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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

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DEVELOPMENT OF GUIDANCE ON THE APPLICATION OF GHS CRITERIA

Application of GHS criteria to substances of unknown or variable composition, complex reaction products or biological materials (UVCB), in specific petroleum substances

Transmitted by the International Petroleum Industry Environmental Conservation Association (IPIECA)[1]

Background

1. IPIECA has been developing guidance on the application of GHS criteria to petroleum substances according to the work plan presented at the thirteenth session of the Sub-Committee (informal document UN/SCEGHS/13/INF.4). At the fourteenth session IPIECA listed issues that could result in divergent classification of petroleum substances (informal document UN/SCEGHS/14/INF.10). These issues have been informally discussed at the fourteenth, fifteenth, and sixteenth sessions, which resulted in useful feedback from the Sub-Committee.

[1] In accordance with ST/SG/AC.10/C.4/32, paragraph 82.

Development of guidance

2. The guidance may be found in the annex to this document. The guidance has been developed with input from experienced technical experts on the field of petroleum substance toxicology and addresses crude oil and petroleum substances produced from oil and gas operations. In response to the feedback received from the Sub-Committee a technical support document has been developed, in which the principles of the guidance will be explained with examples using scientific literature.

Benefits of guidance

3. IPIECA believes that the guidance presented in the Annex, if endorsed by the Sub-Committee, 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” or “category” concept, resulting in a full use of available data hereby minimising the need for animal testing;

(b) Transparent use of GHS principles for the classification of complex, multi-constituent substances;

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

(d) Consistent classification reduces costs for industry and States.

4. We acknowledge that achieving these benefits is dependent on the pursuit of a credible approach, which is well communicated and understood by the affected parties. IPIECA recognises that the GHS permits States to implement the GHS as they deem appropriate.

5. By providing relevant sector-specific guidance the hazard classification of petroleum substances should globally be consistent regardless of regional differences in the implementation of GHS or classification of individual petroleum substance constituents.

Annex

(English only)

Guidance on the application of GHS criteria to substances of unknown or variable composition, complex reaction products or biological materials (UVCB), in specific petroleum substances

Background

1. This document provides supplemental guidance for the classification and labelling of petroleum substances, a class of UVCBs.

2. The consistent classification and labelling of petroleum substances is not straightforward due to the complex nature and chemistry of the 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 process streams as well as an understanding of the physical and chemical similarities of stream groupings, which is important in determining the extent to which similar petroleum substances can be grouped for classification.

The GHS would benefit from more detailed guidance on the classification of petroleum substances, based on the industry's experience in characterizing their hazards.

3. The purpose of this document is to provide supplemental guidance to facilitate a consistent approach to the classification and labelling of petroleum substances. The approach identified has been developed independent of specific regulatory approaches that exist or may be proposed and represents the global oil industry's recommended approach under GHS. The framework for the supplemental guidance includes recognition:

(a) That petroleum substances are in fact substances and not mixtures;

(b) That they are logically arranged in groups of "similar" substances, facilitating read-across for purposes of consistent classification and minimizing unnecessary animal testing; and

(c) That in the absence of data on the substance or read-across data for similar substances, there are certain hazardous constituents which should be considered in classification decisions.

The nature of petroleum substances

4. Petroleum substances are chemicals derived from crude oil by physical separation (i.e. distillation), which may be followed by chemical modification (e.g. hydrogenation, cracking, etc). There are many different types of crude oil and each consists of many thousands of chemicals, predominantly hydrocarbons. Furthermore, no two crude oils are compositionally the same. Thus, since the composition of any distillation fractions derived from crude oil will be dependent on the source crude oil itself, and the distillate fractions may be subject to a variety of

chemical modifications, it follows that petroleum substances will be of variable chemical composition, broadly defined by their physico-chemical properties.

5. Petroleum substances are, therefore, classed as "Unknown or Variable composition, Complex reaction products and Biological substances" (UVCB substances). For this reason petroleum substances cannot be produced to meet specific chemical specifications. Rather, specifications for petroleum substances are normally related to several physical chemical specifications (such as boiling range, flash point, viscosity) that establish specification limits related to the intended use of the material.

CAS descriptions of petroleum substances

6. According to the definitions in Chapter 1.3.3.1 of the GHS (second revised edition), 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 streams meet the GHS definition of substance and are hence considered to be substances.

