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Committee of Experts on the Transport of Dangerous Goods and on the Globally Harmonized System of Classification and Labelling of Chemicals

Sub-Committee of Experts on the Globally Harmonized System of Classification and Labelling of Chemicals **3 December 2018**

Thirty- sixth session
Geneva, 5-7 December 2018
Item 6 of the provisional agenda
Development of guidance on the application of GHS criteria

Update of the IPIECA Guidance on the Application of Globally Harmonized System (GHS) Criteria to Petroleum Substances

Transmitted by the International Petroleum Industry Environmental Conservation Association (IPIECA)

Background

1. Various industry sectors are working to ensure that their members are familiar with the GHS framework. Outreach efforts have occurred in industries such as the metals and mining, petroleum, and chemicals. These industries aim to ensure awareness of members and provide guidance and interpretation relevant to substances and mixtures specific to their industries.

2. The concept of sector guidance is consistent with the aims of the UN Strategic Approach to International Chemicals Management (SAICM). SAICM goals include promoting industry participation and responsibility; establishing a clearinghouse for information on chemical safety to optimize the use of resources; strengthening the exchange of technical information among the academic, industrial, governmental, and intergovernmental sectors; and other goals related to chemicals management.

3. IPIECA initially published the *Guidance on the Application of Globally Harmonized System (GHS) Criteria to Petroleum Substances* in 2010. It has been IPIECA's experience that, while the GHS principles are robust, there are complexities and idiosyncrasies associated with their application to specific materials such as petroleum substances.

Benefits of the guidance

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

(a) Application of the "grouping" concept and read-across methodology, resulting in a full use of available data, thereby minimizing the need for animal testing;

(b) Transparent use of GHS principles for the classification of petroleum UVCBs;

(c) Consistent and reliable classification of petroleum substances, resulting in appropriate hazard communication to reduce the risks arising from their handling and storage;

(d) Consistent classification, reducing costs for industry and countries.

5. 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 results of petroleum substances should be globally consistent regardless of regional differences in the implementation of GHS or classification of individual petroleum substance constituents.

Status of the guidance

6. There is a link to the 2010 IPIECA GHS guidance on the UN GHS website under GHS guidance, Section 2: Sector-specific guidance at:

http://www.ipieca.org/resources/good-practice/guidance-on-the-application-of-globally-harmonized-system-ghs-criteria-to-petroleum-substances/

7. IPIECA has been working on a revision of the guidance to ensure that the guidance reflects current research and scientific developments and is consistent with updated versions of the GHS.

8. At the thirty-fifth session, IPIECA invited the Sub-Committee to submit comments for the revision of the 2010 IPIECA GHS Guidance. IPIECA did not receive any comments from the Sub-Committee.

9. The attached draft revised guidance refers to the seventh revised edition of the GHS (2017)—the most recent version available at the time of writing—and includes new research on the hazards of petroleum-related substances and constituents.

10. The IPIECA GHS guidance suggests arranging petroleum substances logically in groups of "similar" substances (product groups), which facilitates read-across for purposes of consistent classification and minimizes unnecessary testing. The IPIECA guidance also informs the user that there are certain hazardous constituents that should be considered in classification decisions when there is limited data on the complete substance. Without this relevant information, the uninformed might view all petroleum substances as conventional mixtures and base all classification decisions solely on constituent information.

11. The draft 2018 IPIECA GHS guidance focuses on human health hazards. It includes a detailed discussion of a Weight-of-Evidence (WoE) approach and presents a stepwise path to determining the best data for classification. An updated classification flowchart utilizes a three-tiered approach in which substance-specific toxicity data are considered first, followed by read-across data and then data for hazardous constituents.

12. The Technical Support Document portion of the draft guidance provides substance-specific and toxicological information for petroleum substance hazardous constituents. Two case studies are included that use UVCB health hazard data in the tiered approach to classify the hazards of petroleum products. These case studies highlight the importance of evaluating and prioritizing substance-specific data when performing WoE-based hazard classifications of UVCB substances.

13. The draft 2018 IPIECA GHS guidance is still in draft format because IPIECA is awaiting publication of new data on petroleum process stream speciation. IPIECA will inform the Sub-Committee when the revised IPIECA GHS guidance has been finalized.

