineral oils have been conducted by several regulatory bodies. In particular, the Scientific Opinion on Mineral Oil Hydrocarbons in food will be reviewed, followed by a discussion of the opportunities to strengthen the data used to support this risk assessment.

13:30 **Mineral Oil Hydrocarbons in Food, Scientific Opinion of the Scientific Panel on Contaminants in the Food Chain (CONTAM)**
Marco Binaglia, European Food Safety Authority

13:50 **Interpretation of Exposure Data and Path Forward**
David Tennant, Food Chemical Risk Analysis

14:10 **Panel Discussion**
Peter Boogaard, Shell
Jean-Pierre Cravedi, French National Institute for Agricultural Research
David Tennant, Food Chemical Risk Analysis
Diane Benford, UK Food Standards

5. Regulatory Framework

Moderator: Dirk Danneels, European Wax Federation

Mineral oils used in food and non-food applications are subject to regulation by several pieces of legislation. Consideration will be given to the potential overlaps and gaps among these different regulatory frameworks.

14:40	**Comparison of Various European Food Regulations** Rachida Semail, Keller and Heckman
15:00	**Understanding the Requirements of EU Food Contact Regulations (Non-plastic material)** Annette Schaefer, DG SANCO
15:20	**Question and Answers**
15:30	**Coffee Break**

6. Analytical Methods for Mineral Oils

Moderator: Dirk Danneels, European Wax Federation

Various test methods exist for the analysis of mineral oils. Considering the limitations and uncertainties of the various methods, the applicability of the most appropriate method(s) will be discussed.

15:45	**The Composition and Analyses of Oil Fractions Present in Food** Jan Beens, Consultant, University of Amsterdam and Free University of Amsterdam
16:05	**Latest Developments on MOSH/MOAH Methods** Philipp Stolper, FOGRA
16:25	**Safety of Recycled Paperboard: Mineral Oil Content Determination, Migration to Food, and Clean-Up Strategies** Ilaria Braschi, University of Bologna
16:45	**Panel Discussion** **Consider EFSA recommendation on need for certified reference standards and reference materials for Mineral Oils** Jan Beens Stuart Forbes Philipp Stolper
17:15	**Wrap Up Day 1** Juan-Carlos Carrillo, Shell
17:30	**End of Day 1**

Day 2: Wednesday 11 September 2013

Day 2: Objectives and Goals

09:00	**Welcome and Goals of Day 2** Juan-Carlos, Carrillo, Shell

Breakout Sessions

Moderator: Dirk Danneels, European Wax Federation

09:15	**Discussion Group 1: Toxicology and Risk Assessment**
	Peter Boogaard / Jean-Pierre Cravedi
	Discussion Group 2: Analytical Methods
	Stuart Forbes / Jan Beens / Philipp Stolper
	Discussion Group 3: Downstream Users
	Erich Frank / Jan Cardon / Andre Adam / Jonathan Briggs

Report back from Discussion Groups

10:45	**Toxicology and Risk Assessment**
	Analytical Methods
	Downstream Users
11:45	**Lunch**

Discuss recommendations from MOCRINIS Workshop

13:00	Barry Simpson

Wrap up / agreement on Final Recommendations

14:00	Juan-Carlos Carrillo, Shell

14:45 End of Day 2 MOCRINIS Workshop

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