ipieca

The application of Globally Harmonized System (GHS) criteria to petroleum substances

Oil and gas industry guidance and technical support document

Environment

Advancing environmental and social performance across oil and gas

www.ipieca.org

Second Edition

Second Edition, September 2019.

Photographs reproduced courtesy of the following: cover (top left): GracePhotos/Shutterstock.com; (centre) Avigator Fortuner/Shutterstock.com; (bottom centre): totojang1977/Shutterstock.com; (bottom right): Choosakdi Kabyubon/Shutterstock.com.

This publication has been developed to support the implementation of IPIECA's mission and vision. While every effort has been made to ensure the accuracy of the information, it is intended to provide general guidance only. It is not designed to provide legal or other advice, nor should it be relied upon as a substitute for appropriate technical expertise or professional advice. All attempts have been made to ensure that the information is correct at the date of publication. This publication does not constitute a mandatory commitment which members of IPIECA are obliged to adopt. The views and conclusions expressed herein do not necessarily reflect the views of all IPIECA members or the individuals, companies and institutions that contributed to this publication.

While reasonable precautions have been taken to ensure that the information contained in this publication is accurate and timely, this publication is distributed without warranty of any kind, express or implied. IPIECA neither endorses nor accepts responsibility for the content or availability of any website referred to, or linked to, in this publication. The responsibility for the interpretation and use of this publication lies with the user and in no event will IPIECA or any of its members past, present or future regardless of their negligence, assume liability for any foreseeable or unforeseeable use made thereof, which liability is hereby excluded. Consequently, such use is at the recipient's own risk on the basis that any use by the recipient constitutes agreement to the terms of this disclaimer. This disclaimer should be construed in accordance with English law.

Acknowledgements

IPIECA would like to thank the member companies of the IPIECA GHS Task Force for their contributions to the development of this document.

The application of Globally Harmonized System (GHS) criteria to petroleum substances

Oil and gas industry guidance and technical support document

ipieca Advancing environmental and social performance across oil and gas

14th Floor, City Tower, 40 Basinghall Street, London EC2V 5DE, United Kingdom
Telephone: +44 (0)20 7633 2388 E-mail: info@ipieca.org Website: www.ipieca.org

Contents

Executive summary

This guidance was developed by IPIECA to facilitate appropriate human health hazard classification and labelling of petroleum substances within the 'unknown or variable composition, complex reaction products and biological (UVCB) material' group. It was developed with input from experienced technical experts in petroleum substance toxicology, and addresses crude oil and petroleum substances produced from oil and gas operations. The guidance includes a technical support document (see pages 17–33) in which the principles of the guidance are explained with reference to relevant scientific literature. This guidance does not cover classification for environmental hazards.

The original version of this guidance was published by IPIECA on 17 June 2010. It was developed in close consultation with the United Nations (UN) Sub-Committee of Experts on the Globally Harmonized System (GHS) of Classification and Labelling of Chemicals (the Sub-Committee or UNSCEGHS). Efforts on the guidance commenced at the 13th session of the Sub-Committee in July 2007, where IPIECA presented a work plan which was endorsed by the Sub-Committee. At the 14th session of the Sub-Committee, IPIECA listed issues that could result in the divergent classification of petroleum substances. These issues were discussed informally at the 14th, 15th, 16th and 17th sessions of the Sub-Committee. At its 18th session in December 2009, the Sub-Committee endorsed the concept of sector-specific guidance by creating a web page on the UN Economic Commission for Europe (UNECE) website, which links to third-party sector-specific guidance.

This second edition of the guidance, published in September 2019, reflects changes to the GHS as well as new toxicological data from studies of petroleum substances. As the author, IPIECA remains responsible for the contents and maintenance of this guidance.

IPIECA believes that utilization of the guidance will result in global harmonization of the hazard classification of petroleum substances that are broadly traded in international commerce. Additional benefits of the guidance are:

a. application of the 'grouping' concept and read-across methodology, resulting in the full use of available data, thereby minimizing the need for animal testing;
b. transparent use of GHS principles for the classification of petroleum UVCB substances;
c. consistent and reliable classification of petroleum substances, resulting in appropriate hazard communication, to reduce the risks arising from their handling and storage; and
d. consistent classification, which reduces costs for industry and countries.

This guidance refers to the seventh revised edition of the *UN Globally Harmonized System of Classification and Labelling of Chemicals (GHS)* (the GHS) published in 2017, which is the most recent version available at the time of publication. IPIECA will periodically revise its guidance to ensure that it reflects current research and scientific developments, is consistent with updated versions of the GHS, and incorporates future comments by competent authorities. As appropriate, IPIECA will update the UNSCEGHS on changes to the guidance.

IPIECA encourages countries and industry to fully utilize this guidance in the application of the GHS criteria to petroleum substances. By providing relevant sector-specific guidance, the hazard classification of petroleum substances should be globally consistent regardless of regional differences in the implementation of GHS or classification of individual petroleum substance constituents. However, the end user of this guidance is responsible for understanding and complying with local statutes, if any, regarding the hazard classification of petroleum products.

Comments on this guidance are welcome and should be sent to Rob Cox of IPIECA at rob.cox@ipieca.org.

Background

This document provides supplemental guidance for the classification and labelling of petroleum substances for human health hazards. The guidance does not cover classification for environmental hazards.

The consistent classification and labelling of petroleum substances is not straightforward due to the complex nature and chemistry of these substances. Consistent application of the *Globally Harmonized System of Classification and Labelling of Chemicals (GHS)* requires an understanding of the influence of refining processes on the chemical composition of various refinery process streams, as well as an understanding of the physical and chemical similarities of these streams. This is important in determining the extent to which similar petroleum substances can be grouped for hazard classification purposes.

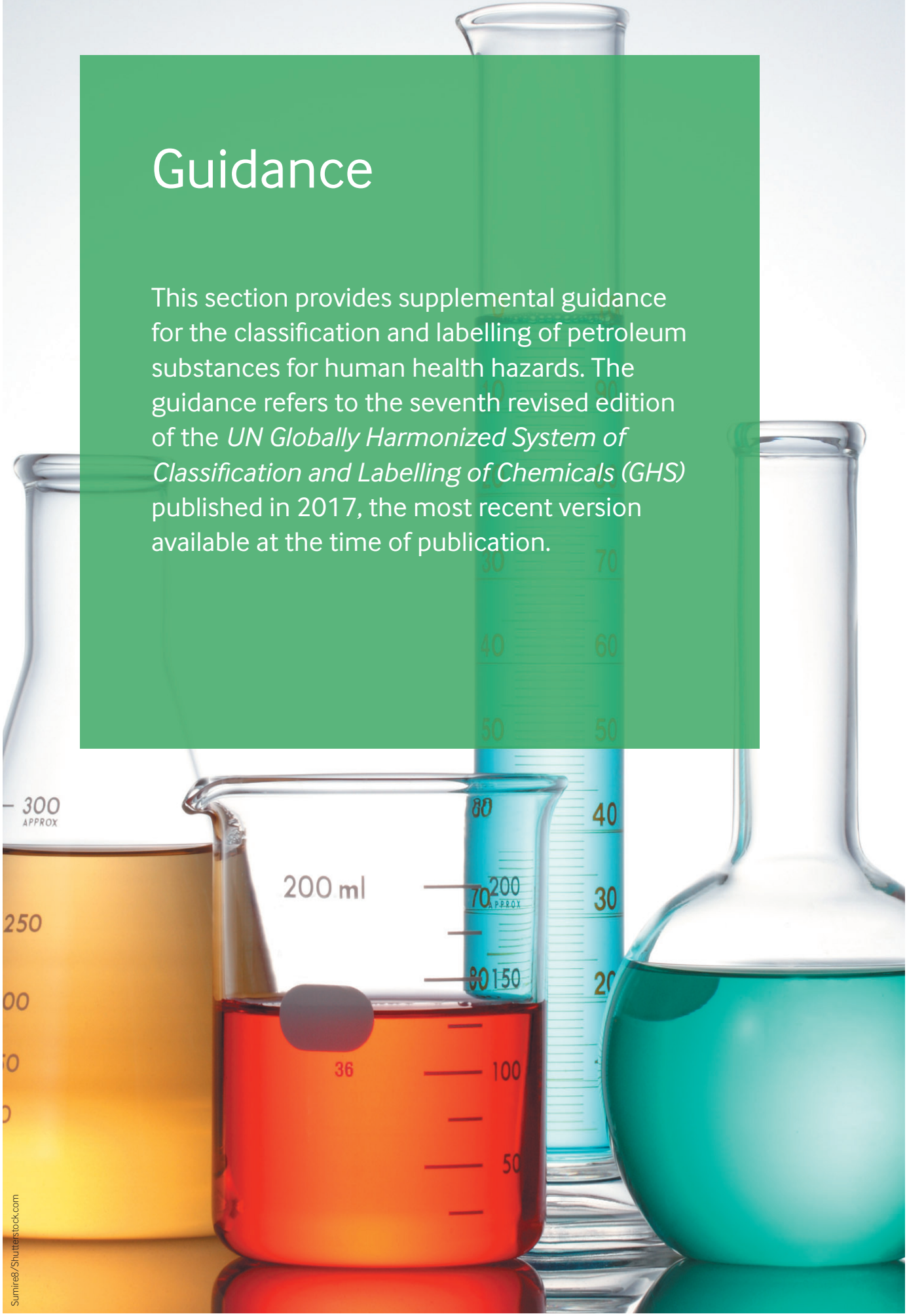
The petroleum sector's application of GHS principles would benefit from specific guidance on the classification of petroleum substances as types of 'unknown or variable composition, complex reaction product and/or biological (UVCB) materials', based on the industry's experience in characterizing the hazards of these substances.

The purpose of this document is to provide supplemental guidance to facilitate a consistent approach to hazard classification and labelling of petroleum substances. The approach described herein has been developed independently of specific regulatory approaches that exist or may be proposed in various countries or regions, and represents the global oil industry's recommended approach to the application of GHS criteria. The framework for the supplemental guidance includes recognition that:

a. petroleum substances are UVCBs, not mixtures;
b. petroleum substances are logically arranged in groups of 'similar' UVCBs based on processing history and physical-chemical properties, which facilitates read-across for purposes of consistent classification and minimizes unnecessary animal testing; and
c. there are specific hazardous constituents that should be considered in hazard classification decisions.

Guidance

This section provides supplemental guidance for the classification and labelling of petroleum substances for human health hazards. The guidance refers to the seventh revised edition of the *UN Globally Harmonized System of Classification and Labelling of Chemicals (GHS)* published in 2017, the most recent version available at the time of publication.



Sumire8/Shutterstock.com

The application of Globally Harmonized System (GHS) criteria to petroleum substances

THE NATURE OF PETROLEUM SUBSTANCES

Petroleum substances are UVCBs derived from crude oil by physical separation (i.e. distillation), which may be followed by chemical modification (e.g. hydrogenation, cracking, etc.) (see Figure 1). There are many different types of crude oil, and each consists of a significant number of constituents, predominantly hydrocarbons. Furthermore, no two crude oils are compositionally the same. Therefore, as the composition of any distillation fraction derived from crude oil will be dependent on the source crude oil itself, and the distillate fractions may be subject to a variety of processing modifications, it follows that petroleum substances (with the exception of some liquified petroleum gases) will be of variable chemical composition, broadly defined by their physical-chemical properties.

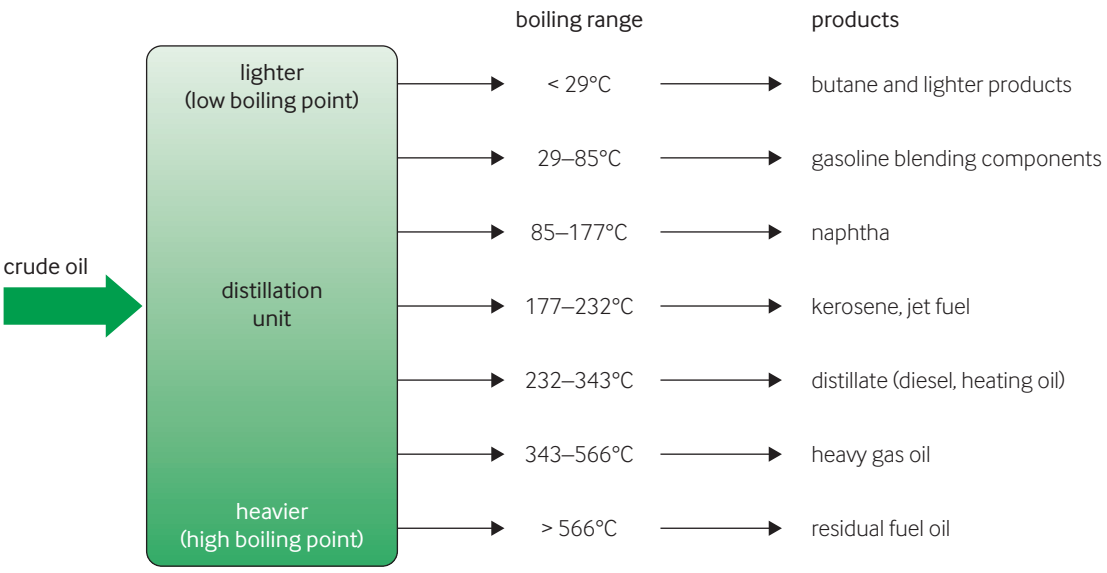
Petroleum substances are, therefore, classed as UVCB substances. They cannot be sufficiently identified by their chemical composition because either the number of constituents is relatively large, the composition is unknown, and/or the variability of composition is relatively large or poorly predictable. A UVCB substance has no definite molecular formula representation. For this reason, petroleum substances cannot be produced to meet specific chemical specifications. Rather, additional types of information are required to identify the substance, including physical-chemical properties (such as boiling range, flash point, viscosity) that establish compositional boundaries related to the intended use of the material.