7. Although petroleum substances are of complex composition they are defined as substances and each has 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 physico-chemical parameters such as either a boiling range or a carbon number range or both will be 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).*

8. Although the CAS definition is imprecise, it nevertheless does limit wide variation of composition for a given petroleum substance.

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

Grouping of petroleum substances for classification purposes

10. Petroleum substances are usually described in terms of starting material, production process and ranges of physico-chemical properties such as boiling point or carbon number. In order to maximise the use of available information and minimise animal testing, petroleum substances can be arranged into groups or categories of "similar" substances.

11. The rationale for such groupings is that since all petroleum substances within a group are derived from similar starting materials and have similar physico-chemical properties and generally similar chemical composition, these substances exhibit broadly similar hazard properties. Classification may then be addressed on a group rather than on a single substance basis.

12. Such grouping schemes have been devised by CONCAWE (Conservation of Clean Air and Water in Europe, the oil companies' European association for environment, health and safety in refining and distribution) and subsequently adopted in the European Union (EU) in the Existing Substances Regulation (1993) and the Dangerous Substances Directive (1993) and also by the American Petroleum Institute in their activities to fulfil the requirements of the United States High Production Volume (HPV) Challenge program of the United States (U.S.) Environmental Protection Agency (2007).

13. Toxicity and environmental information is available on some members of each of the groups of petroleum substances and these data can be 'read-across' to all members of the petroleum substance group. These data have been summarized by the American Petroleum Institute (API) (see Robust Study Summaries prepared for the High Production Volume (HPV) Programme; http://www.petroleumhpv.org) and CONCAWE (see the CONCAWE Product dossiers; www.concawe.be) and should be used as the prime sources of information.

14. The major petroleum substance groups for which data exist and/or for which read-across is possible are:

(a) Crude oil
(b) Petroleum gases
(c) Naphthas/gasolines
(d) Kerosines
(e) Gas oils
(f) Heavy Fuel oils
(g) Residual aromatic extracts
(h) Distillate aromatic extracts
(i) Treated distillate aromatic extracts
(j) Lubricant base oils
(k) Petroleum waxes
(l) Petrolatums
(m) Foots oils
(n) Slack waxes
(o) Bitumens (Asphalts) and Vacuum residues
(p) Petroleum cokes

This list reflects the major groups of petroleum substances. In some regions major groups are divided into subgroups to meet regional regulatory requirements. More detailed information about grouping is available through the American Petroleum Institute (API) and CONCAWE.

15. 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.

16. Some petroleum substances may contain specific constituents which may be classified as hazardous, e.g., as acutely toxic or as carcinogens, mutagens, specific target organ toxicants (e.g. neurotoxicants), or reproductive toxicants. However, tests may show that the full petroleum substance may not in itself be hazardous. This is because hazardous constituents may not be present in toxicologically significant amounts or the physical properties of the petroleum substance may affect the bioavailability of the hazardous constituent.

Classifying petroleum substances under GHS

17. GHS establishes the principle (section 1.3.2.2) that where test data are available for a substance or mixture, then the classification of the substance or mixture should be based on these data. Such a principle is applied to petroleum substances. In the absence of test data on the specific petroleum substance itself, read-across from a similar petroleum substance should be applied.

18. As described above, petroleum substances in each of the groups have similar physico-chemical properties, similar chemical composition and therefore have similar hazard properties. In certain specific cases read-across between groups is also possible provided the groups have a similarity of composition. This may occur because the manufacturing processes may result in some overlap in chemical composition between groups. Such read-across is accomplished on a case-by-case basis.

19. In some cases data may not be available for the petroleum substance per-se and reliable read-across may not be possible. As stated, petroleum substances may contain specific constituents which may themselves be classified as hazardous. 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*". In the absence of specific data for the complete substance, consideration of the amount and significance of such hazardous constituents may then provide a basis for the classification of the whole petroleum substance.

20. The potentially hazardous constituents of concern that may occur in the different groups of petroleum substances are indicated in Table 1.

