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Critical review of the relationship between IP346 and dermal carcinogenic activity

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ABSTRACT

The IP 346 method was adopted as a screening assay to predict the carcinogenicity of specific petroleum streams. Its application is based on a strong correlation with results from over 100 mouse dermal carcinogenicity studies, which were reported in a series of publications and formally documented in Concawe Report 94/51 [1]. This correlation was used to establish the basis for defining a cancer hazard classification threshold for specific petroleum categories. It has been adopted in EU legislation through the use of note L as per the former Dangerous Substance Directive No 67/548 EC and continued in the Classification, Labelling and Packaging (CLP) Regulation (EC) No 1272/2008.

The purpose of this report is to review the current state of the science to determine if the IP 346 method continues to be fit for purpose to predict the carcinogenic potential of certain categories of petroleum streams. A systematic literature search was conducted to identify any new petroleum stream carcinogenicity studies published since 1994 that were correlated with IP 346 data.

Thirty-six new carcinogenicity study results were identified, with 29 of these on substances within the scope of the IP 346 method. With the addition of these new sample results and their complementary IP 346 test results, specificity and accuracy were not significantly changed, and most importantly, sensitivity was slightly increased to 93% for all petroleum streams, and increased to 86% for lubricant base oils.

Therefore, based on an analysis of the results of additional studies identified since publication of Concawe report 94/51, the IP 346 method and the original criteria developed in 1994 continue to be fit for purpose for the prediction of carcinogenic potential for lubricant base oils, treated distillate aromatic extracts and foots oils.

KEYWORDS

IP346, Screening Assay, Carcinogenicity, Oil Industry Note L, Other Lubricant Base Oils [OLBO], Foots Oils, Treated Distillate Aromatic Extracts [tDAE].

INTERNET

This report is available as an Adobe pdf file on the Concawe website (www.concawe.org).

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1. CONTEXT AND PURPOSE OF THE DOCUMENT

The IP 346 method (Determination of Polycyclic Aromatics in Unused Lubricating Base Oils and Asphaltene Free Petroleum Fractions – Dimethyl Sulphoxide Extraction Refractive Index Method) [2] occupies a critical cornerstone in the petroleum industry strategy for ensuring that the carcinogenicity of defined categories of petroleum products (namely Other Lubricant Base Oils [OLBO], Foots Oils and treated Distillate Aromatic Extracts [tDAE]) have been assessed and the hazards correctly identified [3]. Since 1994 [1], IP 346 has been used to define a cancer hazard classification threshold for substances in different petroleum categories through the use of note L as per the former Dangerous Substance Directive No 67/548 EC and re-established in the Classification, Labelling and Packaging (CLP) Regulation (EC) No 1272/2008 of 16 December 2008:

"The classification as a carcinogen need not apply if it can be shown that the substance contains less than 3% DMSO extract as measured by IP 346 'Determination of polycyclic aromatics in unused lubricating base oils and asphaltene free petroleum fractions — Dimethyl sulphoxide extraction refractive index method', Institute of Petroleum, London. This note applies only to certain complex oil-derived substances".

The underlying strength of the use of IP 346 as a predictor of carcinogenic activity is that it is based on a comparison of results (% w/w) with the findings of skin cancer in mouse skin painting studies [1]. This comparison showed a strong correlation between skin cancer incidence and DMSO extractable content (specifically ≥3% w/w), where the extractable portion has been shown to correlate with the polycyclic aromatic content (PCA) of the substance. Based on this relationship, the IP 346 has been applied by the petroleum industry to differentiate those mineral hydrocarbon base stocks that are likely to be dermal carcinogens from those that are unlikely to be so.

As the original testing and comparisons were undertaken in the 1980s and 1990s, a new literature review on carcinogenicity studies published since 1994 is considered essential in order to confirm the assumptions underpinning the IP 346 application for classification and labelling of specific petroleum substances remain valid.

