~~Confidential~~

Helsinki, 24 October 2022

Addressees
Registrant(s) of 269-822-7/68334-30-5 as listed in the last Appendix of this decision

Date of submission of the dossier subject to this decision
31/08/2021

Registered substance subject to this decision ("the Substance")
Substance name: Fuels, diesel
EC number: 269-822-7
CAS number: 68334-30-5

Decision number: Please refer to the REACH-IT message which delivered this communication (in format CCH-D-XXXXXXXXXX-XX-XX/F)

DECISION ON A COMPLIANCE CHECK

Under Article 41 of Regulation (EC) No 1907/2006 (REACH), you must submit the information listed below, by the deadline of ***29 January 2025***.

Requested information must be generated using the Substance unless otherwise specified.

A. Information required from all the Registrants subject to Annex IX of REACH

1. Sub-chronic toxicity study (90-day) (Annex IX, Section 8.6.2.; test method: OECD TG 408) by oral route, in rats

2. Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.; test method: OECD TG 414) by oral route, in one species (rat or rabbit)

Reasons for the request(s) are explained in the following appendices:

- Appendix entitled "Reasons common to several requests";
- Appendix entitled "Reasons to request information required under Annex IX of REACH".

Information required depends on your tonnage band

You must provide the information listed above for all REACH Annexes applicable to you, and in accordance with Articles 10(a) and 12(1) of REACH:

- the information specified in Annexes VII to X to REACH, for registration at more than 1000 tpa.

You are only required to share the costs of information that you must submit to fulfil your information requirements.

How to comply with your information requirements

To comply with your information requirements you must submit the information requested by this decision in an updated registration dossier by the deadline indicated above. You must also update the chemical safety report, where relevant, including any changes to classification and labelling, based on the newly generated information.

You must follow the general testing and reporting requirements provided under the Appendix entitled "Requirements to fulfil when conducting and reporting new tests for REACH purposes". In addition, you should follow the general recommendations provided under the Appendix entitled "General recommendations when conducting and reporting new tests for REACH purposes". For references used in this decision, please consult the Appendix entitled "List of references".

Appeal

This decision, when adopted under Article 51 of REACH, may be appealed to the Board of Appeal of ECHA within three months of its notification to you. Please refer to http://echa.europa.eu/regulations/appeals for further information.

Failure to comply

If you do not comply with the information required by this decision by the deadline indicated above, ECHA will notify the enforcement authorities of your Member State.

Authorised[1] under the authority of Mike Rasenberg, Director of Hazard Assessment

[1] As this is an electronic document, it is not physically signed. This communication has been approved according to ECHA's internal decision-approval process.

Appendix on Reasons common to several requests

1. **Assessment of your read-across approach under Annex XI, Section 1.5.**

You seek to adapt the information requirements for the following standard information requirements by grouping substances in the category and applying a read-across approach in accordance with Annex XI, Section 1.5:

- Sub-chronic toxicity study (90-day), (Annex IX, Section 8.6.2.)
- Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.)

ECHA has considered the scientific and regulatory validity of your grouping and read-across approach in general before assessing the specific standard information requirements in the following appendices.

Grouping of substances and read-across approach

Annex XI, Section 1.5. specifies two conditions which must be fulfilled whenever a read-across approach is used. Firstly, there needs to be structural similarity between substances which results in a likelihood that the substances have similar physicochemical, toxicological and ecotoxicological properties so that the substances may be considered as a group or category (addressed under 'Scope of the grouping'). Secondly, it is required that the relevant properties of a substance within the group may be predicted from data for reference substance(s) within the group (addressed under 'Assessment of prediction(s)').

Additional information on what is necessary when justifying a read-across approach can be found in the ECHA Guidance R.6. and related documents[2,3].

A. Scope of the grouping

Description of the grouping

In your registration dossier you have formed a group (category) of 'Vacuum gas oils, hydrocracked gas oils and distillate fuels (VHGO)'. You have provided read-across justification documents in IUCLID Section 13 [redacted]) and attached to endpoints [redacted]).

Your category includes the following group members:

[1] Fuels, diesel (EC No. 269-822-7; CAS No. 68334-30-5; referred to as "the Substance" thereafter);
[2] Light vacuum gas oil (EC No. 265-059-9; CAS No. 64741-58-8);
[3] Fuels, diesel, no. 2 (EC No. 270-676-1; CAS No. 68476-34-6);
[4] Distillates (petroleum), light hydrocracked (EC No. 265-078-2; CAS No. 64741-77-1);
[5] Fuel oil, no. 2 (EC No. 270-671-4; CAS No. 68476-30-2);
[6] Vacuum gas oil (EC No. 265-049-4; CAS No. 64741-49-7);
[7] Gas oils (petroleum), hydrodesulfurized light vacuum / gas oils (petroleum), hydrodesulfurized light vacuum (EC No. 265-190-1; CAS No. 64742-87-6);
[8] Fuel oil, no. 4 (EC No. 270-673-5; CAS No. 68476-31-3); and
[9] Gas oils (petroleum), hydrotreated light vacuum (EC No. 295-407-5)(ECHA notes that this is an inactive registration).