Table 1: Petroleum substance groups and their specific (potentially hazardous) constituents

Petroleum substance groups	Relevant Hazard Classes	Possible Constituents of Concern
Crude oil	Carcinogenicity, mutagenicity, acute toxicity	H_2S[a], Benzene[b], PAH[c]
Petroleum Gases	Carcinogenicity/mutagenicity, acute toxicity	1,3-Butadiene[d], H_2S[a]
Naphthas/Gasolines	Carcinogenicity/mutagenicity	Benzene[b]
	Specific target organ toxicity	n-Hexane, Toluene, Benzene
	Reproductive effects	n-Hexane, Toluene, Xylene
Kerosines	------	------
Gasoils	Carcinogenicity	PAH[c]
Heavy fuel oil	Carcinogenicity, acute toxicity	PAH[c], H_2S[a]
Residual aromatic extracts	------	------
Distillate aromatic extracts	Carcinogenicity	PAH[c]
Treated distillate aromatic extracts	Carcinogenicity	PAH[c]
Lubricant base oils	Carcinogenicity	PAH[c]
Petroleum waxes	------	------
Petrolatums	Carcinogenicity	PAH[c]
Foots oils	Carcinogenicity	PAH[c]
Slack waxes	Carcinogenicity	PAH[c]
Bitumens (asphalts) and vacuum residues	------	------
Petroleum cokes	------	------

[a] *Hydrogen sulphide 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 (PAH) 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').*

Specific classification guidance by hazard class

Acute toxicity

21. Hydrogen sulphide is an acutely toxic gas, which can be released from some groups of petroleum substances (for example 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 the headspace during storage and transport and adequate warning for this should be in place (see transport regulations).

22. Even if a petroleum substance is not classified due to the presence of hydrogen sulphide, for good product stewardship, if headspace accumulation of hydrogen sulphide is possible, regardless of measured concentrations of hydrogen sulphide in the petroleum substance, it is advised to include appropriate warnings on the Safety Data Sheet (SDS).

Skin irritation

23. There is generally sufficient read-across data to assess the skin irritancy hazard of most petroleum substances. 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

24. 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.

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

(a) this is consistent with the cut-off values/concentration limits for Category 1 mutagens (such as benzene and 1,3-butadiene) as laid out in section 1.3.3.1.3 of the GHS;

(b) there is no evidence from human epidemiology studies that warrant classification as a Category 1A mutagen

Carcinogenicity

26. 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 ring Polycyclic Aromatic Hydrocarbons (PAH). 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 should be applied. More specific scientific information about 1,3-butadiene and benzene in petroleum substances can be found in the technical support document.

27. For petroleum substances containing PAHs, the skin carcinogenic potential is related to the level of specific 3-7 fused-ring PAHs. While concentrations of specific 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 PAH may occur at biologically insignificant concentrations, but the total PAH-content may be biologically 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)

(c) DMSO extractables as determined by IP 346 (CONCAWE 1994; Energy Institute, 1992)

28. More specific scientific information about PAH in petroleum substances and the test methods above can be found in the technical support document.

29. 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

30. Examples of constituents which may be classified for this hazard class are n-hexane, toluene, xylene. More specific scientific information about n-hexane, toluene, and xylenes in petroleum substances can be found in the technical support document.

Specific target organ toxicity following single exposure

31. Exposure to high levels of certain low boiling point hydrocarbons may cause narcotic effects (included in Category 3: Transient target organ 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.

Specific target organ toxicity following repeated exposure

32. Constituents that may be present in some groups of petroleum substances that may be classified as STOT are for example n-hexane, toluene, and benzene. More specific scientific information about n-hexane, toluene, and benzene in petroleum substances can be found in the technical support document.

Aspiration

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

Environmental hazards

34. For environmental classification, the principles laid out in section 4.1.2 of GHS can be applied using either test data for the overall substance or read-across to a similar substance. Unlike the approach for classification of several health hazard classes, the use of data on constituents is not appropriate to derive the environmental classification for biodegradation and bioaccumulation of a petroleum substance. As petroleum substances are complex substances, specific test methods may be required. Specific guidance on environmental tests with complex substances is laid out in Annex 9 of the GHS (A9.1.10 (d) and A9.3.5.10).

Animal testing and animal welfare

35. IPIECA shares the concerns on 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 and environmental data while significantly reducing the overall number of tests needed. The similarity of many petroleum substances allows for their grouping into categories based on chemical composition. Petroleum substances representative of each category are used as test materials to develop health and environmental effects information which can be extrapolated to all the substances in their category. This will avoid unnecessarily testing similar complex substances.

36. In addition, when testing is necessary, IPIECA strongly recommends that the number of laboratory animals used be minimized to the greatest extent possible within the constraints of the regulatory requirements and that studies be conducted according to component authority and OECD guidelines. In addition, where possible laboratories accredited by the Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC), or equivalent organisations, for excellence in animal care should be used.

Information requirements

37. To be able to use the above schemes it requires that the person making the classification has access to the required data.