CHEMICAL ABSTRACT SERVICE (CAS) DESCRIPTIONS OF PETROLEUM SUBSTANCES

According to the definitions in Section 1.3.3.1 of the GHS, 'substances' are defined as:

> *'Chemical elements and their compounds in the natural state or obtained by any production process, including any additive necessary to preserve the stability of the product and any impurities deriving from the process used, but excluding any solvent which may be separated without affecting the stability of the substance or changing its composition.'*

Figure 1 General distillation of crude oil



Source: adapted from EIA, 2012

Petroleum substances meet this definition and are, hence, considered substances.

This guidance document applies only to petroleum substances produced in a refinery and not to intentionally formulated petroleum products placed on the market. These formulated products are considered mixtures for which relevant GHS criteria should be applied.

Although petroleum substances are of complex composition, they are defined as substances, each having a Chemical Abstract Service (CAS) number and associated CAS definition. The CAS definition typically identifies the starting material and the last process step that a substance will have undergone during its production. In many cases, indications of important physical-chemical parameters such as boiling point, combustibility characteristics, and/or a carbon number range, are included in the CAS definition. An example of a typical CAS definition for a petroleum substance is provided below.

Example of a typical CAS definition

Substance:	Gas oils (petroleum), straight run.
CAS definition:	A complex combination of hydrocarbons produced by the distillation of crude oil. It consists of hydrocarbons having carbon numbers predominantly in the range of C11 through C25 and boiling in the range of approximately 205°C to 400°C (410°F to 752°F).

Despite their inherent imprecision, CAS definitions provide a limit to the compositional variation of individual petroleum substances.

Regulatory authorities around the world have included petroleum substances and other UVCBs on their chemical inventories. Chemical inventories that include petroleum substances exist in Australia, Canada, China, the European Union, Japan, Korea, New Zealand, Philippines, Taiwan and the United States of America (US).

GROUPING OF PETROLEUM SUBSTANCES FOR CLASSIFICATION PURPOSES

Petroleum substances are usually described in terms of starting material, production process, and ranges of physical-chemical properties. With this knowledge, they can be arranged into groups having similar physical-chemical, performance and toxicological properties in order to maximize the use of available information and reduce the need for additional laboratory animal testing.

The rationale for such grouping is based on the notion that petroleum substances within a group are derived from similar starting materials, have similar physical-chemical properties, and generally have similar chemical composition, resulting in substances exhibiting broadly similar hazard properties. Classification may then be addressed on a group rather than on a single substance basis.

Such grouping schemes have been developed by Concawe (Environmental Science for European Refining) and subsequently adopted in the European Union (EU) in the classification, labelling and packaging (CLP) Regulation (2008). These schemes have also been adopted by the American Petroleum Institute (API) in their activities to fulfil the requirements of the US High Production Volume (HPV) Challenge Program (US EPA, 2007).

Toxicity data are available on some members of each of the groups of petroleum substances. These data can be applied by 'read-across' to all other members of the petroleum substance group. The data have been summarized by API (see the robust study summaries prepared for the HPV programme at http://www.petroleumhpv.org) and Concawe (see Concawe (2017), *Hazard Classification and Labelling of Petroleum Substances in the European Economic Area*), and should be consulted along with searches of recently published scientific literature.

The major petroleum substance groups for which data exist and/or for which read-across is possible are shown in Table 1 on page 8.

Table 1 API HPV and Concawe petroleum substance groups

API HPV SUBSTANCE GROUP	CONCAWE SUBSTANCE GROUP
Aromatic extracts	• Distillate aromatic extracts • Treated distillate aromatic extracts • Untreated aromatic extracts • Residual aromatic extracts
Asphalt	• Bitumen • Oxidized asphalt
Crude oil	• Crude oil
Gasoline blending streams	• Low boiling point naphthas (gasolines)
Gas oils	• Straight run gas oils • Vacuum gas oils, hydrocracked gas oils and distillate fuels • Cracked gas oils • Other gas oils
Heavy fuel oils	• Heavy fuel oil components
Kerosene/Jet fuel	• Kerosenes • MK-1 diesel fuel
Lubricating grease thickeners	Not applicable
Lubricating oil base stocks	• Highly refined base oils • Unrefined/acid treated oils • Other lubricant base oils • Foots oils
Petroleum coke	• Petroleum cokes
Petroleum gases	• Petroleum gases • Other petroleum gases
Reclaimed substances	Not applicable
Waxes and related materials	• Paraffin and hydrocarbon waxes • Slack waxes • Petrolatums
Not applicable	• Sulphur

The table above reflects the major groups of petroleum substances. In some geographical regions, these groups may be divided into subgroups to meet regional regulatory requirements. These subgroups will differ primarily on having narrower physical-chemical properties. More detailed information about grouping is available through the API and Concawe.

By using the grouping system of petroleum substances and a tiered approach to the classification of petroleum substances, the potential hazards of petroleum substances can be accurately and consistently identified and communicated.

CLASSIFYING PETROLEUM SUBSTANCES UNDER GLOBALLY HARMONIZED SYSTEMS

Industry has adopted a tiered approach for evaluating data sets with which to classify a substance that is considered consistent with GHS principles. In this approach, substance toxicity data are preferred for making classification determinations, followed by read-across data, and, lastly in the absence of any other information, data for individual hazardous constituents of the substance. The hazardous constituents of concern that may occur in different groups of petroleum substances are shown in Table 2 on page 10.

In the absence of adequate toxicity data on a specific petroleum substance, read-across from a similar petroleum substance (typically from the same petroleum substance group) should be applied. Petroleum substances within each of the groups are likely to have similar hazard properties because they have similar chemical composition and physical-chemical properties. In some cases, read-across between substance groups may be justified, provided the groups have a similar constituent composition due to manufacturing processes that result in compositional overlap across substances. Professional scientific judgment for use of read-across must be made on a case-by-case basis.

In some cases, adequate toxicity data may not be available for a specific petroleum substance. Likewise, the available data for similar petroleum substance groups may not be sufficient for reliable read-across. In that case, the percentage composition and toxic potency of a known hazardous constituent is considered for classifying the substance. The GHS provides detailed guidance on the appropriate cut-off values/ concentration limits used for classifying substances within specific categories of health hazards.

Section 1.3.3.1.3 in the GHS states: *'Note also that where impurities, additives or individual constituents of a substance or mixture have been identified and are themselves classified, they should be taken into account during classification if they exceed the cut-off value/ concentration limit for a given hazard class.'* Therefore, in cases where a petroleum substance has a robust toxicity data set and contains known hazardous constituents at or above the GHS cut-off values/concentration limits, a decision must be made as to whether the substance's toxicity data are of sufficient strength to justify not relying on the hazardous constituent cut-off values/ concentration limits as the basis for classification. The use of a weight-of-evidence (WoE) approach is appropriate for making this determination (Section 1.3.2.4.8 in the GHS).

The WoE approach to data utilization is a means of systematically considering all of the available data to make conclusions on mixture or substance health hazards and risks. It is routinely applied in the arenas of human and environmental health risk assessment, which often draw from multiple scientific disciplines.

ECHA (2018) describes the WoE approach as using *'a combination of information from several independent sources to give sufficient evidence to fulfil an information requirement.'* This approach is needed when the information from a single line of evidence is not sufficiently strong to support a decision on hazard or risk, or when one or more studies provide variable contradicting conclusions.

The central tenet of the WoE approach is quantifying the specific end point of health interest (hazard potency or risk) using information from the various scientific disciplines, giving greater weight to data derived from the most scientifically rigorous methodologies. These disciplines may include, but are not limited to, published scientific literature, epidemiology studies, existing laboratory animal studies, read-across analyses from chemical analogues, Quantitative Structure-Activity Relationship (QSAR) modelling predictions, and in vitro studies. The more information that is considered, the stronger the WoE-based decision. Given the potential depth and breadth of data, the information must be carefully structured, organized and presented, with consideration given to the robustness and reliability of different data sources.

The weighting of the available data from a given study will depend on several factors, including data quality, consistency of results across studies, the nature and severity of effects, and relevance of the available data to the compound, mixture or substance being considered.

Table 2 Selected petroleum substance groups and their specific hazardous constituents

API HPV SUBSTANCE GROUP	CONCAWE SUBSTANCE GROUP	RELEVANT HAZARD CLASSES TO BE EVALUATED	POSSIBLE CONSTITUENTS OF CONCERN
Aromatic extracts	• Distillate aromatic extracts • Treated distillate aromatic extracts • Residual aromatic extracts	Carcinogenicity, reproductive effects	PAHs[c]
Asphalt	• Bitumen • Oxidized asphalt	–	H_2S
Crude oil	Not applicable	Carcinogenicity, mutagenicity, specific target organ toxicity, acute toxicity	H_2S,[a] benzene,[b] PAHs,[c] naphthalene
Gasoline blending streams	• Low boiling point naphthas (gasolines)	Carcinogenicity, mutagenicity, specific target organ toxicity	Benzene[b]
		Specific target organ toxicity	n-Hexane, toluene, benzene
		Reproductive effects, specific target organ toxicity	n-Hexane, toluene
Gas oils	• Straight run gas oils • Vacuum gas oils, hydrocracked gas oils and distillate fuels • Cracked gas oils • Other gas oils • MK-1 diesel fuels	Carcinogenicity, reproductive effects	PAHs,[c] naphthalene
Heavy fuel oils	• Heavy fuel oil components	Carcinogenicity, reproductive effects, acute toxicity	PAHs,[c] H_2S[a]
Kerosene/Jet fuel	• Kerosenes	–	Naphthalene
Lubricating grease thickeners	Not applicable	–	–
Lubricating oil base stocks	• Highly refined base oils • Unrefined/acid treated oils • Lubricant base oils • Foots oils	Carcinogenicity, reproductive effects	PAHs[c]
Petroleum coke	Not applicable	–	–
Petroleum gases	• Petroleum gases • Other petroleum gases	Carcinogenicity, mutagenicity, acute toxicity	1,3-butadiene,[d] H_2S[a]
Reclaimed substances	Not applicable	–	–
Waxes and related materials	• Paraffin and hydrocarbon waxes • Slack waxes • Petrolatums	Carcinogenicity, reproductive effects	PAHs[c]
Not applicable	• Sulphur	–	–

[a] Hydrogen sulphide is an acutely toxic gas, which can be released from some groups of petroleum substances.

[b] Benzene is classified by the International Agency for Research on Cancer (IARC) as a Group 1 carcinogen ('Carcinogenic to humans').

[c] Several 3-7 fused-ring polycyclic aromatic hydrocarbons (PAHs) are classified as Group 1 or 2 carcinogens ('Carcinogenic to humans' or 'Probably/possibly carcinogenic to humans') by IARC. Others are not classified or non-classifiable.

[d] 1,3-Butadiene is classified by IARC as a Group 1 carcinogen ('Carcinogenic to humans').

See the API HPV Category Assessment Document for the respective substance group at http://www.petroleumhpv.org/

Health Canada (2018) points out that a WoE approach is understood as a decision-making process that *'avoids relying solely on any one piece of information or line of evidence.'* In the context of risk assessments conducted under Canadian regulatory guidelines, the assessment approach will generally include:

a. gathering available and relevant information from multiple sources, including stakeholder submissions of information through voluntary or mandatory surveys, or information requirements for new substances notifications;
b. critically assessing the quality or reliability of individual studies or pieces of information, or the sources of summarized information (for example, international assessments);
c. assembling similar information for a parameter or end point to develop individual lines of evidence;
d. critically assessing each line of evidence based on overall strength or confidence in the information and its relevance to the assessment outcome; and
e. combining the lines of evidence to characterize risk and reach an assessment conclusion, in consideration of their relative strengths, consistency and coherency.

While WoE as applied in this guidance is not for the purposes of risk assessment, this same series of steps is relevant to assisting in the determination of hazard classification of petroleum substances using the GHS. WoE approaches may be used to decide whether the GHS classification should be based on toxicology data for a petroleum substance, or read-across from an analogue substance, when individual hazardous constituents are present.

A WoE analysis may indicate that, although a hazardous constituent of a petroleum substance may be present at or above a GHS cut-off concentration, high-quality data for the petroleum substance indicates that the constituent-driven health effect is not observed. The presence of other constituents in the substance may antagonize the adverse impacts of the hazardous constituent in question. For example, a specific target organ toxicity (STOT) classified constituent may require metabolism to produce the putative effect. However, one or more of the other constituents in the petroleum substance may inhibit the absorption and/or metabolism of the constituent, thereby rendering it less hazardous within the substance than if absorbed and metabolized alone (Gaskill and Bruce, 2016). The GHS (section 1.3.2.4.5.1) specifically addresses this condition by stating, *'A substance or mixture need not be classified when it can be shown by conclusive experimental data from internationally acceptable test methods that the substance or mixture is not biologically available.'*

Such a case would require that the WoE analysis includes data indicating that (1) exposure to a substance-specific percentage of the hazardous constituent results in less toxicity than exposure to the constituent alone, and (2) one or more components of the substance are known to antagonize the effect of the hazard. A combination of in vivo toxicity, in vivo or in vitro pharmacokinetic, (Q)SAR and epidemiology data may all be used to jointly point to this conclusion.

The tiered approach to the classification of petroleum substances is shown in Figure 2 on page 12.