Action requested

14. The Sub-Committee is invited to take note of the attached revised draft 2018 IPIECA GHS Guidance.

Annex

For ease of reference, attached is the draft *2018 IPIECA Guidance on the Application of Globally Harmonized System (GHS) Criteria to Petroleum Substances*.

DRAFT

IPIECA

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

Guidance document for the oil and gas industry

Fuels and products

THE GLOBAL OIL AND GAS INDUSTRY ASSOCIATION FOR ENVIRONMENTAL AND SOCIAL ISSUES

www.ipieca.org

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

Guidance document for the oil and gas industry

IPIECA

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Guidance on the Application of GHS Criteria to Petroleum Substances, a Class of UVCBs

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Foreword

IPIECA is the global oil and gas industry association for environmental and social issues. It develops, shares, and promotes good practices and knowledge to help the industry improve its environmental and social performance, and is the industry's principal channel of communication with the United Nations.

Through its member-led working groups and executive leadership, IPIECA brings together the collective expertise of oil and gas companies and associations. Its unique position within the industry enables its members to respond effectively to key environmental and social issues.

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 or 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 in which the principles of the guidance are explained using relevant scientific literature. This guidance does not cover classification for environmental hazards.

In 2010, IPIECA developed this guidance in close consultation with the UN Sub-Committee of Experts on the Globally Harmonized System (GHS) of Classification and Labelling of Chemicals (Sub-Committee or UNSCEGHS). Efforts on this guidance commenced at the thirteenth session of the Sub-Committee where IPIECA presented a work plan which was endorsed by the Sub-Committee. At the fourteenth session of the Sub-Committee, IPIECA listed issues that could result in divergent classification of petroleum substances. These issues have been informally discussed at the fourteenth, fifteenth, sixteenth, and seventeenth sessions of the Sub-Committee. At its eighteenth session, the Sub-Committee endorsed the concept of sector-specific guidance by creating a webpage on the UN Economic Commission for Europe (UNECE) website, which links to third-party sector-specific guidance. In 2018, IPIECA updated this guidance to reflect 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 hazard classification of petroleum substances broadly traded in international commerce. Additional benefits of the guidance are:

a. Application of the "grouping" concept and read-across methodology, resulting in a full use of available data thereby minimizing the need for animal testing;

b. Transparent use of GHS principles for the classification of petroleum UVCBs;

c. Consistent and reliable classification of petroleum substances, resulting in appropriate hazard communication, to reduce the risks arising from their handling and storage;

d. Consistent classification, which reduces costs for industry and countries.

This guidance refers to the seventh revised edition of GHS (2017), the most recent version available at the time of publication. IPIECA will periodically revise this guidance to ensure 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 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

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

2. 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.

3. The petroleum sector's application of GHS principles would benefit from specific guidance on the classification of petroleum substances as a type of Unknown or Variable composition, Complex reaction product and/or Biological (UVCB) material, based on the industry's experience in characterizing the hazards of these substances.

4. 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 independent of specific regulatory approaches that exist or may be proposed in various countries or regions, and represents the global oil industry's recommended approach under GHS. 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, facilitating read-across for purposes of consistent classification and minimizing unnecessary animal testing; and

   c. There are specific hazardous constituents which should be considered in hazard classification decisions.

Guidance

The Nature of Petroleum Substances

5. 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.) (Figure 1). There are many different types of crude oil and each consists of many thousands 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.