38. It is recommended that they also:

(a) Maintain records on the level of substance constituents – when they are used as a basis for classification;

(b) Ensure that the studies used to derive a classification are of a consistent and reliable quality; and

(c) Have access to the documentation that provides the read across argumentation.

Advantages of the proposed approach

39. (a) Allows full GHS criteria to be explored;

(b) Full use of available data;

(c) Consistent with GHS and represents a consistent international oil and gas industry view;

(d) The actual hazard of the petroleum substance is the same regardless of where it is sold globally. By considering the petroleum substance as a whole for classification the communicated hazards and classification of the petroleum substance should be similar and reliable on a global basis regardless of regional differences in the classification of the constituents;

(e) IPIECA recognises that the GHS permits competent authorities to implement the GHS as the country deems appropriate. By providing relevant sector-specific guidance the hazard classification of the petroleum substance should globally be consistent regardless of regional differences in the implementation of GHS or classification of individual petroleum substance constituents.

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Technical support document

1. This technical support document provides scientific background information for specific petroleum substance constituents and illustrates how the IPIECA approach would be used to assess health hazards specific to petroleum substances. The GHS defines cut-off values/concentration limits for each hazard class. As described in section 1.3.3.1.3 of the GHS these cut-off values/concentration limits also apply to individual constituents of a substance.

2. The use of the cut-off values/concentration limits is described in section 1.3.3.2 of the GHS. Section 1.3.3.2.3 states that "*On occasion, conclusive data may show that the hazard of an ingredient will not be evident when present at a level above the generic GHS cut-off value(s)/concentration limit(s). In these cases the mixture could be classified according those data*". This technical support document aims to provide a scientifically sound basis for the application of the generic cut-off values/concentration limits adopted in the GHS or for a deviation thereof.

Polycyclic aromatic hydrocarbons (PAH)

3. Polycyclic aromatic hydrocarbons (PAH) may be present in crude oil and be fractionated into certain petroleum streams during the refining process. Specific 3-7 fused-ring 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)".

4. 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 PAH 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. Individual PAH may occur at biologically insignificant concentrations, but the total PAH-content may be biologically important.

5. Representative substances from most of the petroleum product groups have been evaluated for skin cancer potential using the mouse epidermal carcinogenesis model. Currently, two tests are used for estimating the carcinogenic potential of certain product groupings, specifically:

(a) treated distillate aromatic extracts,
(b) lubricant base oils, and
(c) foots oils.

These tests consider the total PAH content of petroleum substances, rather than specific PAHs.

6. IP 346 is a chemical method that gravimetrically measures DMSO-extractables which include PAHs. The method is limited to the product groups mentioned above. 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).

7. 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 PAH 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 (Blackburn et al., 1986; 1988; Roy et al., 1988b).

8. Several studies show that results of both IP346 and the modified Ames test correlate well with the results of epidermal carcinogenicity bioassays. Overall, petroleum substances containing less than 3% w/w DMSO extractables as measured by IP346 are not carcinogenic to skin. This approach has been accepted in the EU and is reflected in the CLP legislation (http://ecb.jrc.ec.europa.eu/). The same holds true for petroleum substances which are negative (i.e. mutagenicitry index < 1.0) in the modified Ames test (Przygoda et al., 1992; Reddy et al., 1992; Roy et al., 1988b).

Benzene

9. Benzene may affect haematology in laboratory animals after repeated exposure. In humans, benzene is associated with acute myelogenous leukemia. Benzene is classified by the International Agency for Research on Cancer (IARC) as ‘carcinogenic to humans (Group 1)’.

Benzene content of naphtha streams

10. An analytical study of 226 naphtha streams conducted by PERF showed that the “most likely” average benzene concentration is around one percent. Measured concentrations of benzene ranged from “non-detect” in isomerized naphthas to a high of 20% in reformate.

Carcinogenicity

11. Benzene is associated with acute myelogenous leukemia in humans. No appropriate animal model for acute myelogenous leukemia has been identified. Therefore, animal data do not provide a solid basis to predict potential carcinogenic effects of petroleum streams based on benzene content.

12. Therefore, 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% 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 repeated exposure

13. 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 common clinical finding in benzene hematotoxicity is cytopenia, which is a decrease in various cellular elements of the circulating blood manifested as anaemia, leukopenia, or thrombocytopenia in humans and in animals.

14. Data on high-benzene petroleum streams (naphtha) show that repeated exposure 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 1894 ppm (8050 mg/m^3), the "no observed adverse effect level" (NOAEL) is 464 ppm (1970 mg/m^3) (Dalbey and Feuston, 1996).