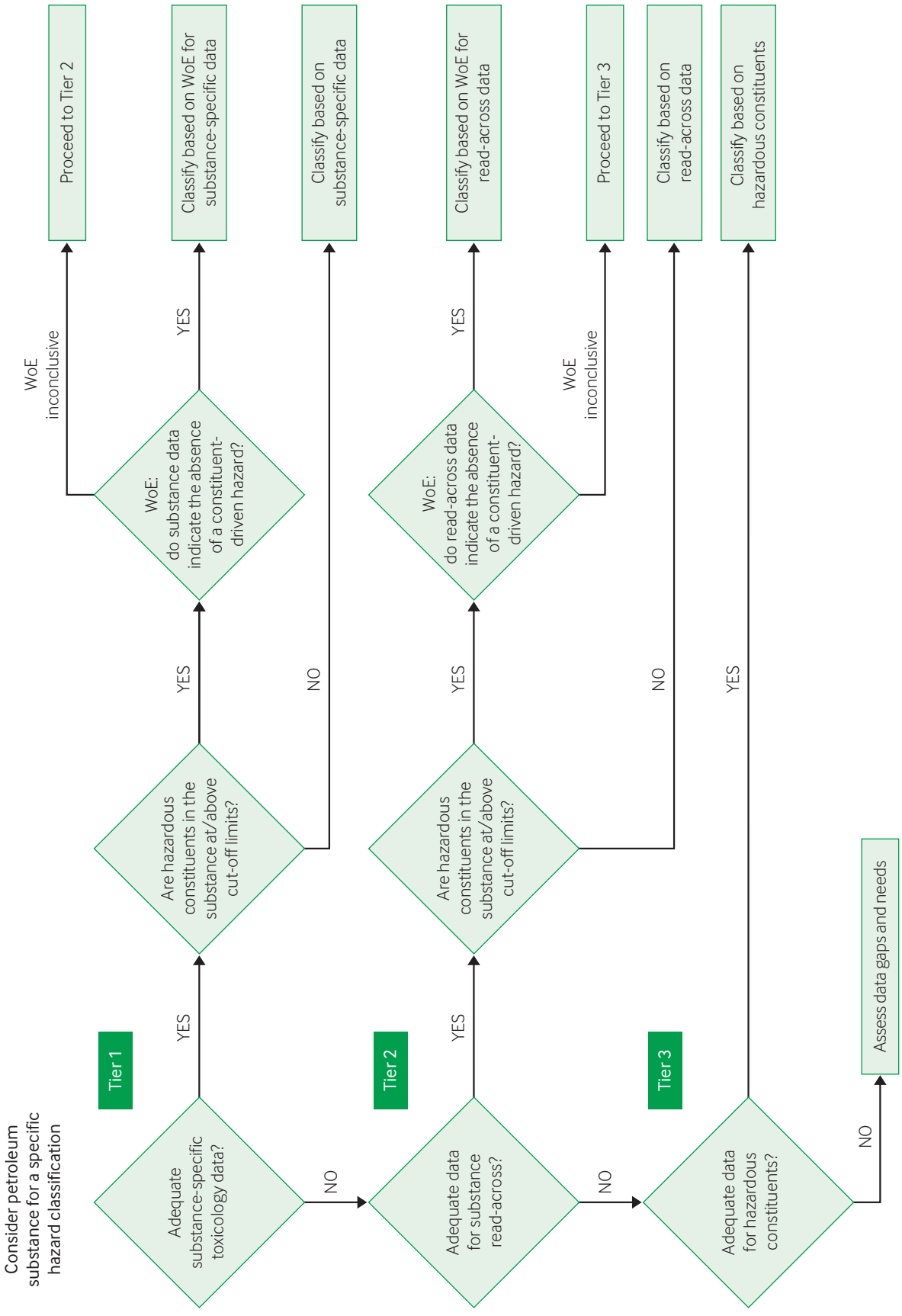


Figure 2 Classification process for health effects

SPECIFIC CLASSIFICATION GUIDANCE BY HAZARD CLASS

Acute toxicity

Hydrogen sulphide is a naturally occurring, acutely toxic gas, which can be released from some groups of petroleum substances (e.g. crude oil, petroleum gases, heavy fuel oil streams, etc.). The levels of hydrogen sulphide are generally below the specified concentration limits that warrant classification. However, hydrogen sulphide may collect in a container headspace during storage and transport. Adequate warning for this possibility should be in place (see Appendix A.4.3.7 in the GHS).

A petroleum substance may not be classified for acute toxicity from hydrogen sulphide if the levels are below the cut-off value/concentration limit. However, if headspace accumulation of hydrogen sulphide is likely, regardless of measured levels in the petroleum substance, it is advisable to include appropriate warnings on the safety data sheet (SDS).

Skin and eye irritation and corrosion

There are generally sufficient read-across data to assess the eye and skin irritancy and corrosion hazard of most petroleum substances; these data should be considered as the primary source of data for determining hazard classification. It should also be noted that petroleum substances (hydrocarbons in general) may cause defatting of the skin, leading to skin dryness and cracking. It is recommended that appropriate warnings are included on the SDS.

Germ cell mutagenicity

Constituents generally accepted as mutagenic in petroleum substances are 1,3-butadiene and benzene. More specific scientific information about benzene and 1,3-butadiene in petroleum substances can be found in the technical support document on pages 23 and 24, respectively.

In the absence of reliable data on the substance or from read-across, classification as mutagen Category 1B is recommended, where:

a. it is consistent with applicable cut-off values/ concentration limits for Category 1 mutagens (such as benzene and 1,3-butadiene); and
b. there is no evidence from human epidemiology studies that warrant classification as a Category 1A mutagen.

Carcinogenicity

Constituents that may be found in petroleum substances and which are generally accepted as carcinogenic include 1,3-butadiene, benzene and some 3-7 fused-ring polycyclic aromatic hydrocarbons (PAHs). In the absence of reliable data on the substance or from read-across for 1,3-butadiene and benzene, the cut-off values/ concentration limits as laid out in Section 1.3.3.1.3 of the GHS should be applied. More specific scientific information about benzene and 1,3-butadiene in petroleum substances can be found in the technical support document on pages 23 and 24, respectively.

For petroleum substances containing PAHs, the skin carcinogenic potential is related to the level of 3-7 fused-ring PAHs. While concentrations of individual PAHs can be determined, and certain PAHs are classified as carcinogenic (e.g. by IARC[1]), the skin carcinogenic potential of petroleum substances should normally be assessed based on the whole substance, taking into account the total PAH content. This is because individual PAHs may occur at toxicologically insignificant concentrations, but the total PAH-content may be toxicologically important. Some examples of tests that are widely accepted as being able to determine the carcinogenic potential of specific petroleum substances containing 3-7 fused-ring PAHs are listed below:

a. Skin painting studies in mice (Freeman and McKee, 1993).
b. Modified Ames test E-1687 (Blackburn *et al.,* 1986; ASTM, 2004; Concawe, 2012).
c. Dimethylsulphoxide (DMSO) extractables as determined by IP 346 (Concawe, 1994, 2016; Institute of Petroleum, 1993).

[1] International Agency for Research on Cancer. https://www.iarc.fr/

More specific scientific information about PAHs in petroleum substances and the test methods above can be found in the technical support document on pages 22–23.

In the absence of reliable data on the substance or from read-across, classification as carcinogen Category 1B is recommended, where:

a. this is consistent with the cut-off values/ concentration limits for Category 1 carcinogens as laid out in Section 1.3.3.1.3 of the GHS; and
b. there is no evidence from human epidemiology studies that warrant classification as a Category 1A carcinogen.

Reproductive toxicity

Examples of constituents which may be classified for this hazard class are PAHs, n-hexane, and toluene. More specific scientific information can be found in the technical support document on pages 22–27.

Specific target organ toxicity following single exposure (STOT-SE)

Exposure to high levels of certain low boiling point hydrocarbons may cause narcotic effects. These narcotic effects may occur when exposed to high concentrations of petroleum substances with a relatively low boiling point, for example petroleum gases and naphthas/gasolines. These effects are covered under STOT-SE Category 3: transient target organ effects, because central nervous system (CNS) depression and other narcotic effects in humans and/or animal studies are reversible. For effects that are not transient, the substance should be considered for Category 1 or 2.

Specific target organ toxicity following repeated exposure (STOT-RE)

Constituents that may be present in some groups of petroleum substances that are classified as STOT-RE include benzene, n-hexane and toluene. More specific scientific information about benzene, n-hexane and toluene in petroleum substances can be found in the technical support document on pages 23–27.

Aspiration

Petroleum substances may present an aspiration hazard, depending on their viscosity. Guidance on classification for this hazard class is laid out in Section 3.10 of the GHS.

ANIMAL TESTING AND ANIMAL WELFARE

IPIECA shares the concerns for the welfare of experimental animals described in section 1.3.2.4.6 of the GHS. Application of this guidance can maximize the use of existing health data while significantly reducing the overall number of animals needed. The similarity of many petroleum substances allows for their grouping by toxicological similarity based on chemical composition. Petroleum substances that are representative of each group, or considered to represent the most hazardous member of the category, are used as test materials to develop health effects data that can be extrapolated to all the substances in their respective group. This will reduce the testing of similar complex substances.

Ongoing research is being conducted by an international scientific consortium overseen by Concawe. The Cat-App project (Concawe, 2018) approach is to *'integrate innovations in (i) in vitro testing, (ii) high-throughput genomics and (iii) integrative data analyses and visualization into a transparent workflow for read-across assessment of UVCBs'*. The latest publications and guidance on read-across methodology should be considered in UVCB classification in an effort to leverage state-of-the-art science as well as reduce animal usage.

When laboratory animal testing is necessary, IPIECA strongly recommends minimizing the number of laboratory animals used to the greatest extent possible within the constraints of the regulatory requirements, and conducting studies according to competent scientific and OECD guidelines. Where possible, laboratories accredited by the Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC) or equivalent organizations should be used.

INFORMATION REQUIREMENTS

To use the above schemes for classification purposes, the individuals making the classification must have access to the required data and apply the GHS criteria.

It is recommended that the individuals making the classification also:

a. maintain records on the level of substance constituents, when they are used as a basis for classification decisions;
b. ensure that the studies used to derive a classification decision are of a consistent and reliable quality; and
c. have access to the documentation that provides the read-across rationale.

ADVANTAGES OF THE PROPOSED APPROACH

Advantages of the proposed approach are as follows:

a. It supplements GHS criteria with tools (e.g. grouping of substances, information on constituents of concern) to classify petroleum substances that are of unknown and variable composition.
b. It makes full use of available test data, thereby minimizing animal testing.
c. It is consistent with GHS and represents a universal oil and gas industry view.
d. It outlines the critical aspects to be considered in the determination of hazard classification and hazard communication of the petroleum substance in a similar and reliable way across the globe, regardless of regional differences in the classification of the constituents.

IPIECA recognizes that the GHS permits competent authorities to implement the GHS as the country deems appropriate. This may include different nation-specific concentration limits that influence classification. By providing relevant sector-specific guidance, the hazard classification of the petroleum substance should be globally consistent regardless of regional differences in the implementation of GHS or classification of individual petroleum substance constituents.

REFERENCES AND FURTHER READING

ASTM (2004). ASTM Standard E-1687-04: *Standard Test Method for Determining Carcinogenic Potential of Virgin Base Oils in Metalworking Fluids*. American Society for Testing and Materials (ASTM International), West Conshohocken, PA, US. https://www.astm.org/DATABASE.CART/HISTORICAL/E1687-04.htm

API (2018). 'Petroleum High Production Volume (HPV) Testing Group' (website). American Petroleum Institute. http://www.petroleumhpv.org

Blackburn, G. R., Deitch, R. A., Schreiner, C. A. and Mackerer, C. R. (1986). 'Predicting carcinogenicity of petroleum distillation fractions using a modified Salmonella mutagenicity assay.' In *Cell Biology and Toxicology*, Vol. 2, Issue 1, pp. 63-84. https://link.springer.com/article/10.1007/BF00117708

Concawe (1994). *The use of the dimethyl sulphoxide (DMSO) extract by the IP 346 method as an indicator of the carcinogenicity of lubricant base oils and distillate aromatic extracts*. Concawe report no. 94/51. https://www.concawe.eu/wp-content/uploads/2017/01/rpt9451ocr-2005-00417-01-e.pdf

Concawe (2012). *Use of the modified Ames test as an indicator of the carcinogenicity of residual aromatic extracts*. Concawe report no. 12/12. https://www.concawe.eu/wp-content/uploads/2017/01/rpt_12-12-2013-00133-01-e.pdf

Concawe (2016). *Critical review of relationship between IP346 and dermal carcinogenetic activity*. Concawe report no. 6/16. https://www.concawe.eu/wp-content/uploads/2017/01/report-6-16-final-version-3.pdf

Concawe (2017). *Hazard classification and labelling of petroleum substances in the European Economic Area – 2017*. Concawe report no. 13/17. https://www.concawe.eu/wp-content/uploads/2017/11/Rpt_17-13.pdf

Concawe (2018). 'Cat-App Project. New technologies to underpin category approaches and read-across in regulatory programmes' (website). https://www.concawe.eu/cat-app/

ECHA (2018). 'Weight of Evidence. (How to avoid unnecessary testing on animals)' (website). European Chemicals Agency. https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/weight-of-evidence

EIA (2012). 'Crude oil distillation and the definition of refinery capacity' (website). US Energy Information Administration. https://www.eia.gov/todayinenergy/detail.php?id=6970