[2] Read-Across Assessment Framework (RAAF). 2017
[3] Read-across assessment framework (RAAF) - considerations on multi-constituent substances and UVCBs. 2017

You provide the following reasoning for the grouping the substances: "*The VHGO category is formed on the principle that VHGO substances have similar physical-chemical properties, broadly similar composition and present similar health, safety and environmental hazards".*

You define the structural basis for the grouping as "*The domain of this category is established by the refining processes by which the category members are produced and the boiling point / carbon number ranges.*"

You have also proposed that supporting information from other categories, such as Other Gas Oils (OGO) category may be used because of "*chemical similarity of substances from more detailed analytical investigation of substance composition and variability (using for example two dimensional gas chromatography) as well as consideration of physical properties and biological responses.*"

B. Predictions for toxicological properties

You have provided the following reasoning for the prediction of toxicological properties:

(1) "*The VHGO category is formed on the principle that VHGO substances have similar physical-chemical properties, broadly similar composition and present similar health, safety and environmental hazards*."

(2)

(2) Further, based on knowledge of the composition of the substances, you state: "Where data-gaps exist, testing is proposed on the basis of a hypothesis which predicts that greatest hazard to health is due to high content of PAH constituents (PAH hypothesis) with additional testing to take into account the full chemical space of the category." This is based on the idea: *"Based on the existing data across the continuum of petroleum substances, Concawe hypothesises that higher tier toxicological effects such as genotoxicity, repeated dose systemic toxicity, reprotoxicity (developmental and fertility) and carcinogenicity are associated with the level and types of polycyclic aromatic hydrocarbons (PAHs)."* You further elaborate that *"It is therefore hypothesised that the reproductive toxicity of VHGO will be related to the types and levels of aromatics present, and will generally follow a pattern of increasing severity with increased percentage of 3 – 7 ring PACs. Any trend for the developmental toxicity of gas oils would thus be hypothetically described in terms of increasing aromatic content and number of fused aromatic rings. For VHGO specifically, which has predominantly 2- and 3-ring PACs, it is hypothesised that there is low potential for adverse effects in developmental reproductive toxicity tests from exposure to VHGOs."*

In addition, you state that *"To take account of the variable composition, hazard properties are determined using a worst case approach based on the data available for VHGO substances. Where limited or no data exist for VHGO substances, read-across is conducted from similar substances in the Other Gas Oils (OGO) category."* You consider that the categories with overlapping constituent compositions can be used to provide supporting information on the toxic potential of comparable constituent compositions in the VHGO category.

Based on above, ECHA understands that you predict the properties of the Substance using a read-across hypothesis which assumes that different compounds have the same type of effects. The properties of your Substance are predicted to be quantitatively equal to those of the source substance(s).

ECHA notes the following shortcomings with regards to predictions of toxicological properties.

Firstly, with regard to your hypothesis that VHGO substances have similar physical-chemical properties, broadly similar composition and present similar health, safety and environmental hazards.

Data density

Annex XI, Section 1.5. provides that "*substances whose physicochemical, toxicological and eco-toxicological properties are likely to be similar or follow a regular pattern as result of structural similarity may be considered as a group or 'category' of substances.*

According to the ECHA Guidance, one of the factors in determining the robustness of a category is the density and distribution of the available data across the category.[4] To identify a regular pattern and/or to derive reliable prediction of the properties of the members of the category, adequate and reliable information covering the range of structural variations identified among the category members needs to be available.

To support your category hypothesis that the toxicological properties within the VHGO are similar based on similar health hazards, you have provided the following data:

- *Information in the endpoint study records of the registration dossier*

You have indicated that there are no repeated dose toxicity or acceptable pre-natal developmental toxicity (PNDT) studies via oral route for the category members. Instead, you have provided:

- sub-acute, sub-chronic (90-day) and chronic repeated dose toxicity studies via the dermal route conducted using the VHGO category members including the Substance;
- sub-acute, sub-chronic (90-day) toxicity studies via the inhalation route, conducted with the Substance only;
- PNDT studies conducted with the category members including the Substance via the the dermal and the inhalation route.

You have also provided supporting oral and dermal sub-acute and sub-chronic (90-day) toxicity studies conducted on a Kerosine (CAS 8008-20-6) or a highly refined base oil (e.g. White mineral oil, CAS No 8042-47-5) as well as oral and inhalation PNDT studies conducted on a white mineral oils (CAS No 8042-47-5 or CAS 8012-95-1). You consider that these substances have similar constituent pools as the VHGO's but do not contain significant amounts of the PAH constituents, and can provide (only) supporting evidence that there is a lower concern for other pools of constituents e.g. aliphatics (paraffinics and naphthenics) and mono- or di-aromatics present in VHGO's.

- *Information in the justification documents*

In the justification documents, you have provided information to support the identification of a substance constituting a worst-case with regard to the content in polycyclic aromatic hydrocarbons (PAH) containing 4 or more aromatic rings. This information consists of references to national and international assessment reports, scientific publications and supporting mechanistic studies conducted on petroleum substances, which address some of the hydrocarbon classes present in the Substance. You describe that several studies on sub-chronic toxicity, pre natal developmental toxicity, and toxicity to reproduction conducted on substances that are claimed to be predominantly aliphatic in composition (paraffins, iso-paraffins and naphthenics) did not demonstrate reproductive toxicity effects. On the other hand, the information from the substances with a higher content in aromatics, particularly in PAH content, showed developmental toxicity which is hypothesised to be attributed to the interaction of certain PAH substances with the aryl hydrocarbon receptor.

In addition, you refer to the supporting data from ongoing in vitro research programs focusing on

[4] ECHA Guidance R.6: QSARs and grouping of Chemicals, Section R.6.2.1.5.

- a battery of *in vitro* assays for developmental toxicity,
- mechanistic information in the AhR knockout rats; and
- use biological response data to inform grouping and read across assessments of petroleum products ("Cat-App").