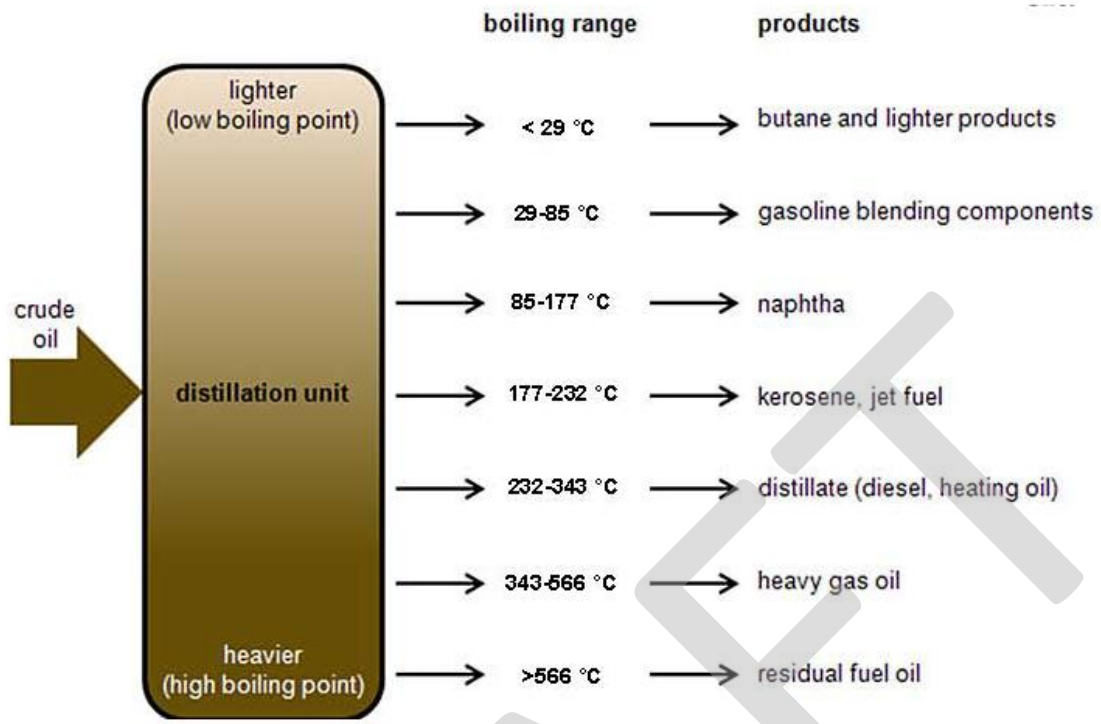


Figure 1. General Distillation of Crude Oil (based on EIA, 2012)

6. 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.

CAS Descriptions of Petroleum Substances

7. 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.

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

8. 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.

9. Although petroleum substances are of complex composition, they are defined as substances, each having a 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 an indication 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 follows:

> Gas oils (petroleum), straight run
>
> 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).

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

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

Grouping of Petroleum Substances for Classification Purposes

12. 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.

13. 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.

14. 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 United States High Production Volume (HPV) Challenge program (USEPA, 2007).

15. 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. These data have been summarized by API (see robust study summaries prepared for the HPV program; http://www.petroleumhpv.org) and Concawe (see Hazard Classification and Labelling of Petroleum Substances in the European

Economic Area; www.concawe.eu) 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.

Table 1: API HPV and European Union Petroleum Substance Groups

API HPV Substance Groups	European Union Substance Groups
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	Sulfur

16. This list 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 API and Concawe.

17. 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 identified and communicated on a consistent basis.

Classifying Petroleum Substances under GHS

18. 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**.

Table 2: Selected Petroleum Substance Groups and Their Specific (Potentially Hazardous) Carcinogenic, Mutagenic, or Reproductive Toxicant Constituents (Concawe, 2017; API, 2018)

API HPV Substance Groups	**European Union Substance Groups**	**Relevant Hazard Classes to be Evaluated**[e]	**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 oil and distillate fuels Cracked gas oils Other gas oils MK-1 diesels fuel	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	NA	------	------

Lubricating oil base stocks	Highly refined base oils Unrefined/acid treated oils Lubricant base oils Foots oils	Carcinogenicity, reproductive effects	PAHs[c]
Petroleum coke	NA	------	------
Petroleum gases	Petroleum gases Other petroleum gases	Carcinogenicity, mutagenicity, acute toxicity	1,3-Butadiene[d], H_2S[a]
Reclaimed substances	NA	------	------
Waxes and related materials	Paraffinic and hydrocarbon waxes Slack waxes Petrolatums	Carcinogenicity, reproductive effects	PAHs[c]
Not applicable	Sulfur	------	------

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

[b] *Benzene is classified by 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").*
API HPV Category Assessment Document for the respective substance group: http://www.petroleumhpv.org/

19. 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.

20. 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 to classify within specific categories of health hazards.

21. GHS section 1.3.3.1.3 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 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 (GHS Section 1.3.2.4.8).