Freeman, J J. and McKee, R. H. (1993). 'The Objectives and Goals of Dermal Carcinogenicity Testing of Petroleum Liquids.' In *Health Risk Assessment: Dermal and Inhalation Exposure and Absorption of Toxicants*, pp. 283-289. Wang, R. G. M., Knaack, J. B. and Maibach, H. I., eds. CRC Press, Boca Raton. https://www.crcpress.com/Revival-Health-Risk-Assessment-Dermal-and-Inhalation-Exposure-and-Absorption/Wang-Knaak-Maibach/p/book/9781138560185

Gaskill, S. J. and Bruce, E. D. (2016). 'Binary Mixtures of Polycyclic Aromatic Hydrocarbons Display Nonadditive Mixture Interactions in an In Vitro Liver Cell Model.' In *Risk Analysis*, Vol. 36, Issue 5, pp. 968-991. https://onlinelibrary.wiley.com/doi/10.1111/risa.12475

Health Canada (2018). 'Application of weight of evidence and precaution in risk assessment' (website). https://www.canada.ca/en/health-canada/services/chemical-substances/fact-sheets/application-weight-of-evidence-precaution-risk-assessments.html

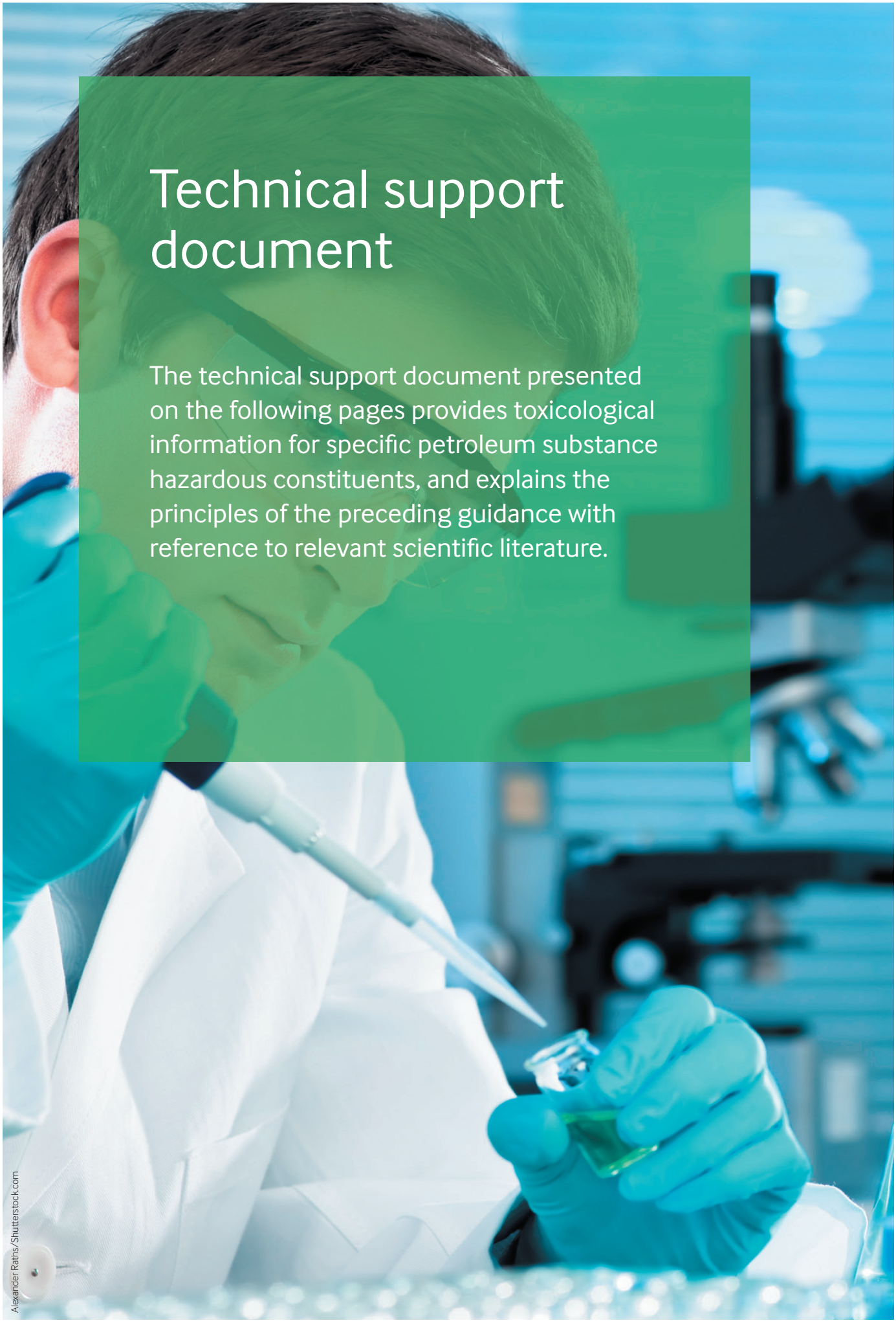
Institute of Petroleum (1993). *Test Standard IP 346/80. Determination of polycyclic aromatics in petroleum fractions by dimethyl sulphoxide refractive index method.* London, 1993.

United Nations (2017). *Globally Harmonized System of Classification and Labelling of Chemicals (GHS).* Seventh revised edition. United Nations, New York and Geneva. https://www.unece.org/trans/danger/publi/ghs/ghs_rev07/07files_e.html

US EPA (2007). 'High Production Volume (HPV) Chemicals Challenge Program.' US Environmental Protection Agency.

Technical support document

The technical support document presented on the following pages provides toxicological information for specific petroleum substance hazardous constituents, and explains the principles of the preceding guidance with reference to relevant scientific literature.



Alexander Raths/Shutterstock.com

The application of Globally Harmonized System (GHS) criteria to petroleum substances

INTRODUCTION

This technical support document provides toxicological information for specific petroleum substance hazardous constituents. The IPIECA approach, described in the guidance document and in Clark *et al.* (2013), provides a framework for evaluating and utilizing various tiers of toxicological data to classify one or more health hazard categories specific to each petroleum substance group. This includes using substance-specific data of sufficient quality, read-across data and, in some cases, toxicity data for individual hazardous constituents. Two case studies are provided to illustrate the use of unknown or variable composition, complex reaction products or biological (UVCB) substance-specific toxicology data to determine the most appropriate hazard classifications. Hazard data for individual hazardous constituents are also discussed for use in cases where the weight of evidence (WoE) supports use of these data instead of substance-specific data or surrogate read-across. The seventh revised edition of the UN *Globally Harmonized System of Classification and Labelling of Chemicals (GHS)* (the GHS) published in 2017 (section 1.3.3.2) defines cut-off values/concentration limits to be used for each hazard class when the WoE does not support the use of substance-specific or read-across toxicity data. The GHS indicates that the use of cut-off values/concentration limits may also apply to individual constituents of a substance.[2] The variability in concentrations of hazardous constituents found in petroleum substance streams has been evaluated in a recent comprehensive study (PERF, 2018). This variability may impact the final classification of petroleum substance streams based on the use of cut-off values/concentration limits, where applicable based on a WoE approach, for the hazardous constituents listed in Table 2 on page 10.

UVCB CASE STUDIES: THE WEIGHT-OF-EVIDENCE APPROACH TO USING SUBSTANCE-SPECIFIC DATA

Two case studies (mineral lubricating oil containing polycyclic aromatic hydrocarbons (PAHs), and light straight-run naphtha) are provided here as examples of using UVCB data in the tiered approach (described in the guidance and shown in Figure 2 on page 12) to properly classify hazards of petroleum products. Due to the complexity of UVCBs, classifying these petroleum products based strictly on the presence of hazardous constituent cut-off value/concentration limits using mixtures rules outlined in the GHS can result in improper hazard classification. These case studies highlight the importance of evaluating and prioritizing substance-specific data when performing WoE-based hazard classification of UVCB substances.

Mineral lubricating oil containing polycyclic aromatic hydrocarbons

Petroleum-derived mineral lubricating oils are composed primarily of aliphatic and aromatic hydrocarbons. There are nearly 100 mineral oils that have specific CAS numbers.[3] A subset of PAHs is considered the relevant hazardous constituent for mineral lubricating oils; their presence is dependent on the manufacturing process and refining severity. While the typical manufacturing process has been optimized to maximize the removal of potentially carcinogenic PAHs, some petroleum-based mineral oils may not be sufficiently refined to be non-carcinogenic. Based on available data, the hazardous constituents of concern identified for these mineral oils were PAHs. In this example, the concentration of benzo(a)pyrene (a carcinogenic PAH constituent), is less

[2] There may be national and regional differences in cut-off values/concentration limits. Further, in some regions, classification is based strictly on cut-off values/concentration limits, whereas in other parts of the world, classification is not required if experimental evidence is available demonstrating that the stipulated effects do not occur at the cut-off value/classification limits.

[3] See page 7 for CAS definition.

than 0.01%, which would not require classification for carcinogenicity using the GHS cut-off value/ concentration limits. However, substance-specific rodent skin carcinogenicity data on the example oil are available, showing a statistically significant increase in tumours in mice. Animal test data have consistently shown that individual PAH levels alone are not good predictors of a carcinogenic outcome (McKee *et al.,* 1989, Agarwal *et al.,* 1988). This is a case in which the carcinogenic potential of this mineral oil would not be properly identified if an evaluator relied solely on individual PAH values rather than relying on adequate substance-specific data. Evaluation of mineral lubricating oils in general should focus on animal testing results of the whole substance or appropriate screening tools as discussed further in the section on PAHs on pages 22–23.

Light straight-run naphtha

Naphtha is a generic term used to describe petroleum-derived volatile, flammable hydrocarbon fractions. Naphthas are used in the production of solvents and in gasoline blends. Their hydrocarbon content is predominantly 4- to 10-carbon chain length aliphatic compounds. An example naphtha stream is presented in Table 3 on page 20. It should be noted that straight-run naphtha streams are themselves variable in chemical content—the constituents shown in Tables 3 and 4 (page 20) are for purposes of illustration of the tiered approach and should not be used to classify naphtha streams in general.

If the example straight-run naphtha stream shown in Table 3 was treated as a mixture, there are 15 constituents that would drive classifications for various specific hazards.

However, applying the tiered approach, it is determined that adequately robust toxicological testing data for most of the hazard end points are available for this straight-run naphtha stream. Using these substance-specific data, it was determined that light straight-run naphtha does not require classification for eye irritation, specific target organ toxicity, reproductive toxicity or germ cell mutagenicity. Classification for aspiration toxicity was warranted based on the viscosity of the example straight-run naphtha stream. However, evaluation of the available data indicates the absence of adequate carcinogenicity studies for naphtha substances (e.g. move from Tier 1 to Tier 2 in Figure 2).

Additionally, adequate carcinogenicity data from studies of chemically-similar substances are not available for read-across (e.g. move from Tier 2 to Tier 3 in Figure 2). The presence of benzene in straight-run naphtha suggests the potential for carcinogenic hazards. Therefore, in the absence of other information, the example straight-run naphtha comprised of 0.1% or higher benzene may be classified as Carcinogen Category 1B. The resulting hazard classification for this example of straight-run naphtha is shown in Table 4.

These examples highlight the susceptibility of constituent-only information to over- or under-classify complex substances such as UVCBs. They illustrate the need to consider both substance-specific data and hazardous constituent information for proper hazard classification of UVCB products.

Table 3 Hazard classification for an example straight-run naphtha identified using the GHS mixtures approach

CASRN†	NAME	WEIGHT %	SKIN IRRITATION	EYE IRRITATION	ASPIRATION TOXICITY	STOT-SE: CNS DEPRESSION	STOT-RE	REPRO-DUCTIVE TOXICITY	CARCINO-GENICITY	GERM CELL MUTAGENICITY
78-78-4	isopentane	22.49			Cat 1	Cat 3				
109-66-0	n-pentane	16.27			Cat 1	Cat 3				
107-83-5	2-methylpentane	7.00	Cat 2	Cat 2B	Cat 1	Cat 3				
110-54-3	n-hexane	6.26	Cat 2		Cat 1	Cat 3	Cat 2 N Syst*	Cat 2 - F		
106-97-8	n-butane	5.58								
96-37-7	methylcyclopentane	4.57			Cat 1					
96-14-0	3-methylpentane	3.70	Cat 2	Cat 2A	Cat 1					
108-87-2	methylcyclohexane	2.48	Cat 2		Cat 1	Cat 3				
2453-00-1	1,3 dimethylcyclopentane	2.26			Cat 1					
142-82-5	n-heptane	2.00	Cat 2		Cat 1	Cat 3				
287-92-3	cyclopentane	1.73			Cat 1	Cat 3				
110-82-7	cyclohexane	1.67	Cat 2		Cat 1	Cat 3				
589-34-4	3-methylhexane	1.42			Cat 1					
108-88-3	toluene	1.12	Cat 2		Cat 1	Cat 3	Cat 2 CNS**	Cat 2 - D		
71-43-2	benzene	0.70	Cat 2	Cat 2A	Cat 1		Cat 1 Blood		Cat 1A	Cat 1B
100-42-4	ethylbenzene	0.28							Cat 2	
Threshold concentration (%)			10	3	None	20	1	0.1	0.1	0.1
Mixture classification			**Cat 2**	**Cat 2A**	**Cat 1**	**Cat 3**	**Cat 2**	**Cat 2 F&D**	**Cat 1A**	**Cat 1B**

† CASRN = Chemical Abstract Service Registry Number * Peripheral nervous system ** Central nervous system F = Fertility D = Developmental toxicity

Table 4 Hazard classification for an example straight-run naphtha identified using the substance-specific data applied via the WoE approach

CASRN†	NAME	WEIGHT %	SKIN IRRITATION	EYE IRRITATION	ASPIRATION TOXICITY	STOT-SE: CNS DEPRESSION	STOT-RE	REPRO-DUCTIVE TOXICITY	CARCINO-GENICITY	GERM CELL MUTAGENICITY
64741-46-4	Light straight-run naphtha	100	Cat 2	Neg	Cat 1	Cat 3	Neg	Neg	Cat 1B[a]	Neg

† CASRN = Chemical Abstract Service Registry Number Neg = Negative result from testing of the whole substance [a] Based on benzene content ≥ 0.1%

The remainder of this technical support document describes common hazardous constituents of petroleum substances. Where available, adequate substance-specific (Tier 1) or read-across (Tier 2) data are discussed. This section only includes the relevant hazard class associated with the presence of each hazardous constituent in petroleum substances (as highlighted in Table 2 on page 10). Other hazard classes not relevant for classification or hazard communication are outside the scope of this document, and references to comprehensive reviews are provided.