We have assessed the available data on the Substance and on the category members and identified the following deficiencies:

- *Information in the endpoint study records of the registration dossier*

As concluded under the relevant endpoint sections in Appendix A (for the Substance) and under the issue '*Reliability and adequacy of the source studies*' below (for the source substances; detailed reasons under the relevant endpoint sections in Appendix IX), the available dataset for the sub-chronic toxicity study (90-day) and the developmental toxicity studies in the dossier have significant deficiencies affecting their reliability and adequacy.

Firstly, the dermal and inhalation repeated dose toxicity and PNDT studies that you provided are not a reliable basis to support your read-across hypothesis as dermal and inhalation route are not the most appropriate route for repeated dose and PNDT toxicity studies. This is explained in Appendix A.1 for repeated dose toxicity and Appendix A.2 for PNDT. Secondly, multiple studies do not have adequate and reliable coverage of the key parameters foreseen to be investigated in the corresponding test methods referred to in Article 13(3). This is explained in Appendix A.1 for repeated dose toxicity and Appendix A.2 for PNDT.

Due to the inappropriate route, together with failure to cover key parameters of the Test Guidelines, it is concluded that no study is provided for 90-day repeated-dose toxicity, nor for pre-natal developmental toxicity, which is adequate and reliable.

In your comments on the draft decision you recognise the deficiencies and you announce your intention to improve the read-across approach with further testing in the VHGO category, including testing proposals and generating supporting data. However, ECHA assesses compliance based on the existing dossier and cannot take future updates and testing into account in this decision-making process.

In addition, in these comments and the supplementary information, you also provided information on chemical composition of VHGO category members, as a basis for better describing structural similarity between VHGO category members and for selecting test material for future testing within the VHGO category. However, you have not explained why this information is relevant to the current draft decision and how it relates to any deficiency noted here.

- *Information in the justification documents*

ECHA acknowledges that adequate and reliable information from substances with overlapping constituent pools as well as other assessment reports and scientific publications can provide supporting information on the toxic potential of comparable hydrocarbon pools in the VHGO category. However, the study summaries presented in the justification document are not available in the registration dossier to allow independent assessment of the information. Particularly, although the test materials are identified by CAS No. and/or chemical name or the hydrocarbon class, their compositions are either not described at all or not sufficiently described. This information is of a particular importance to evaluate the relevance of the supporting information.

Furthermore, the *in vitro* studies (including Cat-App) can provide information to strengthen the proposed hypothesis that the toxicological/biological activity of the substances is dependent on the level and types of PAHs. However, *in vitro* studies do not capture the complexity of systemic interactions, *in vivo* toxicokinetics and the large number of targets/mechanisms associated with repeated dose and reproductive (including developmental) toxicity. Due to the complexity of the systemic interactions, *in vivo* toxicokinetics and the large number of targets/mechanisms associated with repeated dose and reproductive (including developmental) toxicity, the information from these *in vitro* studies are not suitable to compare the toxicological properties of the Substance and of the source substance(s). The mechanistic studies in AhR knockout rats do not provide information on the toxicity of the substances in the category.

In your comment on the draft decision numbered 7, you argue "On their own the in vitro tests are not intended to fully replace in vivo testing, but it is expected that along with proposed testing as part of the category, the in vitro tests can be used as a prediction and/or part of the 'weight of evidence' to support the proposed in vivo testing." You have summarised information on in vitro studies that were performed. ECHA agrees that the in vitro tests do not replace in vivo testing. These in vitro tests are performed on extracts of the substance, and may not represent the toxicological properties of the substance. For these reasons and the reasons given above, the information from these *in vitro* studies are not suitable to compare the toxicological properties of the Substance and of the source substance(s).

As a conclusion, the provided information does not allow to confirm your category hypothesis that the toxicological properties of the substances within the VHGO category are similar.

Secondly, with regard to your hypothesis that the greatest hazard to health is due to high content of PAH constituents (PAH hypothesis).

Read-across hypothesis is inadequate

A read-across hypothesis must be provided, establishing why a prediction for a toxicological or ecotoxicological property is reliable. Firstly, this hypothesis should be based on recognition of the structural similarities and differences between the substances (Guidance on IRs and CSA, Section R.6.). Secondly, it should explain why the differences in the chemical structures should not influence the toxicological properties or should do so in a regular pattern, taking into account that variations in chemical structure can affect both toxicokinetics (uptake and bioavailability) and toxicodynamics (e.g. interactions with receptors and enzymes) of substances (Guidance on IRs and CSA, Section R.6.2.1.3).

As indicated above, your read-across hypothesis is based on the assumption that the greatest hazard to health is due to high content of PAH constituents (PAH hypothesis). You have not classified the substances in the category as Carcinogenic, Germ Cell Mutagenic, or Reproductive Toxicant Category 1, in line with the classification of model PAHs such as Benzo(a)pyrene. You provide estimations of PAH constituents (3+ ring aromatics) from 6.8 to 0.4% by mass of the category members. In respect of non-PAH constituents, you have provided information for "[redacted]", "[redacted]". You argue "*These do not contain significant amounts of the PAH constituents considered to be the drivers of toxicological hazard for VHGO, but have other constituents in common. They help to demonstrate that no significant toxicological hazard is expected from other aliphatic (paraffinic and naphthenic) and aromatic (mono- and di- aromatic) constituents*."