15. The observed LOAEL is above the guidance values of Tables 3.9.1 and 3.9.2 of the GHS. Therefore it is concluded that petroleum naphtha streams should not be classified for STOT repeated exposure based on benzene haematological effects.

1,3-Butadiene

16. In humans, 1,3-butadiene is associated with leukemia. 1,3-Butadiene is classified by the International Agency for Research on Cancer (IARC) as "probably carcinogenic to humans (Group 2A)".

1,3-Butadiene content of petroleum gas streams

17. An analytical study of 32 gas streams conducted by PERF (1997) showed that the "most likely" average 1,3-butadiene concentration is around 0.1 percent. Measured concentrations of 1,3-butadiene ranged from "non-detect" in certain LPG to a high of 11% in olefins from the cracked-gas plant.

Carcinogenicity

18. 1,3-Butadiene is associated with leukemia in humans. No appropriate animal model for leukemia has been identified. Therefore, animal data do not provide a solid basis to predict potential carcinogenic effects of petroleum streams based on 1,3-butadiene content.

19. Therefore, 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 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. For petroleum streams containing > 0.1% 1,3-butadiene (petroleum gases), even in absence of carcinogenic effects in animal studies, it is recommended to classify for carcinogenicity.

n-Hexane

Hexane content of naphtha streams

20. An analytical study of 173 naphtha streams conducted by PERF (1997) showed that the "most likely" average hexane concentration is around two percent. Measured concentrations of n-hexane ranged from "non-detect" in certain heavy cat-cracked and coker naphthas to a high of 14% in straight run naphtha (PERF, 1997). These data also suggest that the n-hexane concentration of most naphtha streams is not likely to exceed 10%.

Reproductive toxicity

21. n-Hexane is classified in the European Union as Category 3 reprotoxicant, R-62 (possible risk of impaired fertility), or GHS Category 2 (suspected of damaging fertility or the unborn child) because of studies demonstrating adverse male reproductive effects (testicular toxicity).

22. 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.

23. The studies include:

One generation reproduction study, conducted in Sprague-Dawley rats at 100, 500, and 1500 ppm. Exposures were for 100 days pre-mating and during mating and gestation. No adverse reproductive or developmental effects were noted (API, 1986).

Two generation reproduction study, conducted in Sprague-Dawley rats at concentrations of 900, 3000 and 9000 ppm. Exposures were 6 hours/day 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 treatment related findings were observed. No adverse effects on reproduction were noted (Daughtrey, et al. 1994).

24. It is concluded not to classify petroleum naphtha streams for male reproductive effects because n-hexane is not likely to be present in petroleum naphtha streams at concentrations that are hazardous.

Neurotoxicity

25. n-Hexane is classified in the European Union as R-48/20, or GHS Cat 2 because it is known to cause distal axonal neuropathy in man and experimental animals, usually manifesting clinically as peripheral neuropathy.

26. 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 n-hexane concentrations of 900, 3000, and 9000 ppm 6 hr/day, 5 days/week, for 13 weeks was conducted. Functional Observational Battery tests were conducted at 6 different time points throughout the study and motor activity was evaluated monthly. Exposure had no significant effects on the neurobehavioral or motor activity endpoints evaluated and no significant neuropathological findings were reported (API 1990).

27. 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 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% in the cat reformed naphtha (Schreiner, et al, 2000b), and 1.56% in the cat-cracked naphtha (Lapin et al, 2001).

28. It is concluded not to classify petroleum naphtha streams for specific target organ toxicity (neurotoxic effects) because n-hexane is not likely to be present in petroleum naphtha streams at concentrations that are hazardous.

Specific target organ toxicity

29. See Ototoxicity discussion below

Toluene

Toluene content of naphtha streams

30. An analytical study of 216 naphtha streams conducted by PERF showed that the "most likely" average toluene concentration is around four percent. Measured concentrations of toluene ranged from "non-detect" in certain SR naphtha and isomerization naphthas to a high of 32% in reformate. The data also indicate that there are likely to be a significant number of streams that exceed 3% toluene (PERF, 1997).

Developmental toxicity

31. Toluene is classified in the European Union as Category 3 reprotoxicant, R-63 or GHS Cat 2 because of animal study results suggesting that it causes developmental toxicity.