HYDROGEN SULPHIDE

Relevant substance groups

Hydrogen sulphide may be found in crude oil, heavy fuel oils and some petroleum gases. Small amounts of hydrogen sulphide may volatilize from heated bitumen/asphalt. Although these substance groups may not release hydrogen sulphide in ambient air at acutely toxic concentrations, they (particularly sour crude oil) may generate high levels in the headspaces of confined spaces, such as storage tanks and cargo holds. Acute toxicity is considered to be the relevant hazard end point associated with the presence of hydrogen sulphide in petroleum substances. Other end points are not expected to contribute to the classification of petroleum streams, and a summary of this information can be found in the ACGIH Threshold Limit Value (TLV) documentation for hydrogen sulphide (ACGIH, 2010) as well as the EU SCOEL (SCOEL, 2007).

Acute toxicity

Hydrogen sulphide has a low odour threshold in humans, ranging from approximately 0.0002 ppm to 0.3 ppm (Milby and Baselt, 1999, as cited in ACGIH, 2010). However, fatigue of the olfactory neurons may occur, rendering the odour warning properties moot. In humans, inhaling a few breaths of 1,000–2,000 ppm hydrogen sulphide can be life-threatening due to central nervous system (CNS) toxicity (Nordic Council of Ministers, 2001, as cited by ACGIH, 2010). In rats, LC_{50} values of approximately 300–600 ppm have been derived following two to six-hour exposures (Tansey *et al.,* 1981 and Prior *et al.,* 1988, as cited by ACGIH, 2010).

NAPHTHALENE

Relevant substance groups

Naphthalene has been identified in several petroleum substance groups including crude oil, gas oils and kerosene/jet fuel. Carcinogenicity is considered the relevant hazard end point associated with the presence of naphthalene in petroleum substances. Specific details of the carcinogenic potential of naphthalene are discussed below. However, naphthalene is often found in petroleum substances containing other carcinogenic constituents such as benzene and PAHs. Other hazard end points related to naphthalene are not expected to contribute to the classification of petroleum substances and are covered in other reports (ATSDR, 2005).

Carcinogenicity

Naphthalene has been shown to be carcinogenic in animal studies. Olfactory neuroblastoma and respiratory epithelial adenomas were observed in both male and female mice exposed to naphthalene in a two-year NTP[4] inhalation study (NTP, 2000). Based on these results, naphthalene is categorized as a Category 2 carcinogen (suspected of causing cancer in humans) using criteria shown in Table 3.6.1 in the GHS. It is worth noting that an expert panel convened at a 2006 Naphthalene State of the Science Symposium reviewed the reported whole animal cancer bioassays for naphthalene, focusing on the NTP mouse and rat tumours (North *et al.,* 2008). The panel found that naphthalene concentrations used in both NTP bioassays exceeded the maximum tolerated dose (MTD), eliciting inflammation at or near 100% incidences in both sexes of both species, strongly suggesting that cytotoxicity played a significant role in the tumour responses observed in the target tissues. An in-depth assessment of the mechanism of action and relevancy to cancer risk in humans is beyond the scope of this document and is discussed elsewhere (Lewis, 2012; NTP, 2000). Additionally, a WoE evaluation has been published in the literature that supports a non-mutagenic mode of action (MoA) with a threshold for naphthalene tumorigenicity (Bailey *et al.,* 2016).

[4] National Toxicology Program, US Department of Health and Human Sciences. https://ntp.niehs.nih.gov/

POLYCYCLIC AROMATIC HYDROCARBONS

PAHs are a group of chemicals that are formed during the incomplete burning of coal, oil, gas, wood, garbage or other organic substances. They can either be derived synthetically or occur naturally. PAHs can be present in crude oil and may be fractionated into certain petroleum streams during the refining process, including aromatic extracts, asphalt, heavy fuel oils, petroleum coke and lubricating oils (API, 2018). PAHs represent a class of chemical compounds with hazardous properties such as carcinogenicity and reproductive effects. Specific 3-7 fused-ringed PAHs are classified by the International Agency for Research on Cancer (IARC) as 'carcinogenic to humans (Group 1)' or as 'probably/possibly carcinogenic to humans (Group 2A/B).'

Carcinogenicity

It is known that the PAH fraction in petroleum substances can present a carcinogenic hazard to skin (Chasey and McKee, 1993; McKee *et al.,* 1989; Roy *et al.,* 1988a). The mutagenicity and skin carcinogenic potential of petroleum substances containing PAHs is related to the level of 3-7 fused-ring PAHs (Hermann *et al.,* 1979; Roy *et al.,* 1988a). While concentrations of specific PAHs can be determined, the skin carcinogenic potential of petroleum substances should be assessed based on the whole substance, taking into account the total PAH content. Currently, two tests (IP 346 and ASTM E-1687) are used for estimating the carcinogenic potential of certain product groupings including:

a. treated distillate aromatic extracts;
b. lubricant base oils;
c. foots oils; and
d. residual aromatic extracts (RAE) (ASTM E-1687 only).

IP 346 and ASTM E-1687 consider the total PAH content of petroleum substances, rather than specific PAHs.

IP 346 is a chemical method that gravimetrically measures dimethyl sulphoxide (DMSO) extractables, which include PAHs. The method is applicable to the product groups mentioned above (with the exception of RAE, as IP 346 is not considered an accurate screening method for carcinogenicity of these substances). Results of IP 346 tests have a strong correlation with the results of epidermal carcinogenicity bioassays (Booth *et al.,* 1998; Chasey *et al.,* 1993; Doak *et al.,* 1985; Roy *et al.,* 1988a; Concawe, 2016). Petroleum substances containing less than 3% w/w DMSO extractables as measured by IP 346 are not carcinogenic to skin. Where IP 346 testing indicates a w/w DMSO extractable value ≥ 3% for the product groups above (excluding RAEs), the substance must be classified for carcinogenicity in the EU and is reflected in the Classification, Labelling and Packaging (CLP) legislation as Note L. The IP 346 test is also used in Australia for identifying and classifying for carcinogenicity of virgin petroleum oils.

ASTM E-1687 is commonly known as the modified Ames test. It is based upon the standard *Salmonella* mutagenesis assay but is modified to enhance sensitivity to PAHs in oils. ASTM E-1687 is applicable to virgin base oils with viscosities of 18 cSt (90 SUS) or greater at 40°C. Whereas IP 346 is an analytical test, ASTM E-1687 is a biological test that identifies mutagenic activity in the DMSO-extractables of an oil. Results from ASTM E-1687 have a high correlation with the results of epidermal carcinogenicity bioassays for petroleum substances with median boiling points > 260°C to those with initial boiling points of ~577°C (Blackburn *et al.,* 1986; Roy *et al.,* 1988b). Petroleum substances in this boiling range which produced mutagenicity indices < 1.0 in the modified Ames test are not carcinogenic to skin (Przygoda *et al.,* 1992; Reddy *et al.,* 1992; Roy *et al.,* 1988b). The correlation between mutagenicity and carcinogenicity for RAEs appears to differ from the correlation established for lubricant base oils. Additional validation of the modified Ames test for its use as a screening method for potential carcinogenicity of RAEs indicate that RAEs with a mutagenicity index ≥ 0.4 demonstrated potential carcinogenic activity in mouse skin painting studies. RAEs with a mutagenicity index < 0.4 did not demonstrate any carcinogenic activity (Concawe, 2012). The approach for RAEs has been accepted in the EU and is reflected in the CLP legislation as Oil Industry Note 10 (Concawe, 2017).

Reproductive toxicity

A limited number of developmental toxicity studies of high-boiling petroleum substances and other petroleum streams have been published in the scientific literature (Feuston *et al.,* 1989; Feuston and Mackerer, 1996a; Feuston and Mackerer, 1996b; Feuston *et al.,* 1997a; Feuston *et al.,* 1997b). Certain high-boiling petroleum substances have been reported to cause evidence of developmental toxicity in animal studies. Among these substances, the end points of developmental toxicity

most often affected included an increased incidence of resorptions (and a corresponding decrease in the number of live fetuses per litter) and a decrease in fetal body weight.

A few individual PAHs have been evaluated for their potential to cause developmental toxicity. For example, benzo(a)pyrene has been reported to cause an increase in the percentage of resorptions and a decrease in fetal body weight among the offspring of pregnant rats exposed by subcutaneous injection (Bui *et al.,* 1986). In addition, decreased fetal survival was reported among the offspring of pregnant rats exposed by inhalation to benzo(a)pyrene (Archibong *et al.,* 2002).

However, because a single petroleum stream is typically composed of thousands of chemicals, it is not feasible to test each individual component of a petroleum stream for developmental toxicity. Further, even if it were feasible to test every component, the developmental toxicity of such complex mixtures is unlikely to be defined by a simple, additive approach (i.e. summing the toxicities of the individual components). Feuston *et al.* (1994) found that developmental toxicity (i.e. increased resorptions and decreased fetal body weight) was correlated with the concentrations of PAHs composed of 3 through 7 rings. Unlike carcinogenicity, however, a predictive test for the fetotoxic effects of PAHs has not been developed. Thus, classification of petroleum substances as developmental toxicants must rely on the WoE approach outlined in this document.

BENZENE

Relevant substance groups

Benzene has been identified in several petroleum substance groups including crude oil, naphthas and gasoline. The default classification cut-off value/ concentration limit for Category 1 carcinogens is 0.1%. Mutagenicity, carcinogenicity and specific target organ toxicity are considered the relevant end points associated with the presence of benzene in petroleum substances. Other hazard end points are not expected to contribute to the classification of petroleum substances and are covered in other reports (ATSDR, 2007).

Mutagenicity

Benzene has been shown to be genotoxic in vivo in both somatic and germ cells, and is classified as a Category 1B mutagen (IARC, 2012). Criteria for classification of germ cell mutagenicity is shown in table 3.5.1 in the GHS. Chapter 3.5.5 of the GHS should be consulted for classification of mutagenicity for products based on their benzene content.

Carcinogenicity

Benzene is classified as a group 1A carcinogen (IARC, 1982, 1987, 2012; DHHS, 2016; ACGIH, 2001a). Criteria for classification of carcinogenicity is shown in table 3.6.1 in the GHS. Benzene is associated with acute myelogenous leukemia in humans.

Reliable data (see section 1.3.2.4 in the GHS) from human epidemiology studies should be the first tier in classification for petroleum streams potentially containing benzene (e.g. naphthas). If reliable human epidemiology data are not available, it is recommended that the level of benzene is taken into account. For petroleum streams containing ≥ 0.1% benzene (e.g. naphthas), even in the absence of carcinogenic effects in animal studies, classification for carcinogenicity is recommended.

Specific target organ toxicity (STOT) after single exposure (SE)

Benzene is classified as a Category 3 STOT-SE compound due to its narcotic effects (transient target organ effects) (ATSDR, 2007). Criteria for classification of STOT after single exposure is shown in table 3.8.1 in the GHS.

Specific target organ toxicity (STOT) after repeated exposure (RE)

Benzene is classified as a Category 1 STOT-RE compound due to its haematologic effects. Criteria for classification of STOT after repeated exposure is shown in table 3.9.1 in the GHS. Tables 3.9.1 and 3.9.2 indicate recommended cut-off values based on the route of exposure.

The most characteristic systemic effect resulting from intermediate and chronic benzene exposure is arrested development of blood cells. Early biomarkers of exposure to relatively low levels of benzene include depressed numbers of one or more of the circulating blood cell types. A clinical finding in benzene haematotoxicity is cytopenia, which is a decrease in various cellular elements of the circulating blood manifested as anaemia, leucopenia, or thrombocytopenia in humans and in animals.

Data on high-benzene concentration petroleum streams (e.g. naphthas) show that repeated inhalation exposure for 90 days to full-range catalytic reformed naphtha (63% aromatics) resulted in a reduced white blood cell (WBC) count in sham treated controls and naphtha treated groups in both sexes compared to untreated controls. Additionally, the WBC count was decreased by approximately 24% in the high dose females when compared to the sham controls. The Lowest Observed Adverse Effect Level (LOAEL) for decreased WBC in females is 1,894 ppm (8,050 mg/m^3), and the No Observed Adverse Effect Level (NOAEL) is 464 ppm (1,970 mg/m^3) (Dalbey and Feuston, 1996).

For Category 1 classification, the guidance value for inhalation of vapours is set at 0.2 mg/L indicating that effects seen at or below this concentration should be classified as Category 1. The corresponding value for Category 2 is set between 0.2 and 1 mg/L. The observed 90-day LOAEL of 8,050 mg/m^3 or 8 mg/L for high-benzene naphtha is above these guidance values (Dalbey and Feuston, 1996). Therefore, it is concluded that petroleum naphtha streams should not be classified for STOT-RE based on benzene haematological effects.