2. INTRODUCTION

The Institute of Petroleum method IP 346 is a critical method for the prediction of carcinogenicity for substances in the petroleum categories Other Lubricating Base Oils, Treated Distillate Aromatic Extracts, and Foots Oils under REACH/CLP. The analytical method was last updated in 2004, and the last comprehensive review of the available data underpinning the application of this method for predicting carcinogenic activity was published by Concawe in 1994. This represents the first complete review of the relationship between IP 346 and carcinogenic activity since publication of the 1994 Concawe report, with the objective of identifying any relevant new information pertaining to the IP 346 method and its effectiveness for predicting the carcinogenic hazards of certain petroleum substances.

3. LITERATURE REVIEW

A systematic literature review strategy was defined to identify any relevant reports pertaining to the carcinogenic activity of petroleum substances published since 1992, the year of the Workshop on the Carcinogenicity of Coal and Petroleum Derived Substances held at the EC Joint Research Centre at Ispra, Italy [1]. This workshop led to the adoption of IP 346 as a parameter for prediction of carcinogenic activity of OLBO, Foots Oils and tDAE into European Classification and Labelling legislation.

Generally, the search strategy was designed to capture new literature pertaining to the following:

-New carcinogenicity data pertaining to petroleum streams / categories for which IP 346 is applicable to provide the latest analysis.

-Overview of the state of emerging regulations to provide an understanding of the broader regulatory acceptance of IP 346 for carcinogenicity assessment

Briefly, The Medline and Toxfile databases were searched to identify relevant reports/studies published since 1992 based on the criteria detailed in Appendix 1. The search resulted in the generation of a list of potential ‘hits’ consisting of 1,429 titles and abstracts. These titles and abstracts were reviewed for relevance. Reports not relating to human or mammalian carcinogenicity or the mutagenicity of chemicals were discarded. Review of the remaining titles and abstracts led to the prioritization of 126 reports which were reviewed to identify any relevant information. A detailed summary of the search strategy and exclusion criteria can be found in Appendix 1.

4. REVIEW OF IP 346 METHOD

Institute of Petroleum (now Energy Institute) method IP 346 was first published in 1980 and last updated in 2004. The method relies on the ability of dimethyl sulfoxide to extract polar organic compounds including polycyclic aromatic compounds (PCA) from petroleum substances [4]. Some of the PCA extracted by the method are associated with carcinogenicity of certain petroleum streams. After back-extraction into cyclohexane, the solvent is removed and the DMSO-extract is weighed and expressed as a weight percent of the starting material (% w/w DMSO Extractables).

4.1. METHOD SCOPE

Chemical domain

The IP 346 method defines the chemical scope of applicability, based on the specific types of samples for which the inter-laboratory validation study was conducted, as lubricating base oils with at least 95% of components boiling above 300°C. Therefore, the IP 346 method specifically applies to “unused, additive-free lubricating base oils having an atmospheric boiling point of 300°C minimum at 5% recovered sample”. The method may apply to samples outside of this range, but the method precision has not been determined for such materials. For samples containing between 5-95% of components boiling below 300°C at 100 kPa, the sample must be topped by laboratory fractionation prior to proceeding with the assay. For samples containing greater than 95% of components boiling below 300°C at 100 kPa, the method cannot be conducted. Due to the ability of asphaltenes to partition into DMSO during extraction of petroleum substances, as indicated by the method title, streams containing asphaltenes are outside the scope of this method. In addition, IARC recognizes that the IP 346 may not be ideal for the assessment of streams derived from naphthenic crude oils as it may lead to false positive results [5].