32. A distillate fraction of light cat-reformed naphtha, containing 5.78 wt% toluene, was evaluated in a reproductive/developmental toxicity screening study (OECD 421). Exposures were to male and female Sprague-Dawley rats at concentrations of 750, 2500 and 7500 ppm, 6 h/day, 7 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 (Schreiner et al, 2000a).

33. The highest exposure concentration in this study is equivalent to 27,750 mg/m^3, of which 5.78%, or about 1600 mg/m^3 (420 ppm), represents exposure to toluene. The "no observed effect level" (NOEL) in the toluene developmental toxicity study conducted by API was 750 ppm.

34. A developmental toxicity evaluation of unleaded gasoline containing 8% toluene was conducted in rats at concentrations of 1000, 3000, and 9000 ppm, which did not produce any evidence of developmental toxicity (Roberts et al, 2001).

Specific target organ toxicity

35. See Ototoxicity discussion below.

36. Based on scientific data petroleum substances containing up to 8% toluene do not cause developmental toxicity. However, as a conservative approach it is recommended that petroleum substances containing 3% or more toluene be classified for developmental toxicity.

Ototoxicity of individual hydrocarbons

37. There is clear evidence that high concentrations of toluene disrupts the auditory system and causes elevated auditory thresholds in laboratory animals, with rats being the most sensitive species. The evidence in rats suggests that exposure must be to a certain minimum concentration for a certain time period before ototoxicity will develop, but the exact magnitude of that concentration is not known with certainty. The NOAEL for toluene ototoxicity in rats is 700 ppm (2.63 mg/L). This is based on a 16-week study, which represents is longest exposure period studied (CONCAWE, 2005).

38. Hearing dysfunction has also been reported from high exposure of laboratory animals to xylene isomers and n-hexane (CONCAWE, 2005). Para-xylene produced hearing loss in rats repeatedly exposed to concentrations of 900 (3.9 mg/L) with a no observed effect level at 450 ppm, while the lowest effect level for mixed xylenes was reported to be 800 ppm (3.47 mg/L). Some perturbations in brainstem auditory evoked responses have been reported in rats repeatedly exposed to 1000 ppm n-hexane (3.52 mg/L).

39. The GHS document provides guidance values to assist with classification of specific target organ effects (Tables 3.9.1 and 3.9.2) that indicate recommended cut-off values based on the route of exposure. 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 lowest observed effect levels for induction of hearing loss for toluene, xylenes and n-hexane are all above 2.6 mg/L, which is higher than the recommended guidance value for classification of substances as Category 2 target organ toxins.

40. The observed LOAEL for the induction of hearing loss for toluene, xylenes and n-hexane are all above 2.6 mg/L, which is above the guidance values of Tables 3.9.1 and 3.9.2 of the GHS. Therefore it is concluded that petroleum naphtha streams containing toluene, xylenes and n-hexane should not be classified for STOT repeated exposure based on ototoxicity.

Skin carcinogenicity of petroleum middle distillates

41. Petroleum middle distillates are streams contained in the kerosene and gas oil product categories (see 14 d and e in the main body of this document) which boil in the range of about 350-700 degrees F (200 ºC – 350 ºC). Those resulting from the atmospheric distillation of crude oil are called "straight-run" middle distillates, while other streams in this general boiling range can be produced from cracking and other processes.

42. The results of dermal carcinogenicity testing of middle distillates has demonstrated that streams from cracking processes, which contain significant quantities of biologically active 4-6 ring polycyclic aromatic hydrocarbons (PAHs), can cause skin tumors. PAHs are present only at very low concentrations in straight run streams, however it has been observed that some of these streams have also caused skin tumors. Unlike the response from cracked streams, the tumor response from straight run streams is characterized by a lower incidence, longer latency, and the presence of significant chronic irritation and inflammation of the skin (Nessel, 1998).

43. Follow-up studies have shown that diluting straight run middle distillates to reduce the irritant effect also eliminates the tumor response. And evaluation of straight run middle distillates in initiation promotion studies has demonstrated that the materials are promoters and not initiators (Jungen, 1995). These findings, coupled with the lack of mutagenicity of these streams have led to the hypothesis that the tumor response caused by straight run middle distillates resulted from a non-genotoxic mechanism, presumably involving the promotion of pre-existing, spontaneously initiated cells (Nessel, 1998).

44. Based on scientific data it is recommended that middle distillate streams (kerosenes and gas oils) obtained from atmospheric distillation not be classified as a carcinogen since PAH do not occur at biologically significant concentrations. It is also recommended that other middle distillate streams which have been shown to be mutagenic be classified as carcinogen Category 2.

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