22. The WoE approach to data utilization is a means of systematically considering all

the available data to make conclusions on chemical, mixture, and 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.

23. 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.

24. The central tenet of the WoE approach is quantifying the specific endpoint 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 lab animal studies; read-across analyses from chemical analogues; Quantitative Structure-Activity Relationship (QSAR) modeling 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.

25. 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.

26. 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 endpoint 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.

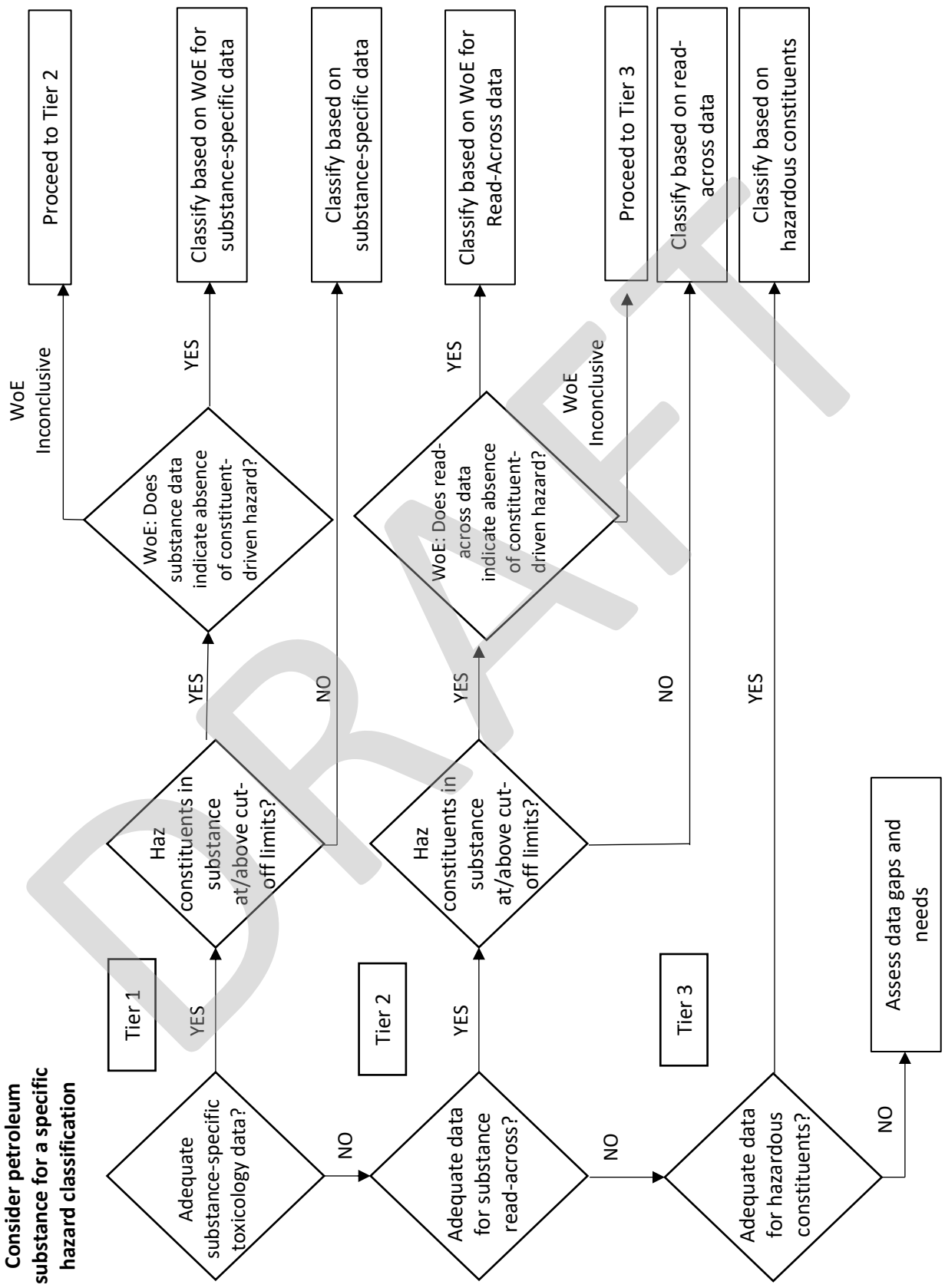
27. While WoE as applied in this guidance is not for the purposes of risk assessment, this same series of steps is relevant to assisting in the determination of GHS classification of petroleum substances. WoE approaches may be used to decide whether the GHS classification should be based on toxicology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

28. 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 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.”