Chemical-biological domain

While the IP 346 method specifically defines the chemical scope to which it applies, the biological applicability of IP 346 results to predict potential carcinogenic hazards is based on a correlation with the results of chronic mouse skin painting studies on specific categories of petroleum substances. Furthermore, these mouse studies were modelled after the original experimental skin carcinogenesis studies which first confirmed putative occupational skin carcinogens in the rabbit ear model in 1915, and in mouse skin shortly thereafter. These carcinogens included coal liquids, shale oils and chimney soot (reviewed by Fujika [6]). In 1924, an unrefined lubricating oil associated with excess cancer among workers in the British textile industry was confirmed as a skin carcinogen by testing in mice [7], and additional work further strengthened the use of the mouse skin model for identifying or confirming human carcinogens for substances including those derived from petroleum [8-10]. Therefore, the IP 346 parameter (% w/w DMSO extractable) is the only chemical method directly correlated with skin cancer activity in experimental studies, and indirectly correlated with human dermal carcinogenicity.

Under CLP, the European Commission acknowledges IP 346 as a suitable predictive screening method to assess the potential carcinogenic hazard, specifically for the members of the Other Lubricant Base Oils, Foots Oils, and Treated Distillate Aromatic Extracts categories listed in Annex VI, based on a 3% w/w cut-off.

The data correlating % w/w DMSO extractables by IP 346 with chronic animal bioassay results as outlined in Concawe Report 94/51 [1] includes samples of substances from 5

petroleum substance categories as defined by Concawe Report 9/15 [3], in addition to 6 experimental mixtures of these categories. The majority of the samples (76/104) fall into the Other Lubricant Base Oils (OLBO) category, with no other single category having greater than 15 samples. Among the remaining 28 samples, only the 6 mixtures have samples that tested both negatively and positively in skin painting studies, whereas the rest of the categories were either exclusively carcinogenic or non-carcinogenic. A summary of the original Concawe data correlating % w/w DMSO extractables by IP 346 with chronic skin painting results, sorted by Concawe Category, is provided in Table 3. Although the 3% w/w cut-off was only adopted as a regulatory threshold for a limited number of petroleum substance categories, it is important to recognize that the correlation between % w/w DMSO extract and skin cancer activity included substances from other categories within the chemical domain. Data for Highly Refined Base Oils (HRBO), Distillate Aromatic Extracts (DAE), Untreated and Acid-treated Oils (UATO) and blends provide valuable data points for the overall correlation, particularly at the extremes of carcinogenic activity i.e. non-carcinogenic and highly carcinogenic.

Since publication of the Concawe IP 346 report, three reports in the literature were identified with a total of 36 previously unpublished IP 346 and animal bioassay results [11-13]. Roy added one previously unpublished result for an OLBO, Blackburn added a total of 32 new results, with twelve on OLBOs, eleven on U/ATOs, three on DAEs, five on Residual Aromatic Extracts (RAE)s, and one on an experimental mixture. Coker added one result each from the Straight Run Gas Oils (SRGO) and Other Fuel Oil Components (OFOC) categories. One study on a tDAE from Chasey and McKee [14] was included as well. In total, there are now 10 unique samples that have animal bioassay data directly correlated to IP 346, of which 133 are within the scope of the IP 346 method as summarized in Appendix 2, Table 4 and Table 5. The IP 346 can only be used for classification purposes within its applicability domain. For other petroleum categories, the IP 346 method may only be used for informational purposes, because of a general lack of carcinogenicity data to correlate to.

The review of five RAE samples from Blackburn, leading to a high number of false positive results among five samples, provides evidence that the IP 346 assay is a less suitable predictive tool for RAEs, therefore this category of substances is not within the chemical-biological domain of the method [11]. For the purpose of this review, RAEs are not included in subsequent IP 346 analyses.

The inclusion of 29 new in-scope results has minimal effects on the overall predictivity of carcinogenicity of the IP 346 assay (Table 1). With the inclusion of these new data, overall accuracy decreased from 94% to 92%, the sensitivity was slightly increased from 92% to 93% and the specificity decreased from 96% to 91%.

[1] Untreated and Acid Treated Oils, Highly Refined Base Oils, Other Lubricant Base oils, Untreated Distillate Aromatic Extracts, and Treated Distillate Aromatic Extracts.