In addition, you have proposed that supporting information from other categories, such as Other Gas Oils (OGO) category may be used because of "*chemical similarity of substances from more detailed analytical investigation of substance composition and variability (using for example two dimensional gas chromatography) as well as consideration of physical properties and biological responses.*"

You consider that PAHs are the worst-case constituents for the substances in the category, but the concentration of individual 3+ ring PAHs in the substances in the category are so low that there is low potential for adverse effects from VHGOs. Moreover you do not classify the substances in line with the classification of model PAHs. This is thus an inherent contradiction in your read-across hypothesis whereby the properties of the Substance are determined by the properties of the PAHs. Further, you have not provided adequate and reliable documentation (detailed composition of substances and test materials; comparison with the VHGO category; a clear hypothesis) to show that the properties of the non-(3+ ring PAH) part of the substances in the category can be predicted from substances which lack PAH constituents. Therefore you have not demonstrated and justified that the properties of the category members can be predicted on the basis of the high content of PAH constituents (PAH hypothesis).

In your comment numbered 6, you additionally state that "We do not consider benzo(a)pyrene to be a representative PAH and do not consider its classification relevant to our hypothesis… Amongst the known effect of constituents in petroleum substances, we support the hypothesis that PAHs, as a group of constituents, are the most toxicologically relevant constituents present in petroleum substances for evaluating their potential hazards, including toxicity to reproduction." You do not consider the classification of benzo(a)pyrene relevant to your read-across hypothesis, and it follows that you agree that the properties of PAHs like benzo(a)pyrene do not determine the properties of the Substance.

In your comment on the draft decision numbered 7, you have summarised information on in vitro studies that were performed, and you argue the in vitro data also strengthens the hypothesis that the types and total amount of specific group of PAHs, mainly 3- to 7-ring PAHs, in petroleum substances do play an important role in determining the developmental toxicity potency of these substances. ECHA considers that this information has already been taken into account in the draft decision.

Further, you have not provided adequate and reliable documentation (detailed composition of substances and test materials; comparison with the VHGO category; a clear hypothesis) to show that the properties of the non-(3+ ring PAH) part of the substances in the category can be predicted from substances which lack PAH constituents. Therefore you have not demonstrated and justified that the properties of the category members can be predicted on the basis of the high content of PAH constituents (PAH hypothesis).

Thirdly, with regard to your hypothesis that supporting information from other categories (e.g. the Other Gas Oils [OGO] category) may be used on the basis of chemical similarity and similar hazard properties, you have not provided information to show the chemical similarity of individual OGO substances with individual VHGO substances. Nonetheless, ECHA notes that at its highest, your hypothesis for prediction is the same as advanced for VHGO substances. Your hypothesis is rejected for the same reasons as set out for the hypothesis that VHGO substances have similar physical-chemical properties, broadly similar composition and present similar health, safety and environmental hazards. As a conclusion, the provided information does not allow to confirm your category hypothesis that the toxicological properties of substances within the OGO category are similar to particular VHGO substances.

Adequacy and reliability of source studies

According to Annex XI, Section 1.5., if the grouping concept is applied then in all cases the results to be read across should:

- be adequate for the purpose of classification and labelling and/or risk assessment;
- have adequate and reliable coverage of the key parameters addressed in the corresponding test method referred to in Article 13(3);
- cover an exposure duration comparable to or longer than the corresponding test method referred to in Article 13(3) if exposure duration is a relevant parameter.

You have provided sub-acute, sub-chronic and chronic repeated dose toxicity studies as well as PNDT studies conducted with the VHGO category members supported by the data on the OGO category members.

For the specific reasons detailed for the relevant information requirements under Appendix A.1 and A.2, these studies do not meet the necessary conditions. Particularly, deficiencies were identified in route of test substance administration, information provided for test material identity as well as in the study design as specified in the corresponding test methods.

C. Conclusions on the grouping of substances and read-across approach

As explained above, you have not established that relevant properties of the Substance can be predicted from data on the source substances. Therefore, your adaptation does not comply with the general rules of adaptation as set out in Annex XI, Section 1.5. and your grouping and read-across approach is rejected.

The information provided in the comment does not change the above conclusion.

Appendix A: Reasons to request information required under Annex IX of REACH

1. Sub-chronic toxicity study (90-day)

A Sub-chronic toxicity study (90 day) is a standard information requirement in Annex IX to REACH.

In your dossier, you have provided following key and supporting studies conducted with the Substance:[5]

i. Supporting - sub acute 68334-30-5 ARCO ATX-89-0008 1992;
ii. Supporting - sub acute 68334-30-5 ARCO ATX-86-0006 1986;
iii. Supporting - subchronic diesel_ARCO_910248_1994;
iv. Supporting - sub acute 68334-30-5 ARCO ATX-93-0169 1994;
v. Key - 90-day PetroleumHPV CAS 68334-30-5 (2012);
vi. Supporting - sub acute 68334-30-5 IIT 1984; GLP not specified
vii. Supporting - sub-acute insert CAS 68334-30-5 API 1222 1980; GLP not specified
viii. Supporting - chronic CAS 68334-30-5 Easley 1982; GLP not specified
ix. Supporting - 68334-30-5_Dalbey 1982; GLP not specified;
x. Key - subchronic Diesel Fuel Obscurant Aerosol Lock et al 1984; GLP not specified;
xi. Supporting - subacute_68334-30-5_Kainz and White 1984; GLP not specified.