1,3-BUTADIENE

Relevant substance groups

1,3-butadiene has been identified in certain petroleum gases. Carcinogenicity and mutagenicity are considered the relevant end points associated with the presence of 1,3-butadiene in petroleum substances. Other hazard end points are not expected to contribute to the classification of petroleum substances and are covered in other reports (ATSDR, 2012).

Mutagenicity

1,3-butadiene has been shown to be mutagenic in animal models. In mice, inhalation of 50, 200, 500 or 1,300 ppm 1,3-butadiene for 6 hours per day for 5 days resulted in micronuclei in mouse bone marrow and peripheral blood erythrocytes using the OECD Guideline 474 study design (Adler *et al.,* 1994).

Carcinogenicity

1,3-butadiene is classified by IARC as 'carcinogenic to humans (Group 1)' based on its association with leukaemia in humans. Multiple organ carcinogenicity was observed in mice exposed to 6.25, 20, 62.5, 200 or 625 ppm 1,3-butadiene via inhalation for 6 hours a day, 5 days a week, for up to 2 years using the OECD Guideline 453 study design (NTP, 1993). While carcinogenicity is observed in rodents, no appropriate animal models for the carcinogenic effect observed in humans (i.e. leukaemia) have been identified. Therefore, reliable data (see section 1.3.2.4 in the GHS) from human epidemiology studies should be the first tier in classification for petroleum substances potentially containing 1,3-butadiene (petroleum gases). If reliable human epidemiology data are not available, it is recommended that the level of 1,3-butadiene is taken into account. Chapter 3.6 of the GHS should be consulted for carcinogenicity.

N-HEXANE

Relevant substance groups

n-hexane has been identified in several petroleum substance groups including naphtha streams and gasoline. Reproductive effects and STOT are considered the relevant end points associated with the presence of n-hexane in petroleum substances. Other hazard end points are not expected to contribute to the classification of petroleum substances and are covered in other reports (ATSDR, 1999).

Reproductive/developmental toxicity

n-hexane has been shown to have reproductive toxicity in animal studies and is classified GHS Category 2 (suspected of damaging fertility or the unborn child) because of studies demonstrating adverse male reproductive effects (testicular toxicity). In rats, the NOAEL and LOAEL of inhaled n-hexane was determined to be 3,000 ppm and 9,000 ppm, respectively, for reduced body weight in offspring of both sexes using the OECD Guideline 416 study design (ECHA, 2017). However, these effects were secondary to frank maternal toxicity and, thus, not considered classifiable as a reproductive effect per GHS guidance. Two reproductive toxicity studies of a commercial hexane sample were conducted which demonstrate the lack of male reproductive effects in a hydrocarbon mixture containing 52% n-hexane.

The studies included:

a. A one-generation reproduction study, conducted in Sprague-Dawley rats for 6 hours per day, 5 days per week at 100, 500 and 1,500 ppm commercial hexane. Exposures were for 100 days pre-mating and during mating and gestation. No adverse reproductive or developmental effects were noted (API, 1986).
b. A two-generation reproduction study, conducted in Sprague-Dawley rats at concentrations of 900, 3,000 and 9,000 ppm commercial hexane. Exposures were 6 hours per day, 5 days per week for 10 weeks prior to mating, as well as during mating, gestation and lactation. Pups at the 9,000 ppm level showed reductions in initial body weight, which was concomitant with parental toxicity, but no other dose-related findings were observed. No adverse effects on reproduction were noted (Daughtrey *et al.,* 1994).

The reproductive toxicity effect (i.e. testicular toxicity) observed in studies with 100% n-hexane has not been observed in studies with commercial hexane containing 52% n-hexane. It is recommended that the information above is included along with other data on petroleum naphthas/gasolines in a WoE evaluation when determining the classification (see McKee and White, 2013).

Specific target organ toxicity (STOT) after single exposure (SE)

n-hexane has been shown to cause CNS effects (drowsiness or dizziness). A key study in humans found that inhalation of 5,000 ppm for 10 minutes resulted in dizziness and a sense of giddiness (Patty and Yant, 1929 as cited in ACGIH, 2001b).

Specific target organ toxicity (STOT) after repeated exposure (RE)

Inhalation of n-hexane has been shown to cause distal axonal neuropathy in humans and experimental animals, and is classified as GHS STOT-RE Category 2. In rats, the Lowest Observed Adverse Effect Concentration (LOAEC) was determined to be 3,000 ppm after 4 weeks of exposure. A No Observed Adverse Effect Concentration (NOAEC) was not determined (Takeuchi *et al.,* 1980). Hearing dysfunction has also been reported from high exposure of laboratory animals to n-hexane (Concawe, 2005). Perturbations in brainstem auditory evoked responses have been reported in rats repeatedly exposed to 1,000 ppm n-hexane (3.52 mg/L) for 18 hours per day over a course of 61 days.

A sub-chronic inhalation study of a commercial hexane sample was conducted which demonstrates the lack of neurotoxic effects in a hydrocarbon mixture containing 52% n-hexane.

Exposure of Sprague-Dawley rats to commercial hexane concentrations of 900, 3,000 and 9,000 ppm for 6 hours per day, 5 days per week for 13 weeks was conducted. Functional observational battery (FOB) tests were conducted at six different time points throughout the study, and motor activity was evaluated monthly. Exposure had no significant effects on the neurobehavioural or motor activity end points that were evaluated, and no significant neuropathological findings were reported (API, 1990).

Three additional sub-chronic (13-week) inhalation studies of naphtha light ends (light alkylate, light cat-cracked, and light cat-reformed) have utilized test batteries to evaluate neurotoxicity potential at total hydrocarbon concentrations as high as 6,646 ppm in the study of light alkylate naphtha and 7,500 ppm in the other two studies. No adverse neurotoxic effects were reported in any of the studies. The distillate fractions of the naphthas contained 4.5% n-hexane in the cat-reformed naphtha (Schreiner *et al.,* 2000) and 1.56% n-hexane in the cat-cracked naphtha (Lapin *et al.,* 2001).

The neurotoxic effect (i.e. distal axonal neuropathy) observed in studies with 100% n-hexane is not observed in studies with commercial hexane containing 52% n-hexane. It is recommended that the information above is included along with other data on petroleum naphthas/gasolines in a WoE evaluation when determining the classification (see McKee and White, 2013).

TOLUENE

Relevant substance groups

Toluene has been identified in several petroleum substance groups including naphthas and gasoline. Reproductive effects and STOT are considered the relevant end points associated with the presence of toluene in petroleum substances. Other hazard end points are not expected to contribute to the classification of petroleum substances and are covered in other reports (ATSDR, 2017).

Reproductive/developmental toxicity

Toluene has been shown to cause reproductive toxicity in animal studies. In rats, the NOAEC was determined to be 600 ppm via inhalation, with the basis for the effect level being decreased sperm count and reduced epididymides weights. Additionally, developmental toxicity was reported in pregnant rats at 1,000 ppm (EU, 2003).

A distillate fraction of light cat-reformed naphtha, containing 5.78% (by weight) toluene, was evaluated in an OECD 421 guideline reproductive/developmental toxicity screening study (Schreiner *et al.,* 2000). Exposures were to male and female Sprague-Dawley rats at naphtha concentrations of 750, 2,500 and 7,500 ppm, for 6 hours per day, 7 days per week for two weeks prior to mating and throughout days 0-10 of gestation. No developmental or reproductive effects were reported from the study.

The highest exposure concentration in this study is equivalent to 27,750 mg/m^3, of which 5.78 %, or about 1,600 mg/m^3 (420 ppm) represents exposure to toluene. At this level, no developmental or reproductive effects were reported from the study.

A developmental inhalation toxicity evaluation of unleaded gasoline containing 8% toluene was conducted in rats at gasoline concentrations of 1,000, 3,000 and 9,000 ppm, which did not produce any evidence of developmental toxicity (Roberts *et al.,* 2001).

Based on the studies presented above, naphtha and gasoline samples containing up to 8% toluene do not cause developmental toxicity. However, it is not known what toluene concentration represents the threshold for developmental effects. It is recommended that the information above is included along with other data on

petroleum naphthas/gasolines in a WoE evaluation when determining the classification (see McKee and White, 2013). In the absence of conclusive substance or read-across data, petroleum substances containing 3% or more toluene may be classified for developmental toxicity.

Specific target organ toxicity (STOT) after single exposure (SE)

Toluene has been shown to cause CNS effects (drowsiness or dizziness) following a single exposure to 75 ppm (< 20 mg/L) for four hours in human volunteers (EU, 2003). A study using those same exposure conditions found rocking gait behaviour and narcosis in rats (BASF, 1980).

Specific target organ toxicity (STOT) after repeated exposure (RE)

Inhalation of toluene has been shown to disrupt the auditory system and cause elevated auditory thresholds in laboratory animals, with rats being the most sensitive species (Pryor and Feeney, 1984; Brandt-Lassen *et al.,* 2000; Gagnaire and Langlais, 2005; McWilliams *et al.,* 2000; EU, 2003). The NOAEL for toluene ototoxicity in rats is 700 ppm (2.63 mg/L). This is based on a 16-week study with 14-hour daily exposure, which represents the longest exposure period studied (Concawe, 2005).

Aspiration Hazard

Based on its physical and chemical properties, toluene has been classified by the GHS as a Category 1 aspiration hazard using criteria shown in Table 3.10.1 in the GHS. It may be fatal if swallowed and enters the airways.

REFERENCES AND FURTHER READING

ACGIH (2001a). 'Benzene.' In *Documentation of the threshold limit values and biological exposure indices*, 7th Edition. American Conference of Governmental Industrial Hygienists, Cincinnati, Ohio. https://www.acgih.org/forms/store/ProductFormPublic/documentation-of-the-threshold-limit-values-and-biological-exposure-indices-7th-ed

ACGIH (2001b). 'n-hexane.' In *Documentation of the threshold limit values and biological exposure indices*, 7th Edition. American Conference of Governmental Industrial Hygienists, Cincinnati, Ohio. https://www.acgih.org/forms/store/ProductFormPublic/documentation-of-the-threshold-limit-values-and-biological-exposure-indices-7th-ed

ACGIH (2007). 'Toluene.' In *Documentation of the threshold limit values and biological exposure indices*, 7th Edition. American Conference of Governmental Industrial Hygienists, Cincinnati, Ohio. https://www.acgih.org/forms/store/ProductFormPublic/documentation-of-the-threshold-limit-values-and-biological-exposure-indices-7th-ed

ACGIH (2010). 'Hydrogen sulphide.' In *Documentation of the threshold limit values and biological exposure indices*, 7th Edition. American Conference of Governmental Industrial Hygienists, Cincinnati, Ohio. https://www.acgih.org/forms/store/ProductFormPublic/documentation-of-the-threshold-limit-values-and-biological-exposure-indices-7th-ed

Adler, I.-D., Cao, J., Filser, J. G., Gassner, P., Kessler, W., Kliesch, U., Neuhäuser-Klaus, A. and Nüsse, M. (1994). 'Mutagenicity of 1,3-butadiene inhalation in somatic and germinal cells of mice.' In *Mutation Research*, Vol. 309, Issue 2, pp. 307-314. https://www.sciencedirect.com/science/article/pii/0027510794901074

Agarwal, R., Shukla, Y., Kumar, S. and Mehrotra, N. K. (1988). 'Evaluation of carcinogenic effect of jute batching oil (JBO-P) fractions following topical application to mouse skin.' In *Archives of Toxicology*, Vol. 62, Issue 6, pp. 406-410. https://link.springer.com/article/10.1007/BF00288342

API (1978). *Teratology study in rats. Toluene*. Final Report submitted to the American Petroleum Institute, Washington D.C. LBI Project No. 20698-4, Litton Bionetics Inc.

API (1981), *Mutagenicity evaluation of toluene in the mouse dominant lethal assay*. Final Report submitted to the American Petroleum Institute, Washington D.C. LBI Project No. 21141-05, Litton Bionetics Inc.

API (1986). *Single-generation inhalation reproduction/ fertility study on a commercial hexane*. American Petroleum Institute, Health and Environmental Sciences Department Publication 33-32864. Washington, DC. https://global.ihs.com/doc_detail.cfm?&item_s_key=00305480&item_key_date=130301&input_doc_number=SINGLE-GENERATION%20INHALATION%20REPRODUCTION%2FFERTILITY%20STUDY%20ON%20A%20COMMERCIAL%20HEXANE&input_doc_title=

API (1990). *Subchronic Inhalation Study of Potential Effects on Behavior and Neuromorphology*. American Petroleum Institute, Health and Environmental Sciences Department Publication 37-31154. Washington, DC.