Table 1. Data for all Concawe categories within scope of the IP 346 method

	Concawe, 1994	Current
# of results	104	133
True positives	34	55
True negatives	64	67
False positives	3	7
False negatives	3	4
Sensitivity	92%	93%
Specificity	96%	91%
Positive predictive value	92%	89%
False positive rate	8%	11%
Negative predictive value	96%	94%
False negative rate	4%	6%
Accuracy	94%	92%

The following summarizes the latest IP 346 data and its performance relative to skin painting results for the specific petroleum stream categories for which IP 346 is applicable.

4.2. OTHER LUBRICANT BASE OILS AND HIGHLY REFINED BASE OILS

13 of 36 new results were for substances in either the OLBO- or HRBO category, the data for which is summarized in Table 2 For these categories only, the positive prediction and overall accuracy are slightly decreased by the inclusion of the new data (81% vs.73% and 92% vs. 89%, respectively). Most importantly, while there is a slight increase in false positives, there are no additional false negatives, which led to slightly decreased specificity (95% vs. 90%) and slightly increased sensitivity (81% vs. 86%).

It should be noted that the IP 346 test method can be used on highly refined base oils but is not used as a regulatory marker for classification purposes, since all HRBOs are highly refined with extremely low aromatic and PCA content and are per definition non-carcinogens. Samples of HRBO used in the original Concawe correlation were all non-carcinogenic due to the low PCA content. In addition, HRBOs (white mineral oils and technical white oils) are produced to meet US FDA specifications which include strict limits on UV absorption in the wavelength range 280-400 nanometers. Similarly, IP 346 is not used as a regulatory marker for DAEs and UATOs, which have high aromatic and PCA content and are clearly carcinogenic.

Table 2. Data for OLBO and HRBO categories

	Concawe, 1994	Current
# of results	79	92
True positives	13	19
True negatives	60	63
False positives	3	7
False negatives	3	3
Sensitivity	81%	86%
Specificity	95%	90%
Positive predictive value	81%	73%
False positive rate	19%	27%
Negative predictive value	95%	95%
False negative rate	5%	5%
Accuracy	92%	89%

4.3. UNTREATED DISTILLATE AROMATIC EXTRACTS, TREATED DISTILLATE AROMATIC EXTRACTS, UNREFINED/ACID TREATED OILS AND BLENDS

For a summary of data on each petroleum category, please refer to Appendix 2, Tables 3-5.

Under CLP, Untreated DAEs and Unrefined/Acid Treated Oils are classified as carcinogenic category 1B, with no exceptions. In contrast, Treated DAEs are classified as carcinogenic category 1B unless it can be shown the substance contains less than 3% w/w DMSO extractables. With the addition of three new DAE results, there are twelve DAEs and seven tDAEs with corresponding IP 346 results. All samples tested positive in skin painting studies, and IP 346 was 100% accurate in predicting these results. A sample with an IP 346 result of 3.7% (w/w) correctly predicted a positive carcinogenicity result (10% Tumour Bearing Animals [TBA]).

In the 1994 report, there were four Unrefined/Acid Treated Oils. This review has identified an additional eleven UATO samples, giving a total of fifteen. In all cases, these substances tested as carcinogens, producing between 5% and 62% TBA, and the IP 346 correctly predicted these results in all cases.

The original report contained six experimental mixtures, of which two were carcinogenic. The IP 346 assay predicted the correct result for all six. Since the original report, one additional false negative result was identified on an experimental mixture, which had an IP 346 value of 1, and produced a 4% incidence of tumours.

Of the four false negatives in the total 2015 database, three are considered such based only on the conservative cut off of 4% TBA as established by industry and did not produce statistically significant increases in tumour incidence (i.e. ≥8% based on the Chi Square Test). The one statistically significant sample had an IP 346 of 2.9% w/w and produced 10% tumour bearing animals.