29. Such a case would require that the WoE analysis include data indicating (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.

30. The tiered approach to the classification of petroleum substances is shown in **Figure 2**.

Figure 2: Classification Process for Health Effects



Specific Classification Guidance by Hazard Class

Acute toxicity

31. Hydrogen sulfide 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 sulfide are generally below the specified concentration limits that warrant classification. However, hydrogen sulfide may collect in a container headspace during storage and transport. Adequate warning for this possibility should be in place (see GHS Appendix A.4.3.7).

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

Skin and eye irritation and corrosion

33. There is generally sufficient read-across data to assess the eye and skin irritancy and corrosion hazard of most petroleum substances, and 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 advised to include appropriate warnings on the SDS.

Germ cell mutagenicity

34. Constituents generally accepted as mutagenic in petroleum substances are 1,3-butadiene and benzene. More specific scientific information about 1,3-butadiene and benzene in petroleum substances can be found in the Technical Support Document.

35. 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

36. Constituents that may be found in petroleum substances and are generally accepted as carcinogenic in petroleum substances are 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 GHS Section 1.3.3.1.3 should be applied. More specific scientific information about 1,3-butadiene and benzene in petroleum substances can be found in the Technical Support Document.

37. 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), 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. Examples of tests widely accepted to determine the carcinogenic potential of specific petroleum substances containing 3-7 fused-ring PAHs are:

a. Skin painting studies in mice (Freeman and McKee, 1993);

b. Modified Ames test E-1687 (Blackburn et al., 1986; ASTM, 2004; Concawe, 2012); and

c. Dimethylsulfoxide (DMSO) extractables as determined by IP 346 (Concawe, 1994; 2016; Institute of Petroleum, 1993).

38. More specific scientific information about PAHs in petroleum substances and the test methods above can be found in the Technical Support Document.

39. 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

40. 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.

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

41. 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, due to central nervous system (CNS) depression and other narcotic effects in humans and/or animal studies, which is transient in nature. If effects are not transient, the substance should be considered for Category 1 or 2.

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

42. Constituents that may be present in some groups of petroleum substances that are classified as STOT-RE include n-hexane, toluene, benzene. More specific scientific information about n-hexane, toluene, and benzene in petroleum substances can be found in the appended Technical Support Document.

Aspiration

43. 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

44. IPIECA shares the concerns about the welfare of experimental animals as described in section 1.3.2.4.6 of the GHS. Therefore, this guidance is designed to 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 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 which can be extrapolated to all the substances in their respective group. This will reduce testing of similar complex substances.

45. 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" (Concawe, 2018). The latest resulting 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.

46. 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

47. 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.

48. 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 Proposed Approach

49. Advantages of the proposed approach are as follows.

a. 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. Full use of available test data thereby minimizing animal testing;

c. Consistent with GHS and representing a universal oil and gas industry view; and

d. Outlines the critical aspects to be considered in the determination of hazard classification, hazard communication, and classification of the petroleum substance in a similar and reliable way across the globe, regardless of regional differences in the classification of the constituents.

50. 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.

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Technical Support Document

Introduction

1. This Technical Support Document provides substance-specific and 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, or, in the absence of these data, toxicity data for individual hazardous constituents. Two case studies are provided to illustrate the use of 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 WoE supports use of these data instead of substance-specific data or surrogate read-across. The GHS (section 1.3.3.2) defines cut-off values/concentration limits to be used for each hazard class when the Weight-of-Evidence (WoE) does not support use of substance-specific or read-across toxicity data. The GHS indicates that use of cut-off values/concentration limits may also apply to individual constituents of a substance[1]. At the time this document was developed, the Petroleum Environmental Research Forum (PERF) was in the process of finalizing a study of the percent composition of hazardous constituents present in a variety of petroleum substance streams. Those data may be incorporated into this guidance once they are available.