You have also adapted the standard information requirement by applying read-across adaptation in accordance with Annex XI, Section 1.5. You have provided the following key and supporting studies conducted with the source substances:[6]

xii. Supporting - for testing proposal - subchronic white oil [redacted] 1987
xiii. Supporting - Kerosine oral subchronic Mattie et al. JP-8 jet fuel 2000
xiv. Supporting - HRBO oral.chronic feeding study P70H and P100H Trimmer 2004
xv. Supporting - sub-acute insert CAS 68476-30-2 API 1218 1980
xvi. Supporting - for test proposal - sub-acute API 8008-20-6 straight run kerosine 1985
xvii. Supporting - sub acute 64741-58-8 ARCO ATX-91-0249 1993
xviii. Supporting - sub acute 64741-77-1 ARCO ATX-91-0094 1992
xix. Supporting - sub-acute 68476-34-6 ARCO ATX-85-0184 1985
xx. Supporting - sub-acute 68476-34-6 ARCO ATX-86-0061 1988
xxi. Supporting - sub-acute 68476-30-2 API 1220 1980
xxii. Supporting - sub-chronic 64741-49-7 [redacted] 1994
xxiii. Supporting - sub-acute 68476-30-2 API 1219 1980
xxiv. Supporting - sub-acute 68476-34-6 ARCO ATX-85-0185 1986
xxv. Supporting - for test proposal - sub-acute ARCO 8008-20-6 straight run kerosine 1992
xxvi. Key - subchronic Vacuum Tower Overheads Mobil 62326 1989
xxvii. Repeated dose toxicity: other routes, IUC4#10/Ch.5.4 (1986)

We have assessed this information and identified the following issue(s):

1. Information provided with the Substance

1.1 Route of administration- dermal route

The Sub-chronic toxicity study (90-day) must be performed by the most appropriate route of administration, having regard to the likely route of human exposure (Annex IX, Section 8.6.1, Column 1).

[5] ECHA notes that the naming of the studies included in the list reflects the naming provided by the Registrant in IUCLID.
[6] *Ibid.*

Column 2 specifies that dermal route of exposure is appropriate if:
(1) skin contact in production and/or use is likely; and
(2) the physicochemical properties suggest a significant rate of absorption through the skin; and
(3) one of the following conditions is met:
(i) toxicity is observed in the acute dermal toxicity test at lower doses than in the oral toxicity test, or
(ii) systemic effects or other evidence of absorption is observed in skin and/or eye irritation studies, or
(iii) *in vitro* tests indicate significant dermal absorption, or
(iv) significant dermal toxicity or dermal penetration is recognised for structurally-related substances.

According to the ECHA Guidance[7], the oral route is considered by default the most appropriate route for repeated dose toxicity testing because it is assumed to maximise systemic availability (internal dose) of most substances.

The studies (i-viii) conducted with the Substance are performed by the dermal route, and you have also provided a justification for the use of the dermal route ("[redacted]"). To justify the dermal route, you have provided the following arguments:
(1) human exposure is principally dermal (skin contact in production and/or use is likely);
(2) although a petroleum substance in its entirety is unlikely to cross the dermal barrier, the physical-chemical characteristics of the UVCB does not prevent the penetration of smaller molecules. You propose that polycyclic aromatic hydrocarbons (PAHs) are the primary driver of toxicity and that these are absorbed through the skin, while the constituents which are not absorbed well after dermal administration are not toxicologically significant;
(3) *(i)* you compare oral and dermal acute toxicity (LD50);
(ii) you note the lack of reported systemic effects or other or other evidence of absorption is observed in skin and/or eye irritation studies;
(iii) you note the lack of in vitro skin absorption measurements for UVCBs;
(iv) you refer to systemic toxicity after dermal administration of a VHGO substance with CAS No 64741-49-7.

In addition to the arguments above, you also refer to the documents from National Institute for Public Health and the Environment (RIVM), The Scientific committee on consumer safety (SCCS), US California/EPA as well as ECHA Guidance in relation to assessing systemic toxicity after dermal administration. You conclude that as there are no intentional or anticipated uses that would result in oral exposure, the testing by the oral route would lead to significant amount of uncertainty (i.e. oral-to-dermal route extrapolation) in risk characterisation.

First, ECHA agrees that for the Substance, human exposure (worker and consumer) is expected to be principally dermal *(1)*. However, related to the other criteria for appropriateness of the dermal route as specified in Column 2 of Annex IX, Section 8.6.1, ECHA has identified the following deficiencies, and accordingly, the dermal route is not an appropriate route.

Regarding criterion (2):
You have not demonstrated that the Substance would have a significant rate of absorption through the skin. The ECHA Guidance[8] notes that a logKow of -1 to 4 is the range where dermal penetration is favourable. In your read-across justification document you explain that "*Petroleum substances are UVCBs consisting of large numbers of hydrocarbon components each with their own partition coefficient n-octanol/water (log Kow) value*." For the Substance,

[7] ECHA Guidance R.7.a, section R.7.5.4.3
[8] ECHA Guidance R.7c, Section R.7.12.2.1

you state (under Partition Coefficient) that "*Calculated log Pow for constituents of this substance range between 1.99E+00 and 1.80E+01*". Furthermore, in the justification document, you have provided a distribution mass of predicted logKow values showing that the largest proportion of the relative mass of the Substance has logKow >6, which indicate poor dermal absorption.

Furthermore, you propose that the smaller PAH constituents which are toxicologically relevant are expected to be available through the dermal route, while the substances constituents that are not absorbed via dermal route, are not responsible for toxicity. However, as detailed in the Appendix on 'Reasons common to several requests', you have not provided reliable and adequate information for ECHA to conclude that the toxicological properties of the VHGO substances including the Substance, are dependent on the level and types of PAHs and that the other constituents do not contribute to the toxicity. Therefore, it cannot be concluded that only the dermally available constituents would induce toxicity.

Regarding criterion (3):
The provided acute toxicity studies do not show that the dermal route is more toxic than the oral route *(3)(i)*.