5. REGULATORY APPLICATION OF IP 346

5.1. EUROPEAN UNION

According to EU Regulation EC 1272/2008 on Classification, Labelling and Packaging (CLP), members of the Other Lubricant Base Oils, Foots Oils and Treated Distillate Aromatic Extracts categories listed in CLP Annex VI are considered carcinogenic (category 1B) unless it can be shown that the substance contains less than 3% w/w DMSO extract. This statement is documented in CLP Note L.

IP 346 should not be applied for classification purposes to other categories, including HRBO, DAE and Acid treated- and untreated oils, as it is not accepted as a regulatory marker for carcinogenicity for substances in these categories.

5.2. CLASSIFICATION UNDER GHS

There is no formal guidance on the classification of petroleum streams for carcinogenicity under the UN Globally Harmonized System (GHS). However, guidance was developed by the International Petroleum Industry Environmental Conservation Association (IPIECA) on how to classify petroleum streams under GHS. Specifically, this guidance states that for the Treated Distillate Aromatic Extracts, Lubricant Base Oils and Foots Oils categories, IP 346 can be used for predicting carcinogenic potential [15].

5.3. UNITED STATES

According to the United States Occupational Safety and Health Administration, “When reliable and good quality data are available to classify a petroleum stream-based on testing of the stream or toxicologically appropriate read-across to a substantially similar stream, -a weight of evidence analysis supported by that data may be relied upon for classification regardless of whether a CMR constituent is present in the stream. A substantially similar stream is one that has a similar starting material, production process, and range of physico-chemical properties (e.g., boiling point and carbon number) and similar constituent compositions.” [16]. Although IP 346 is not specifically referenced, it may be used as part of a weight of evidence justification, based on the rich database of skin painting data as well as the categories defined by the petroleum industry [17-19].

[1] For assessing the outcome of the dermal carcinogenicity studies, a sample has been considered as potentially carcinogenic if 4% or more of the test animals developed tumours. The 4% incidence rate was chosen as being above the typical background level for the untreated controls. For a typical study, this means that for a positive result, at least two of the 50 animals should show evidence of tumour formation. Discussions in the EU Technical Progress Committee Classification and Labelling working group and with IARC have considered this 4% figure to be valid, although possibly over conservative.

5.4. AUSTRALIA

In Inventory Multi-Tiered Assessment and Prioritization (IMAP) assessments, the Australian National Industrial Chemicals Notification and Assessment Scheme (NICNAS) has embraced the use of IP 346 to determine potential carcinogenicity for specific petroleum streams specified under NICNAS [20-22].

5.5. CHINA

China has instituted national standards (GB or SH standards) equivalent or similar to several existing test methods commonly used in the petroleum industry. After validation of the conduct of the IP 346 method in its labs [23], authors from PetroChina Karamay authored the Chinese petroleum industry technical standard NB/SH/T 0838-2010 as a near direct translation of IP 346-2004 [24, 25]. The Chinese national standard for Transformer Oils, GB2536-11 [26], contains a reference to NB/SH/T 0838-2010, similar to its benchmark, IEC 60296-2012 which references IP 346 [27].

6. DISCUSSION AND CONCLUSION

In an attempt during the 1980s to find a replacement for animal skin painting studies, it was shown that gravimetric determination of the DMSO extract of virgin base oils could be correlated to the skin cancer potential assessed by skin painting studies in mice. This method is now referred to as the IP 346 method. According to Note L of CLP, substances with <3% DMSO extract are non-carcinogenic. To date, IP 346 is the only chemical method for assessing the cancer hazards of petroleum streams that is biologically meaningful because it has a direct relationship to the outcome in animal carcinogenicity studies performed on commercial products.

Although IP 346 dates back to the 1980s, it is still a valid and reliable analytical method for estimating Polycyclic Aromatics (PCA) biological relevance. The IP 346 is therefore not a method to measure individual levels of PCA, rather it is the only method to establish the link between refining history with the outcome in mouse skin painting studies by a collective assessment of the DMSO extracted material, which includes PCA and other extractables.