UVCB Case Studies: WoE Approach to Using Substance-Specific Data

2. Two case studies (mineral lubricating oil with PAHs and light straight-run naphtha) are provided here as examples of using UVCB data in the tiered approach described in the guidance text and shown in Figure 2, 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

3. Petroleum-derived mineral lubricating oils are composed primarily of aliphatic and aromatic hydrocarbons. There are nearly 100 mineral oils that have specific CAS numbers. 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.

[1] Note, there may be national and regional differences in cut-off values/concentration limits. Further, it should be noted that 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.

In this example, the concentration of benzo(a)pyrene (a carcinogenic PAH constituent), is less 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 tumors in mice. Animal test data have consistently shown that individual PAH levels alone are not good predictors of carcinogenic outcome (1985; 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 below in the section on PAHs.

Light Straight-Run Naphtha

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

5. Based on application of GHS guidance for mixtures, there are 15 constituents in the example straight-run naphtha stream shown in Table 3 that would drive hazard specific target organ toxicity. These hazard classifications are based on the GHS guidance for mixtures.

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	Reproductive Toxicity	Carcinogenicity	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**

* Peripheral nervous system **Central nervous system F = Fertility D = Developmental toxicity

6. Applying the tiered approach, it is determined that adequately robust toxicological testing data for most of the hazard endpoints 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 Figure 2 Tier 1 to Tier 2). Additionally, adequate carcinogenicity data from studies of chemically-similar substances are not available for read-across (e.g., move from Figure 2 Tier 2 to Tier 3). The presence of benzene in straight-run naphtha suggest 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.

Table 4: Hazard Classification for an Example Straight-Run Naphtha Identified Using the Substance-Specific Data Applied Via WoE Approach

CASRN	Name	Weight %	Skin Irritation	Eye Irritation	Aspiration Toxicity	STOT-SE: CNS Depression	STOT-RE	Reproductive Toxicity	Carcinogenicity	Germ Cell Mutagenicity
64741-46-4	Light straight-run naphtha	100	Cat 2	Neg	Cat 1	Cat 3	Neg	Neg	Cat 1B*	Neg

Neg = negative result from testing of the whole substance
* Based on its similarity to gasoline which has more extensive carcinogenicity data

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

8. The remainder of the 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); 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 Sulfide

Relevant Substance Groups

9. Hydrogen sulfide may be found in in crude oil, heavy fuel oils, and some petroleum gases. Small amounts of hydrogen sulfide may volatilize from heated bitumen/asphalt. Although these substance groups may not release hydrogen sulfide 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 the relevant hazard endpoint associated with the presence of hydrogen sulfide in petroleum substances. Other endpoints 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 sulfide (ACGIH, 2010) as well as the EU SCOEL (SCOEL, 2007).

Acute Toxicity

10. Hydrogen sulfide has a low odor 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 odor warning properties moot. In humans, inhaling a few breaths of 1,000 ppm - 2,000 ppm hydrogen sulfide will result in death 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 ppm - 600 ppm have been derived following two to six-hour exposures (Tansey et al., 1981; Prior et al., 1988; as cited by ACGIH, 2010).

Naphthalene

Relevant Substance Groups

11. Naphthalene has been identified in the following petroleum substance groups: Crude Oil, Gas Oils, and Kerosene/Jet Fuel. Carcinogenicity is considered the relevant hazard endpoint associated with the presence of naphthalene in petroleum substances. Specific details on 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 endpoints are not expected to contribute to the classification of petroleum substances and are covered in other reports (ATSDR, 2005; EPA, 1998).

Carcinogenicity

12. 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 2-year NTP 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 GHS Table 3.6.1. It is worthwhile to note 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 tumors reported (North et al, 2008). This 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, and strongly suggest that cytotoxicity played a significant role in the tumor 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 weight-of-the-evidence has been published in the literature that supports a non-mutagenic mode of action (MOA) with a threshold for naphthalene tumorgenicity (Bailey et al. 2016).

Polycyclic Aromatic Hydrocarbons (PAHs)

13. PAHs are a group of chemicals that are formed during the incomplete burning of coal, oil, gas, wood, garbage, or other organic substances, and they can either be synthetically derived or occur naturally. PAHs are 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

14. It is known that the PAH-fraction in petroleum substances can present a

carcinogenic hazard to skin (Chasey et al., 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 (i.e. IP 346, 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.