There is no evidence of systemic effects or other evidence of absorption observed in skin and/or eye irritation studies *(3)(ii).*

While there is evidence that some constituents of the substance are absorbed (e.g. benzo(a)pyrene), there is not such evidence for the majority of constituents of the substance (3)(iii). As detailed in the Appendix on 'Reasons common to several requests', you have not provided reliable and adequate information for ECHA to conclude that the toxicological properties of the VHGO substances including the Substance, are dependent on the level of benzo(a)pyrene and other PAHs and that the other constituents do not contribute to the toxicity.

You have not provided reliable information to demonstrate that significant dermal toxicity or dermal penetration is recognised for structurally-related substances *(3)(iv).* There is systemic toxicity after dermal exposure in study (xxvi) (Key - subchronic Vacuum Tower Overheads Mobil 62326 1989) with the test material being "64741-49-7 / 64741-49-7; Vacuum Tower Overheads". However, the detailed composition of the test material (and particularly the PAH concentrations) in this study is not provided, and so it is not possible to determine if the test material is representative for, or structurally related to, the Substance.

In your comment on the draft decision numbered 5, you agree that the column 2 criteria are not all met by the Substance.

In your comment on the draft decision numbered 5, regarding criterion 2 (PC properties) above, you argue that the rate of absorption cannot be demonstrated for every molecule in the substance, that identifying an oral hazard has no value in risk assessment and that the criterion is narrow, fails to acknowledge that the substance is used as fuels and that there is an aspiration hazard which means that the Substance cannot be dosed orally. ECHA considers that you have not substantiated your claim for every molecule in the substance, and that to the contrary, as set out above, you have provided a distribution mass of predicted logKow values showing that the largest proportion of the relative mass of the Substance has logKow >6, which indicate poor dermal absorption. ECHA considers that your comment on oral hazard and criterion narrowness and use as a fuel do not provide a substance-specific reason why this legal criterion should not be applied, but reflect a generic disagreement with the REACH regulation provisions. You have not substantiated your claim that the Substance cannot be

dosed orally, as there are multiple way to orally dose a substance with aspiration hazard, and this is not anyway a reasoning why the criterion has been mistakenly applied.

In your comment on the draft decision numbered 5, regarding the set of criteria (3), you note that these rely on the Substance having some inherent dermal toxicity, and agree with ECHA that this is not going to occur with molecules that are too large to pass through the dermis. You comment that the petroleum industry has conducted many dermal studies over the last 50 years is not considered as a valid reason why criteria (3) cannot be applied.

Overall, your comments do not affect the conclusion that the column 2 criteria are not met for the Substance.

Secondly, regarding the most appropriate route of administration, ECHA considers that the dermal route cannot be considered since it is not an appropriate route of administration. However, for a complete analysis, ECHA has evaluated the most appropriate route on the basis that the dermal route were appropriate. There is no reason to believe that the Substance causes route-specific systemic toxicity after dermal exposure, nor that it is more potent after dermal administration, nor that there is any particular difficulty in route-to-route extrapolation for the Substance. Rather, the substance is characterised to cause topical dermal toxicity after dermal administration, which would limit the dose achieved. In response to the arguments raised in your justification for the dermal route, some of these were addressed under the consideration of appropriate route, and the rest here. The hypothesis that the PAHs are solely responsible for toxicity of the Substance, after dermal exposure, is not fully justified, although it is clear that where the PAH concentrations are relatively high, these will drive the toxicity. However, according to Table 4 of "[redacted]", the PAC-2 content of 3-7 ring PAHs is typically below 1% (mass/mass) for the Substance, i.e. a relatively low proportion of total mass and it is not demonstrated that PAH concentrations are sufficiently high so as to drive the toxicity. It would be expected that there would be higher absorption of all constituents into the systemic circulation after oral exposure, as compared with dermal exposure. The potential for enhanced systemic availability after disruption of skin barrier function is not an argument for dermal administration, since the skin damage would likely limit the applied dose, and it represents an artefact of skin damage.

Separately, you have raised arguments based on various guidance documents. ECHA considers that guidance for other legislations than REACH does not over-ride the REACH legal text and guidance, as set out above. You also cite ECHA's Guidance, which cites the requirement for case-by-case examination of the appropriateness of the route; ECHA has undertaken an examination of the case as set out above. ECHA's Guidance also mentions that the dermal route may be more appropriate when there are "*significant qualitative differences in metabolism in comparison with dermal exposure*", with the examples illustrating that the substance might be degraded after oral administration, either by stomach acidity or by first-pass metabolism. You have shown no such qualitative difference in metabolism whereby the substance would be degraded after oral administration, as compared with dermal administration. Accordingly ECHA considers that the use of the oral route does not introduce any special uncertainty for route-to-route extrapolation for the Substance. As a result of the above considerations, your argument based on guidance documents does not provide a basis for changing the choice of most appropriate route.

Summarising there are strong substance-specific reasons for using the oral route to obtain maximal systemic availability of the Substance to evaluate the hazard for repeated-dose toxicity and the oral route is the most appropriate route of administration for this study.

Therefore, the studies (i-viii) conducted with the Substance are not performed by the most appropriate route, and hence do not fulfil the information requirement.

In your comment on the draft decision numbered 5, you argue that the '2012 studies' (of which the only repeated-dose toxicity study is study (v)) are modern studies conducted by the dermal route, and the fact that they have not been conducted via the oral route is insufficient reason to reject them. You further argue that insufficient consideration is given to the weight of evidence of these studies (and other non-oral route studies). Furthermore, you refer to the future studies that are planned to substantiate the read-across for the VHGO category, including OECD 422 studies by the oral route and some dermal 422 studies to justify the historical dermal studies, as well as testing proposals for some other substances in the VHGO category and consider that there is no need to request 90-day study via oral route on the Substance.