The origins of the standard petroleum industry mouse skin painting study lie in the first experimental carcinogenicity studies that confirmed putative occupational carcinogens in the early 20th century. These established the foundation for modern carcinogenicity test guidelines such as OECD TG 451. While there may be some perceived differences between the petroleum industry studies and modern test guidelines, such as the use of a single sex, a single dose level and 2-3x weekly dosing frequency, these optimized parameters were methodically set based on the collective knowledge gained from several hundred studies on petroleum streams. Nearly all studies were chronic, of either 18 or 24-month duration, and conducted with either the C3H or CF1 mouse strains, which are standard strains for carcinogenicity studies, with the C3H, in particular, recognized for its responsiveness to polycyclic aromatic hydrocarbons. Therefore, these studies retain many of the characteristics present in current guidelines, but with optimization for maximal human relevance.

The PCA determined by IP 346 and the skin painting studies on mineral hydrocarbon base oils encompass the carcinogenicity of all constituents of the streams, including any alkylated PCA present and also substances that on their own may not be biologically active, but may potentiate or decrease the activity of carcinogenic constituents found in the oil. Thus, the possible role of co-carcinogens, initiators and promotors is accounted for when assessing the whole substance in mouse skin painting studies and in collective PCA determination using the IP 346 method.

The IP 346 method is a rather simple and straight-forward gravimetric method that most laboratories are capable of performing. The results are obtained rapidly, making it practical for use in refineries to screen products manufactured and sold and ensure they are safe for use. Whilst meeting the objective of protecting human health, and preventing the conduct of countless dermal carcinogenicity tests, the IP 346 was a very early and significant step towards meeting the goals of the 3R's first envisioned by Russell and Burch [28].

In this review of IP 346, out of 89 'Other Lubricant Base Oil' samples tested, 7 samples were false positives and 3 samples were false negatives. Based on conservative limits for tumour incidence (2/50 animals), and a limit of 3% w/w DMSO extractables which maximizes sensitivity, rather than specificity, the accuracy of the assay for OLBOs alone is 89% and the false omission rate is 5%. Further supporting the conservativism of this approach, the mouse protocol is likely to over-estimate the likely cancer hazard in

humans since the mouse strains used are particularly sensitive to tumor formation mediated by PCA. This is supported by reports that suspected human carcinogens produced tumor incidence rates of >50% in C3H mice [9]. Based on these considerations, the 3% w/w threshold is considered highly conservative and adequately protective of human health.

In conclusion, based on a comprehensive updated review incorporating all new petroleum stream carcinogenicity data, the IP 346 method and the original criteria developed in 1994 continue to be fit for purpose for the prediction of carcinogenic potential of other lubricant base oils, treated distillate aromatic extracts and foots oils.

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APPENDIX 1: SEARCH STRATEGY

- PETROLEUM TERMS USED:

  (“Aromatic* extract*” or “base stock*” or “base oil*” or rerefined or “Refin* stream*” or Hydrotreat* or “mineral oil*” or Polycyclic* or polynuclear* or pah? Or pna* or “Refin* process*” or Lubrica* or Petroleum or Oil or oils)

- CANCER TERMS USED:

  (Cancer* or carcino* or toxic* or tumor* or tumour* or mutagen* or genotox* or lymphoma? or micronucleus or NEOPLAS? OR MALIGNAN? OR LEUKEM? Or oncogenic? Or adenoma? Or metastas? OR MUTATE? OR MUTATION?)

- TEST TERMS USED:

  (ip346 or “ip 346” or ”skin painting” or "in vitro" or "in vivo" or assay* or ((cancer* or carcin* or toxic* or health or skin or dermal) n/2 (study or studies or test*)))

- MESH TERMS AS MAJOR HEADING:

  ("toxicity" OR "methods" OR "Mutagens" OR "Polycyclic Hydrocarbons, Aromatic" OR "Carcinogens" OR "adverse effects" OR "Petroleum" OR "Toxicity Tests" OR "Mutagenicity Tests" OR "Lung Neoplasms" OR "Liver Neoplasms" OR "Neoplasms" OR "Breast Neoplasms" OR "Micronucleus Tests" OR "epidemiology" OR "Occupational Exposure" OR "Neoplasms, Experimental" OR "Carcinoma, Hepatocellular" OR "Hydrocarbons" OR "Occupational Diseases" OR "Prostatic Neoplasms" OR "Polycyclic Compounds" OR "Carcinogens, Environmental" OR "Polychlorinated Biphenyls" OR "Colorectal Neoplasms" OR "standards" OR "Skin Neoplasms" OR "Carcinogenicity Tests" OR "Colonic Neoplasms" OR "Comet Assay" OR "Skin" OR "Urinary Bladder Neoplasms" OR "Adenocarcinoma" OR "statistics & numerical data" OR "Mineral Oil")

APPENDIX 2: DATA TABLES

Table 3. Summary of IP 346 data by Concawe Category (1994).

	All	Highly refined base oils	Other lubricant base oils	Unrefined/acid treated oils	Treated distillate aromatic extracts	Untreated distillate aromatic extracts	Blends
# of results	104	3	76	4	6	9	6
True positives	34	0	13	4	6	9	2
True negatives	64	3	57	0	0	0	4
False positives	3	0	3	0	0	0	0
False negatives	3	0	3	0	0	0	0
Sensitivity	92%		81%	100%	100%	100%	100%
Specificity	96%	100%	95%				100%
Positive predictive value	92%		81%	100%	100%	100%	100%
False discovery rate	8%		19%	0%	0%	0%	0%
Negative predictive value	96%	100%	95%				100%
False omission rate	4%	0%	5%				0%
Accuracy	94%	100%	92%	100%	100%	100%	100%
IP 346 range	0.07-39.2	0.1-0.4	0.07-13.3	5.02-9.18	8.02-39.2	3.69-26	0.3-13
% TBA Range	0-93.3	0-0	0-40	12.5-62	36.7-88	10-93.3	0-76.7

Table 4. Summary of IP 346 data by Concawe Category (2015).

	All	Highly refined base oils	Other lubricant base oils	Unrefined/acid treated oils	Treated distillate aromatic extracts	Untreated distillate aromatic extracts	Blends
# of results	133	3	89	15	7	12	7
True positives	55	0	19	15	7	12	2
True negatives	67	3	60	0	0	0	4
False positives	7	0	7	0	0	0	0
False negatives	4	0	3	0	0	0	1
Sensitivity	93%		86%	100%	100%	100%	67%
Specificity	91%	100%	90%				100%
Positive predictive value	89%		73%	100%	100%	100%	100%
False discovery rate	11%		27%	0%	0%	0%	0%
Negative predictive value	94%	100%	95%				80%
False omission rate	6%	0%	5%				20%

	All	Highly refined base oils	Other lubricant base oils	Unrefined/acid treated oils	Treated distillate aromatic extracts	Untreated distillate aromatic extracts	Blends
Accuracy	92%	100%	89%	100%	100%	100%	86%
IP 346 range	0.07-73	0.1-0.4	0.07-13.3	3-14	8.02-39.2	3.69-73	0.3-13
% TBA Range	0-93.3	0-0	0-50	5-62	36.7-88	10-93.3	0-76.7

Table 5. Summary of IP 346 data for substances out of scope of the method

	All	Residual aromatic extracts	Straight run gas oils	Heavy fuel oil components
# of results	140	5	1	1
True positives	60	4	0	1
True negatives	67	0	0	0
False positives	9	1	1	0
False negatives	4	0	0	0
Sensitivity	94%	100%		100%
Specificity	88%	0%	0%	
Positive predictive value	87%	80%	0%	100%
False discovery rate	13%	20%	100%	0%
Negative predictive value	94%			
False omission rate	6%			
Accuracy	91%	80%	0%	100%
IP 346 range	0.07-73	0.31-8	5.8-5.8	42.7-42.7
% TBA Range	0-93.3	0-6	0-0	4-4

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