API (2018). 'Petroleum High Production Volume (HPV) Testing Group' (website). American Petroleum Institute. http://www.petroleumhpv.org

Archibong, A. E., Inyang, F., Ramesh, A., Greenwood, M., Nayyar, T., Kopsombut, P., Hood, D. B. and Nyanda, A. M. (2002). 'Alteration of pregnancy related hormones and fetal survival in F-344 rats exposed by inhalation to benzo(*a*)pyrene'. In *Reproductive Toxicology*, Vol. 16, Issue 6, pp. 801-808. https://www.sciencedirect.com/science/article/pii/S0890623802000588

ATSDR (1995). *Toxicological Profile for Polycyclic Aromatic Hydrocarbons (PAHs)*. Agency for Toxic Substances and Disease Registry, Atlanta, GA. https://www.atsdr.cdc.gov/toxprofiles/tp.asp?id=122&tid=25

ATSDR (1999). *Toxicological Profile for n-Hexane*. Agency for Toxic Substances and Disease Registry, Atlanta, GA. https://www.atsdr.cdc.gov/ToxProfiles/tp.asp?id=393&tid=68

ATSDR (2005). *Toxicological Profile for Naphthalene, 1-Methylnaphthalene, and 2-Methylnaphthalene*. Agency for Toxic Substances and Disease Registry, Atlanta, GA. https://www.atsdr.cdc.gov/toxprofiles/tp.asp?id=240&tid=43

ATSDR (2007). *Toxicological Profile for Benzene*. Agency for Toxic Substances and Disease Registry, Atlanta, GA. https://www.atsdr.cdc.gov/toxprofiles/tp.asp?id=40&tid=14

ATSDR (2012). *Toxicological Profile for 1,3-Butadiene*. Agency for Toxic Substances and Disease Registry, Atlanta, GA. https://www.atsdr.cdc.gov/ToxProfiles/tp.asp?id=459&tid=81

ATSDR (2017). *Toxicological Profile for Toluene*. Agency for Toxic Substances and Disease Registry, Atlanta, GA. https://www.atsdr.cdc.gov/ToxProfiles/tp.asp?id=161&tid=29

Bailey, L. A., Nascarella, M. A., Kerper, L. E. and Rhomberg, L. R. (2016). 'Hypothesis-based weight-of-evidence evaluation and risk assessment for naphthalene carcinogenesis.' In *Critical Reviews in Toxicology*, Vol. 46, No. 1, pp. 1-42. https://www.tandfonline.com/doi/full/10.3109/10408444.2015.1061477

BASF (1980). *Bestimmung der akuten Inhalationstoxizität LC_{50} von Toluol min. 99.5% (Merck AG) als Dampf bei 4stundiger Exposition an Sprague-Dawley-Ratten*.

Blackburn, G. R., Deitch, R. A., Schreiner, C.A. and Mackerer, C. R. (1986). 'Predicting carcinogenicity of petroleum distillation fractions using a modified *Salmonella* mutagenicity assay.' In *Cell Biology and Toxicology*, Vol. 2, Issue 1, pp. 63-84. https://link.springer.com/article/10.1007/BF00117708

Booth, E. D., Brandt, H. C., Loose, R. W. and Watson, W. P. (1998). 'Correlation of 32P-postlabelling-detection of DNA adducts in mouse skin in vivo with the polycyclic aromatic compound content and mutagenicity in Salmonella typhimurium of a range of oil products.' In *Archives of Toxicology*, Vol. 72, Issue 8, pp. 505-513. https://link.springer.com/article/10.1007/s002040050535

Brandt-Lassen, R., Lund, S. P. and Jepsen, G. B. (2000). 'Rats exposed to toluene and noise may develop loss of auditory sensitivity due to synergistic interaction.' In *Noise and Health*, Vol. 3, Issue 9, pp. 33-44. http://www.noiseandhealth.org/article.asp?issn=1463-1741;year=2000;volume=3;issue=9;spage=33;epage=44;aulast=Brandt-Lassen;type=0

Broddle, W. D. (1996). 'Chronic dermal studies of petroleum streams in mice.' In *Fundamental and Applied Toxicology*, Vol. 30, Issue 1, pp. 47-54. https://www.sciencedirect.com/science/article/pii/S0272059096900421

Bui, Q. Q., Tran, M. B. and West, W. L. (1986). A comparative study of the reproductive effects of methadone and benzo [*a*] pyrene in the pregnant and pseudopregnant rat. In *Toxicology*, Vol. 42, Issues 2–3, pp. 195-204. https://www.sciencedirect.com/science/article/pii/0300483X86900090

Carpenter, C. P., Shaffer, C. B., Weir, C. A. and Smyth, H. F. (1944). 'Studies on the inhalation of 1,3-butadiene.' In *Journal of Industrial Hygiene and Toxicology*, Vol. 26, No. 3, pp. 69-78.

Chasey, K. L. and McKee, R. H. (1993). 'Evaluation of the dermal carcinogenicity of lubricant base oils by the mouse skin painting bioassay and other proposed methods.' In *Journal of Applied Toxicology*, Vol. 13, Issue 1, pp. 57-65. https://onlinelibrary.wiley.com/doi/10.1002/jat.2550130112

Clark, C. R., McKee, R. H., Freeman, J. J., Swick, D., Mahagaokar, S., Pigram, G., Roberts, L. G., Smulders, C. J. and Beatty, P. W. (2013). 'A GHS-consistent approach to health hazard classification of petroleum substances, a class of UVCB substances.' In *Regulatory Toxicology and Pharmacology*, Vol. 67, Issue 3, pp. 409-420. https://www.sciencedirect.com/science/article/pii/S0273230013001451

Concawe (2005). *Factors potentially affecting the hearing of petroleum industry workers*. Concawe report No. 5/05, June 2005. https://www.concawe.eu/publication/report-no-505/

Concawe (2012). *Use of the modified Ames test as an indicator of the carcinogenicity of residual aromatic extracts*. Concawe report no. 12/12. https://www.concawe.eu/wp-content/uploads/2017/01/rpt_12-12-2013-00133-01-e.pdf

Concawe (2016). *Critical review of relationship between IP346 and dermal carcinogenetic activity*. Concawe report no. 6/16. https://www.concawe.eu/wp-content/uploads/2017/01/report-6-16-final-version-3.pdf

Concawe (2017). *Hazard classification and labelling of petroleum substances in the European Economic Area – 2017*. Concawe report no. 13/17. https://www.concawe.eu/wp-content/uploads/2017/11/Rpt_17-13.pdf

Dalbey, W. and Feuston, M. (1996). 'Partially Vaporized Full Range Catalytic Reformed Naphtha: Subchronic and Developmental Toxicity Studies in Rats.' In *Inhalation Toxicology*, Vol. 8, Issue 3, pp. 271-284. https://www.tandfonline.com/doi/abs/10.3109/08958379609005435

Daughtrey, W., Neeper-Bradley, T. and Duffy, J. (1994). 'Two-generation reproduction study on commercial hexane solvent.' In *Journal of Applied Toxicology*, Vol. 14, Issue 5, pp. 387-393. https://onlinelibrary.wiley.com/doi/10.1002/jat.2550140512

DHHS (2016). *14th Report on Carcinogens 2016*. U.S. Department of Health and Human Services, Public Health Service, National Toxicology Program. Research Triangle Park, NC. https://ntp.niehs.nih.gov/pubhealth/roc/index-1.html#toc1

Doak, S. M. A., Hend, R. W., Van Der Wiel, A. and Hunt, P. F. (1985). 'Carcinogenic potential of hydrotreated petroleum aromatic extracts.' In *British Journal of Industrial Medicine*, Vol. 42, No. 6, pp. 380-388. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1007495/

ECHA (2017). *Substance Evaluation Conclusion as required by REACH Article 48 and Evaluation Report for n-Hexane*. Evaluating Member State: Germany. Federal Institute for Occupational Safety and Health, Dortmund, Germany. https://echa.europa.eu/documents/10162/167cb34b-2110-c1e4-b50d-45f676bc5280

ECHA (2018a). 'Hydrogen sulphide' (website). European Chemicals Agency. https://echa.europa.eu/registration-dossier/-/registered-dossier/14463/7/4/3

ECHA (2018b). 'Naphthalene' (website). European Chemicals Agency. https://echa.europa.eu/registration-dossier/-/registered-dossier/15924/7/4/2

ECHA (2018c) 'N-hexane' (website). European Chemicals Agency. https://echa.europa.eu/registration-dossier/-/registered-dossier/15741

ECHA (2018d). 'Toluene' (website). European Chemicals Agency. https://echa.europa.eu/registration-dossier/-/registered-dossier/15538/7/4/3

EU (2002). *European Union Risk Assessment Report. 1,3-butadiene*. European Commission Institute for Health and Consumer Protection, European Chemicals Bureau. https://echa.europa.eu/documents/10162/1f512549-5bf8-49a8-ba51-1cf67dc07b72

EU (2003), *European Union Risk Assessment Report. Toluene*. European Commission Institute for Health and Consumer Protection, European Chemicals Bureau. https://echa.europa.eu/documents/10162/24a34bd6-55cd-4e28-ae24-5bae281bf3c2

Feuston, M. H., Kerstetter, S. L., Singer, E. J. and Mehlman, M. A. (1989). 'Developmental Toxicity of Clarified Slurry Oil Applied Dermally to Rats'. In *Toxicology and Industrial Health*, Volume 5, Issue 3, pp. 587-599. https://journals.sagepub.com/doi/pdf/10.1177/074823378900500313

Feuston, M. H., Low, L. K., Hamilton, C. E., and Mackerer, C. R. (1994). 'Correlation of Systemic and Developmental Toxicities with Chemical Component Classes of Refinery Streams'. In *Fundamental and Applied Toxicology*, Vol. 22, Issue 4, pp. 622-630. https://www.sciencedirect.com/science/article/pii/S0272059084710682

Feuston, M. H. and Mackerer, C. R. (1996a). 'Developmental Toxicity of Clarified Slurry Oil, Syntower Bottoms, and Distillate Aromatic Extract Administered as A Single Oral Dose to Pregnant Rats'. In *Journal of Toxicology and Environmental Health*, Vol. 49, Issue 1, pp. 45-66. https://www.tandfonline.com/doi/abs/10.1080/00984108.1996.10662169

Feuston, M. H. and Mackerer, C .R. (1996b). 'Developmental toxicity study in rats exposed dermally to clarified slurry oil for a limited period of gestation. In *Journal of Toxicology and Environmental Health*, Vol. 49, Issue 2, pp. 207-220. https://www.tandfonline.com/doi/abs/10.1080/00984108.1996.10662179

Feuston, M. H., Hamilton, C. E., Schreiner, C, A. and Mackerer, C. R. (1997a). 'Developmental Toxicity of Dermally Applied Crude Oils in Rats'. In *Journal of Toxicology and Environmental Health*, Vol. 52, Issue 1, pp. 79-93. https://www.tandfonline.com/doi/abs/10.1080/00984109708984054

Feuston, M. H., Hamilton, C. E. and Mackerer, C. R. (1997b). 'Systemic and Developmental Toxicity of Dermally Applied Syntower Bottoms in Rats'. In *Fundamental and Applied Toxicology*, Vol. 35, Issue 2, pp. 166-176. https://www.sciencedirect.com/science/article/pii/S0272059096922629

Gagnaire, F. and Langlais, C. (2005). 'Relative ototoxicity of 21 aromatic solvents.' In *Archives of Toxicology*, Vol. 79, Issue 6, pp. 346-354. https://link.springer.com/article/10.1007/s00204-004-0636-2

Gaskill, S. J. and Bruce, E. D. (2016). 'Binary Mixtures of Polycyclic Aromatic Hydrocarbons Display Nonadditive Mixture Interactions in an In Vitro Liver Cell Model.' In *Risk Analysis*, Vol. 36, Issue 5, pp. 968-991. https://onlinelibrary.wiley.com/doi/10.1111/risa.12475

Gibson, J. E. and Hardisty, J. F. (1983). 'Chronic toxicity and oncogenecity bioassay of inhaled toluene in Fischer-344 rats.' In *Fundamental and Applied Toxicology*, Vol. 3, Issue 4, pp. 315-319. https://www.sciencedirect.com/science/article/pii/S0272059083801468

Hackett, P. L., Sikov, M. R, Mast, T. J., Brown, M. G., Buschbom, R. L., Clark, M. L., Decker, J. R., Evanoff, J. J., Rommereim, R. L., Rowe, S. E. and Westerberg, R. B. (1987). *Inhalation Developmental Toxicology Studies of 1,3-Butadiene in the Rat*. Final report no. NIH-401-ES-40131. Prepared for the National Institute of Environmental Health Sciences, National Toxicology Program, Research Triangle Park, NC, by Pacific Northwest Laboratory, operated for the U.S. Department of Energy by Battelle. Document ref. PNL-6414. https://www.osti.gov/biblio/5664174/

Hermann, M., Durand, J. P., Charpentier, J. M., Chaue, O., Hofnung, M., Petroff, N., Vandecasteele, J.-P. and Weill, N. (1979). 'Correlations of Mutagenic Activity with Polynuclear Aromatic Hydrocarbon Content of Various Mineral Oils.' In *Polynuclear Aromatic Hydrocarbons: Chemistry and Biological Effects*, pp. 899-916. Battelle Press, Columbus, Ohio.

IARC (1982). *IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans. Volume 29: Some Industrial Chemicals and Dyestuffs*. International Agency for Research on Cancer, World Health Organization. Lyon, France. https://publications.iarc.fr/Book-And-Report-Series/Iarc-Monographs-On-The-Identification-Of-Carcinogenic-Hazards-To-Humans/Some-Industrial-Chemicals-And-Dyestuffs-1982

IARC (1987). *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Overall Evaluations of Carcinogenicity: An Updating of* IARC Monographs *Volumes 1 to 42. Supplement 7*. International Agency for Research on Cancer, World Health Organization. Lyon, France. https://monographs.iarc.fr/iarc-monographs-on-the-evaluation-of-carcinogenic-risks-to-humans-80/

IARC (2012). *IARC Monographs: Chemical Agents and Related Occupations. Volume 100 F. A Review of Human Carcinogens. IARC Monographs on the evaluation of carcinogenic risks to humans*. International Agency for Research on Cancer, World Health Organization. Lyon, France. https://monographs.iarc.fr/iarc-monographs-on-the-evaluation-of-carcinogenic-risks-to-humans-16/

Kimura, E. T., Ebert, D. M. and Dodge, P. W. (1971). 'Acute toxicity and limits of solvent residue for sixteen organic solvents.' In *Toxicology and Applied Pharmacology*, Vol. 19, Issue 4, pp. 699-704. https://www.sciencedirect.com/science/article/pii/0041008X71903012

Lapin, C., Bui, Q., Breglia, R., Koschier, F., Podhasky, P., Lapadula, E., Roth, R., Schreiner, C., White, R., Clark, C., Mandella, R. and Hoffman, G. (2001). 'Toxicity evaluation of petroleum blending streams: Inhalation subchronic toxicity/neurotoxicity study of a light catalytically cracked naphtha distillate in rats'. In *International Journal of Toxicology*, Vol. 20, Issue 5, pp. 307–319. https://journals.sagepub.com/doi/pdf/10.1080/109158101753253045

Litton Bionetics (1980). *Mutagenicity evaluation of n-hexane in the mouse dominant lethal assay*. Unpublished study by Litton Bionetics Inc., LBI Project Number 21141-01. Final report submitted to the American Petroleum Institute, Washington D.C. EPA document no. FYI-AX-0183-0231.