ECHA considers that if there are studies for the 90-day information requirement which are not performed by the most appropriate route, the studies have to be rejected as they do not fulfil the legal requirements, for the reasons already described above. Consequently, there is a data gap for the Substance and a study by the most appropriate route must be generated and provided. In addition, while you have contested that insufficient consideration has been given to a weight of evidence for these studies, ECHA notes that you have not provided an adaptation according to Annex XI, 1.2, or any argumentation that could be interpreted as such, neither in the dossier nor in your comments. Furthermore, the results of any studies which may become available in the future do not provide a basis for compliance of the existing dossier or substantiate the read-across which is currently rejected for the reasons set out under appendix on Reasons common to several requests.

Finally, you note in your comments that *'as ECHA acknowledge the robustness of this study, and the appropriateness of the route when modelling human exposure, it is likely that Concawe will refer to this study when conducting human risk assessment, as there would be no need for theoretical route-to-route.'* ECHA notes that this decision addresses incompliance with the information requirement and the appropriateness of the study for human risk assessment is not the subject of the assessment made in this decision.

To conclude, your comments do not affect the original conclusion that the information requirement is not fulfilled.

1.2 Route of administration - inhalation route

As indicated under sub-section 1.1. above, the Sub-chronic toxicity study (90-day) must be performed by the most appropriate route of administration, having regard to the likely route of human exposure (Annex IX, Section 8.6.1, Column 1).

Column 2 specifies that inhalation route of exposure is appropriate if exposure of humans via inhalation is likely, taking into account the vapour pressure of the substance and/or the possibility of exposure to aerosols, particles or droplets of an inhalable size.

According to the ECHA Guidance[9], the oral route is by default the most appropriate route for repeated dose toxicity testing because it is assumed to maximise systemic availability (internal dose) of most substances.

The studies (ix-xi) conducted with the Substance are performed by the inhalation route. You have not provided a justification for the use of the inhalation route. For vapour pressure, you state "The vapour pressure of vacuum gas oils, hydrocracked gas oils and distillate fuels is 0.4 kPa at 40°C (CONCAWE, 1996)." In your CSR you state "The inhalation RCR for most contributing scenarios is below [redacted] and in general below [redacted]."

[9] ECHA Guidance R.7.a, section R.7.5.4.3

In respect of whether inhalation is an appropriate route, the vapour pressure at 0.4 kPa at 40°C is low, and would not justify the inhalation route as appropriate (absent other argumentation). You have not shown that there is exposure to aerosols, particles or droplets of an inhalable size. ECHA concludes that inhalation is not an appropriate route of exposure.

Thus, regarding the most appropriate route of administration, ECHA considers that the inhalation route cannot be considered as such, since it is not an appropriate route of administration

Therefore, the studies (ix-xi) conducted with the Substance are not performed by the most appropriate route, and hence do not fulfil the information requirement.

1.3 Study not meeting the key parameters of the guideline

To be considered compliant and enable concluding whether the Substance has dangerous properties and supports the determination of the No-Observed Adverse Effect Level (NOAEL), a study has to meet the requirements of the corresponding OECD TG (i.e. 408 for oral, 411 for dermal, and 413 for inhalation). The key parameter(s) of these test guidelines include, among others:

- testing of at least three dose levels (unless conducted at the limit dose) with concurrent controls
- dosing of the Substance for a minimum of 90 days (13 weeks; sub-chronic study)
- at least 10 male and 10 female animals for each test and control group
- frequency of dosing
    - 6 hours per day on a 5 day per week (or 7 days per week) for OECD TG 413, and
    - at least 6 hours per day on a 7-day per week (based on practical reasons, 5-day per week considered acceptable) for OECD TG 411.

You have provided repeated dose toxicity studies (studies i-viii, dermal route; studies ix-xi, inhalation route) conducted with the Substance.

- The study (vi) was conducted with one dose only (not a limit dose).
- The studies (i, ii, iv, vi, vii, ix, and xi) do not have the required exposure duration of 90 days (13 weeks; sub-chronic study). Specifically, you indicate the studies (i, ii, iv, vi, vii, and xi) as sub-acute with exposure duration of 4 weeks or less. For study (ix) you specify a total of 9 exposure, 1, 2, or 3 times a week.
- The studies (ix, xi) do not have the required 10 males and females for each dose group. Specifically, for study (xi) you indicate that only males were tested, for study (ix) you indicate that 4 rats of each sex were tested. In addition, the studies (i, ii, vi) do not have information to evaluate if the required 10 males and females for each dose group were used in the provided studies.
- The provided studies (ix, x) do not have the required number of daily exposures per week, as specified in the corresponding test guidelines, i.e. at least five times per week, for a sufficient length of time (i.e. at least 6 hours per day). Specifically, for (ix), you indicate "Exposure duration was 2 or 6 hours per day and exposure frequency was once, twice, or three times per week." and for (x), you indicate " 4 hour per day, two days per week for 13 weeks (total of 26 exposures)".

Based on above, the studies (i, ii, iv, vi, vii, ix-xi) conducted with the Substance do not meet the requirements of the corresponding OECD TG (i.e. 411 for dermal and 413 for inhalation), and hence, these studies with the Substance cannot be used to fulfil the information requirement.

1.4 Conclusion on the information provided with the Substance

Based on above, the information provided with the Substance has deficiencies in route of exposure used, details on test substance as well as coverage of key parameters. Therefore, the information requirement is not fulfilled.