15. IP 346 is a chemical method that gravimetrically measures dimethylsulfoxide (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 to 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 percent 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. IP 346 is also used in Australia for identifying and classifying for carcinogenicity of virgin petroleum oils.

16. ASTM E-1687 is commonly known as the modified Ames test. It is based upon the standard *Salmonella* mutagenesis assay but 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; Blackburn et al., 1988; 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 for its use as a screening method for potential carcinogenicity of RAEs indicate that RAE with a mutagenicity index ≥ 0.4 demonstrated potential carcinogenic activity in mouse skin painting studies. RAE 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 Classification, Labelling and Packaging (CLP) legislation as Oil Industry Note 10 (Concawe, 2017).

<u>Reproductive Toxicity</u>

17. 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 endpoints 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.

18. 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).

19. 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 weight-of-evidence approach outlined in this guidance.

Benzene

Relevant Substance Groups

20. Benzene has been identified in the following petroleum substance groups: crude oil, naphthas, and gasoline. The default classification cut-off value/concentration limit for Category 1 carcinogens is 0.1 percent. Mutagenicity, Carcinogenicity and Specific Target Organ Toxicity are considered the relevant endpoints associated with the presence of benzene in petroleum substances. Other hazard endpoints are not expected to contribute to the classification of petroleum substances and are covered in other reports (ATSDR, 2007; EPA, 2002).

Mutagenicity

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

Carcinogenicity

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

23. Reliable data (see GHS section 1.3.2.4) 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 to take the level of benzene into account. For petroleum streams containing ≥0.1 percent benzene (e.g., naphthas), even in absence of carcinogenic effects in animal studies, it is recommended to classify for carcinogenicity.

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

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

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

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

26. 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 hematotoxicity is cytopenia, which is a decrease in various cellular elements of the circulating blood manifested as anemia, leukopenia, or thrombocytopenia in humans and in animals.

27. 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 percent aromatics) resulted in a reduced white blood cell (WBC) count compared to sham treated controls and naphtha treated groups in both sexes compared to untreated controls. Additionally, the WBC count was decreased by approximately 24 percent in the high dose females when compared to the sham controls. The Lowest Observed Adverse Effect Level (LOAEL) for decreased WBC in females is 1894 ppm (8050 mg/m3), and the No Observed Adverse Effect Level (NOAEL) is 464 ppm (1970 mg/m3) (Dalbey and Feuston, 1996).

28. For Category 1 classification, the guidance value for inhalation of vapors 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 8050 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 hematological effects.

1,3-Butadiene

Relevant Substance Groups

29. 1,3-butadiene has been identified in petroleum gases. Carcinogenicity and mutagenicity are considered the relevant endpoints associated with the presence of 1,3-butadiene in petroleum substances. Other hazard endpoints are not expected to contribute to the classification of petroleum substances and are covered in other reports (ATSDR, 2012; EPA, 2002).

Mutagenicity

30. 1,3-butadiene has been shown to be mutagenic in animal models. In mice, inhalation of 50, 200, 500, or 1300 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, 1994).

Carcinogenicity

31. 1,3-Butadiene is classified by the International Agency for Research on Cancer (IARC) as "carcinogenic to humans (Group 1)" based on its association with leukemia 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. leukemia) have been identified. Therefore, reliable data (see GHS section 1.3.2.4) 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 to take the level of 1,3-butadiene into account. Chapter 3.6 of the GHS should be consulted for carcinogenicity.

n-Hexane

Relevant Substance Groups

32. n-Hexane has been identified in the following petroleum substance groups: naphtha streams and gasoline. These data also suggest that the n-hexane concentration of most naphtha streams is not likely to exceed 10 percent. Reproductive effects and STOT are considered the relevant endpoints associated with the presence of n-hexane in petroleum substances. Other hazard endpoints are not expected to contribute to the classification of petroleum substances and are covered in other reports (ATSDR, 1999; EPA, 2005).

Reproductive/Developmental Toxicity

33. 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 3000 ppm and 9000 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 percent n-hexane.