Lewis, R. J. (2012). 'Naphthalene animal carcinogenicity and human relevancy: Overview of industries with naphthalene-containing streams.' In *Regulatory Toxicology and Pharmacololgy*, Vol. 62, Issue 1, pp. 131-137. https://www.sciencedirect.com/science/article/pii/S0273230011002546

Mast, T., Hackett, P., Decker, J., Westerberg, R. B., Sasser, L. B., McClanahan, B. J., Rommereim, R. L. and Evanoff, J. J. (1988). *Inhalation reproductive toxicology studies: sperm morphology study of n-hexane in B6C3F1 mice*. Final report no. NIH-Y01-ES-70153. Prepared for the National Institute of Environmental Health Sciences, National Toxicology Program, Research Triangle Park, NC, by Pacific Northwest Laboratory, operated for the U.S. Department of Energy by Battelle. Document ref. PNL-6672. https://www.osti.gov/biblio/6800315

McKee, R. H., Daughtrey, W. C., Freeman, J. J., Frederici, T. M., Phillips, R. D. and Plutnick, R. T. (1989). 'The dermal carcinogenic potential of unrefined and hydrotreated lubricating oils.' In *Journal of Applied Toxicology*, Vol. 9, Issue 4, pp. 265-270. https://onlinelibrary.wiley.com/doi/10.1002/jat.2550090411

McKee, R. H. and White, R. (2013). 'The Mammalian Toxicological Hazards of Petroleum-Derived Substances: An Overview of the Petroleum Industry Response to the High Production Volume Challenge Program'. In *International Journal of Toxicology*, Vol. 33, Issue 1 Supplement, pp. 4S-16S. https://journals.sagepub.com/doi/full/10.1177/1091581813514024

McWilliams, M. L., Chen, G. D. and Fechter, L. D. (2000). 'Low-Level Toluene Disrupts Auditory Function in Guinea Pigs.' In *Toxicology and Applied Pharmacology*, Vol. 167, Issue 1, pp. 18-29. https://www.sciencedirect.com/science/article/pii/S0041008X00989786

Nessel, C. S., Priston, R. A., McKee, R. H., Cruzan, G., Riley, A. J., Randi, H., Plutnick, R. T. and Simpson, B. J. (1998). 'A Comprehensive Evaluation of the Mechanism of Skin Tumorigenesis by Straight-Run and Cracked Petroleum Middle Distillates.' In *Toxicological Sciences*, Vol. 44, Issue 1, pp. 22-31. https://academic.oup.com/toxsci/article/44/1/22/1708103

North, D. W., Abdo, K. M., Benson, J. M., Dahl, A. R., Morris, J. B., Renne, R. and Witschi, H. (2008). 'A review of whole-animal bioassays of the carcinogenic potential of naphthalene'. In *Regulatory Toxicology and Pharmacology*, Vol. 51, Issue 2, Supplement, pp. 6-14. https://www.sciencedirect.com/science/article/abs/pii/S027323000700147X

NTP (1990). *Toxicology and Carcinogenesis Studies of Toluene (CAS no. 108-88-3) in F344/N Rats and B6C3F1 Mice (Inhalation Studies).* US Department of Health and Human Services, National Toxicology Program, Technical Report Series No. 371. https://ntp.niehs.nih.gov/ntp/htdocs/lt_rpts/tr371.pdf

NTP (1991). *NTP Report on the Toxicity Studies of n-Hexane in B6C3F1 Mice (Inhalation Studies).* U.S. Department of Health and Human Services, National Toxicology Program (NTP), Research Triangle Park, NC. https://ntp.niehs.nih.gov/ntp/htdocs/st_rpts/tox002.pdf

NTP (1992). *Toxicology and Carcinogenesis Studies of Naphthalene (CAS No. 91-20-3) in B6C3F1 Mice (Inhalation Studies).* U.S. Department of Health and Human Services, National Toxicology Program (NTP), Research Triangle Park, NC. https://ntp.niehs.nih.gov/ntp/htdocs/lt_rpts/tr410.pdf

NTP (1993). *Toxicology and Carcinogenesis Studies of 1,3-Butadiene (CAS No. 106-99-0) in B6C3F1 Mice (Inhalation Studies).* U.S. Department of Health and Human Services, National Toxicology Program (NTP), Research Triangle Park, NC. https://ntp.niehs.nih.gov/ntp/htdocs/lt_rpts/tr434.pdf

NTP (2000). *NTP Technical Report on the Toxicology and Carcinogenesis Studies of Naphthalene (CAS No. 91-20-3) in F344/N Rats (Inhalation Studies).* U.S. Department of Health and Human Services, National Toxicology Program (NTP), Research Triangle Park, NC. https://ntp.niehs.nih.gov/ntp/htdocs/lt_rpts/tr500.pdf

NTP (2004). *NTP Technical Report on the Toxicology and Carcinogenesis Studies of Stoddard Solvent IIC (CAS No. 64742-88-7) in F344/N Rats and B6C3F1 Mice (Inhalation Studies).* U.S. Department of Health and Human Services, National Toxicology Program (NTP), Research Triangle Park, NC. https://ntp.niehs.nih.gov/ntp/htdocs/lt_rpts/tr519.pdf

Owen, P. E., Glaister, J. R., Gaunt, I. F. and Pullinger, D. H. (1987). 'Inhalation Toxicity Studies With 1,3-Butadiene 3 Two Year Toxicity/Carcinogenicity Study in Rats.' In *AIHA Journal*, Vol. 48, Issue 5, pp. 407-413. https://oeh.tandfonline.com/doi/abs/10.1080/15298668791384959#.XRvREyMwhQI

PERF (2018). Refinery Stream Composition Data – Update to Speciation Data in API 4723. Petroleum Environmental Research Forum (PERF). American Petroleum Institute (API) Publication 4723-A. Washington, DC. https://standards.globalspec.com/std/13114350/api-publ-4723-a

Pryor, G. T., Dickinson, J. and Feeney, E. (1984). 'Hearing loss in rats first exposed to toluene as weanlings or young adults.' In *Neurobehavioral Toxicology and Teratology*, Vol. 6, Issue 2, pp. 111-119. https://www.researchgate.net/publication/16722862_Hearing_loss_in_rats_first_exposed_to_toluene_as_weanlings_or_as_young_adults

Przygoda, R. T., McKee, R. H., Tummey, A. C. and Traul, K. A. (1992). 'The use of short term assays in the evaluation of the dermal carcinogenic potential of petroleum-derived materials'. In *Environmental and Molecular Mutagenesis*, Volume 19, pp. 20-51.

Reddy, M. V., Blackburn, G. R., Schultz, S. C., Bleicher, W. T. and Mackerer, C. R. (1992). 'DNA adduct levels correlate with mutagenicity and skin carcinogenicity for petroleum oil fractions.' In *Proceedings of the 83rd Annual Meeting*, American Association for Cancer Research, Vol. 13, p.115.

Roberts L., White, R., Bui, Q., Daughtrey, W., Koschier, F., Rodney, S., Schreiner, C., Steup, D., Breglia, R., Rhoden, R., Schroeder, R. and Newton, P. (2001). 'Developmental toxicity evaluation of unleaded gasoline vapor in the rat.' In *Reproductive Toxicology*, Vol. 15, Issue 5, pp. 487-494. https://www.sciencedirect.com/science/article/pii/S0890623801001502

Roy, T. A., Johnson, S. W., Blackburn, G. R., Deitch, R. A., Schreiner, C. A. and Mackerer, C. R. (1988a). 'Estimation of Mutagenic and Dermal Carcinogenic Activities of Petroleum Fractions Based on Polynuclear Aromatic Hydrocarbon Content.' In *Polynuclear Hydrocarbons: A Decade of Progress, Proceedings of the Tenth International Symposium*. M. Cooke and A. J. Dennis, Editors; Battelle Press, Columbus, Ohio, pp. 809-824.

Roy, T. A., Johnson, S. W., Blackburn, G. R. and Mackerer, C. R. (1988b). 'Correlation of mutagenic and dermal carcinogenic activities of mineral oils with polycyclic aromatic compound content.' In *Fundamental and Applied Toxicology*, Vol. 10, Issue 3, pp. 466-476. https://www.sciencedirect.com/science/article/pii/027205908890293X

Saillenfait, A. M., Gallissot, F., Morel, G. and Bonnet, P. (2003). 'Developmental toxicities of ethylbenzene, ortho-, meta-, para-xylene and technical xylene in rats following inhalation exposure.' In *Food and Chemical Toxicology*, Vol. 41, Issue 3, pp. 415-429. https://www.sciencedirect.com/science/article/pii/S0278691502002314

Santucci, K. and Shah, B. (2000). 'Association of Naphthalene with Acute Hemolytic Anemia.' In *Academic Emergency Medicine*, Vol. 7, Issue 1, pp. 42-47. https://onlinelibrary.wiley.com/doi/abs/10.1111/j.1553-2712.2000.tb01889.x

SCOEL (2007). *Recommendation from the Scientific Committee on Occupational Exposure Limits for Hydrogen Sulphide*. SCOEL/SUM/124. June 2007. European Commission, Scientific Committee on Occupational Exposure Limits (SCOEL). http://ec.europa.eu/social/BlobServlet?docId=3864&langId=en

Schnatter, A. R., Glass, D. C., Tang, G., Irons, R. D. and Rushton, L. (2012). 'Myelodysplastic Syndrome and Benzene Exposure Among Petroleum Workers: An International Pooled Analysis.' In *Journal of the National Cancer Institute*, Vol. 104, Issue 22, pp.1724-1737. https://academic.oup.com/jnci/article/104/22/1724/908270

Schreiner, C., Bui, Q., Breglia, R., Burnett, D., Koschier, F., Podhasky, P., White, R., Hoffman, G. and Schroeder, R. (2000). 'Toxicity Evaluation of Petroleum Blending Streams: Reproductive and Developmental Effects of Light Catalytic Reformed Naphtha Distillate in Rats.' In *Journal of Toxicology and Environmental Health*, Part A, Vol. 60, Issue 3, pp. 169-184. https://www.tandfonline.com/doi/abs/10.1080/009841000156475

Shugaev, B. B. (1969). 'Concentrations of Hydrocarbons in Tissues as a Measure of Toxicity.' In *Archives of Environmental Health: An International Journal*, Vol. 18, Issue 6, pp. 878-882. https://www.tandfonline.com/doi/abs/10.1080/00039896.1969.10665509

Snow, L., MacNair, P. and Casto, B.C. (1981). *Mutagenesis testing of toluene in Salmonella strains TA100 and TA98*. Report prepared for the U.S. EPA by Northrup Services, Inc., Research Triangle Park, NC.

Takeuchi, Y., Ono, Y., Hisanaga, N., Kitoh, J. and Sugiura, Y. (1980). 'A Comparative Study on the Neurotoxicity of N-Pentane, N-Hexane, and N-Heptane in the Rat.' In *British Journal of Industrial Medicine*, Vol. 37, No. 3, pp. 241-247. https://www.jstor.org/stable/27723447?seq=1#page_scan_tab_contents

ipieca

IPIECA is the global oil and gas industry association for advancing environmental and social performance. IPIECA convenes a significant portion of the oil and gas industry across the value chain, bringing together the expertise of companies and associations to develop, share and promote good practice and knowledge.

IPIECA is the industry's principal channel of engagement with the United Nations. Its unique position enables its members to support the energy transition and contribute to sustainable development.

MEMBERS

AIP
AMEXHI
Anadarko
API
APPEA
ARA
ARPEL
Baker Hughes
Bechtel
BHP
BP
Canadian Fuels Association
CAPP
Cheniere
Chevron
CNOOC
CNOOC Nexen
ConocoPhillips
Concawe
Encana
Eni
Equinor
ExxonMobil
FIPI
Fuels Europe
Halliburton
Hess
Husky Energy
IBP
INPEX
IOGP
JPEC
Kosmos
Libya NOC
Marathon Oil
McDermott
Murphy Oil
Neptune Energy
Noble Energy
NOGEPA
Norsk olje & gass
Oil & Gas UK
Oil Search
Olie Gas Danmark
OMV
Occidental
PAJ
PDO
Pemex
Pepanz
Petrobras
PETRONAS
PTTEP
Qatar Petroleum
Repsol
Sapia
Saudi Aramco
Schlumberger
Shell
SNH
Suncor Energy
Total
Tullow Oil
UKPIA
VNPI
Wintershall Dea
WLPGA
Woodside
WPC

IPIECA
@IPIECA

www.ipieca.org

14th Floor, City Tower
40 Basinghall Street
London EC2V 5DE
United Kingdom

Telephone: +44 (0)20 7633 2388
Facsimile: +44 (0)20 7633 2389

E-mail: info@ipieca.org