The studies include:

a. One generation reproduction study, conducted in Sprague-Dawley rats 6 hours per day, 5 days per week at 100, 500, and 1500 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. Two generation reproduction study, conducted in Sprague-Dawley rats at concentrations of 900, 3000, and 9000 ppm commercial hexane. Exposures were 6 hours/day, 5 days per week for ten weeks prior to mating, as well as during mating, gestation, and lactation. Pups at 9000 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).

34. The reproductive toxicity effect (i.e., testicular toxicity) observed in studies with 100 percent n-hexane is not observed in studies with commercial hexane containing 52 percent n-hexane. It is recommended to include the information above along with other data on petroleum naphthas/gasolines in a weight of evidence when determining the classification (see McKee 2013).

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

35. n-Hexane has been shown to cause CNS effects (drowsiness or dizziness). A key study in humans found that inhalation of 5000 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)

36. Inhalation of n-hexane has been shown to cause distal axonal neuropathy in humans and experimental animals and is classified GHS STOT-RE Category 2. In rats, the Lowest Observed Adverse Effect Concentration (LOAEC) was determined to be 3000 ppm after 4 weeks of exposure. A No Observed Adverse Effect Concentration (NOAEC) was not determined (Takeuchi, 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 1000 ppm n-hexane (3.52 mg/L) for 18 hours per day over a course of 61 days.

37. 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 percent n-hexane.

38. Exposure of Sprague-Dawley rats to commercial hexane concentrations of 900, 3000, and 9000 ppm six hours/day, five days/week, for 13 weeks was conducted. Functional Observational Battery tests were conducted at six different time points throughout the study and motor activity was evaluated monthly. Exposure had no significant effects on the neurobehavioral or motor activity endpoints that were evaluated and no significant neuropathological findings were reported (API, 1990).

39. 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 6646 ppm in the study of light alkylate naphtha and 7500 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 percent n-hexane in the cat-reformed naphtha (Schreiner, et al., 2000b) and 1.56 percent n-hexane in the cat-cracked naphtha (Lapin et al., 2001).

40. The neurotoxic effect (i.e., distal axonal neuropathy) observed in studies with 100 percent n-hexane is not observed in studies with commercial hexane containing 52 percent n-hexane. It is recommended to include the information above along with other data on petroleum naphthas/gasolines in a weight of evidence when determining the classification (see McKee 2013).

Toluene

Relevant Substance Groups

41. Toluene has been identified in the following petroleum substance groups: naphthas, and gasoline. Reproductive effects and STOT are considered the relevant endpoints associated with the presence of toluene in petroleum substances. Other hazard endpoints are not expected to contribute to the classification of petroleum substances and are covered in other reports (ATSDR, 2017; EPA, 2005).

Reproductive/Developmental toxicity

42. Toluene has been shown to have 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 1000 ppm (EU RAR, 2003).

43. A distillate fraction of light cat-reformed naphtha, containing 5.78 percent (by weight) toluene, was evaluated in a 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, 2500, and 7500 ppm, six hours/day, seven days/week, for two weeks prior to mating and throughout days 0-10 of gestation. No developmental or reproductive effects were reported from the study.

44. The highest exposure concentration in this study is equivalent to 27,750 mg/m3, of which 5.78 percent, or about 1600 mg/m3 (420 ppm), represents exposure to toluene. At this level no developmental or reproductive effects were reported from the study.

45. A developmental inhalation toxicity evaluation of unleaded gasoline containing eight percent toluene was conducted in rats at gasoline concentrations of 1000, 3000, and 9000 ppm, which did not produce any evidence of developmental toxicity (Roberts et al., 2001).

46. Based on the studies presented above, naphtha and gasoline samples containing up to eight percent toluene do not cause developmental toxicity. However, it is not known what toluene concentration represents the threshold for developmental effects. It is recommended to include the information above along with other data on petroleum naphthas/gasolines in a weight of evidence when determining the classification (see McKee 2013). In the absences of conclusive substance or read-across data, petroleum substances containing three percent or more toluene may be classified for developmental toxicity.

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

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

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

48. 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, 1984, Brandt-Lassen, 2000, Gagnaire, 2005, McWilliam, 2000, EU RAR, 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

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

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