Furthermore, although ECHA has not identified deficiencies in the test material characterisation of the Substance in studies in the dossier in 1.1-1.4 above, in your comment on the draft decision numbered 4, you provide information on the chemical characterisation of multiple samples of the Substance, and consider this relevant to the test materials of studies on the Substance. Further, ECHA notes that although you state that samples were "obtained from different registrants over time", there is no documentation of the time of sampling, nor analysis thereof in the 'Supporting analytical data' document. Under any circumstances, ECHA considers there is not a basis to extrapolate from the analysis of the samples analysed in this document to historically obtained samples.

2. Adaptation under Annex XI, Section 1.5

As explained in the Appendix on Reasons common to several requests, section 1, your adaptation is rejected. In addition, the following endpoint-specific deficiencies have been identified in your read-across adaptation:

2.1 Adequacy and reliability of source study

According to Annex XI, Section 1.5., if the grouping concept is applied then in all cases the results to be read across should

- be adequate for the purpose of classification and labelling and/or risk assessment; and
- have adequate and reliable coverage of the key parameters foreseen to be investigated in the corresponding test methods referred to in Article 13(3); and
- cover an exposure duration comparable to or longer than the corresponding test method

2.1.1 Route of administration

As indicated above, the sub-chronic toxicity study must be conducted with the most appropriate route of administration, having regard to the likely route of human exposure (Annex IX, Section 8.6.1, Column 1).

For your adaptation, you have provided 13 dermal repeated dose toxicity studies (xv-xxvii) conducted with the source substances, and you have also provided a justification for the use of the dermal route ("Justif Dermal Route Oct 2019"); this is the same justification as provided for studies on the Substance.

As explained above under '*1.1 Route of administration - dermal route'* for the studies conducted with the Substance, the chosen route, i.e. dermal, is not considered the most appropriate route of administration. Therefore, the source studies (xv-xxvii) are not performed by the most appropriate route, and do not enable ECHA to conclude whether the Substance has dangerous properties, and the studies are not adequate for the purpose of classification and labelling or for the risk assessment.

2.1.2 Test material composition

Under Annex XI, Section 1.5., if the grouping concept is applied then in all cases the results to be read across must be adequate for the purpose of classification and labelling and/or risk assessment.

In order to predict the properties of the Substance, the test material used in the study on the source substance must be representative for the source substance (Article 10 and Recital 19 of REACH; Guidance on IRs and CSA, Section R.4.1.). Therefore, the unambiguous characterisation of the composition of the test material used to generate the source data is required to assess whether the test material is representative for the source substance.

Three repeated dose toxicity studies (xii-xiv) are conducted with the source substances "[redacted] using grouping and read-across adaptation. The justification document in the dossier ("[redacted]") specifies that the source substances as well as the Substance are UVCBs with the composition varying in the quantitative profiles for different hydrocarbon classes including level and types of the PAH constituents. However, the information on the test material compositions of the source studies provided in your dossier is limited to the name and/or numerical identifier (CAS No) and it does not contain information on the quantitative occurrence of the hydrocarbon classes.

ECHA agrees that the composition of the Substance may be linked to the hazardous properties of the Substance and considers that the compositional information is essential to characterise the relationship between the composition and the hazardous properties of the Substance, and to demonstrate that the test material is representative for the source substance and thereby also for the Substance.

Therefore, the provided repeated dose toxicity studies conducted with the source substances (xii-xiv) cannot be considered as adequate and reliable for the purpose of classification and labelling and/or risk assessment.

2.1.3 Coverage of the key parameters and study duration

According to the provisions of Annex IX, Section 8.6.2., information on sub-chronic toxicity study (90-day) shall be provided. The key parameters foreseen to be investigated in a corresponding (OECD TG 408 for oral, OECD TG 411 for dermal and OECD TG 413 for inhalation) sub-chronic toxicity study (90-day) include but are not limited to

- testing of at least three dose levels (unless conducted at the limit dose) with concurrent controls
- dosing of the Substance for a minimum of 90 days (13 weeks; sub-chronic study)
- at least 10 male and 10 female animals for each test and control group
- Ophthalmological examination, full detailed gross necropsy and subsequent histopathology of the listed tissues.
- frequency of dosing
  - daily for OECD TG 408, and
  - at least 6 hours per day on a 7-day per week (based on practical reasons, 5-day per week considered acceptable) for OECD TG 411.

For your adaptation, you have provided repeated dose toxicity studies (studies xii-xiv, oral route; studies xv-xxvii, dermal route;) conducted with the source substances.

- The study (xii) was conducted without a concurrent control group.
- The studies do not have the required exposure duration of 90 days (13 weeks; sub-chronic study). Specifically, you indicate the studies (xv-xxi, xxiii-xxv, xxvii) as sub-acute with exposure duration of 4 weeks or less.
- The studies (xvii, xviii, xx, xxii) do not have information to evaluate if the required 10 males and females for each dose group were used in the provided studies.
- The following key parameters were not evaluated in the study (xiii): histopathological examination of spinal cord (at three levels: cervical, mid-thoracic and lumbar),

pituitary, thyroid, parathyroid, salivary glands, aorta, accessory sex organs, female mammary gland, prostate, skin, and ophthalmological examination. In addition, no details on examinations conducted for study (xxii) were provided.

- The studies (xii, xvi) do not have the required number of daily exposures per week, as specified in the corresponding test guideline, i.e. daily for oral and at least five times per week, for a sufficient length of time (i.e. at least 6 hours per day) for the dermal studies. Specifically, for study (xii, oral), you indicate that animals were dosed 5 times per week and for study (xvi, dermal) 3 times per week only.

Based on above, ECHA concludes that the provided repeated dose toxicity studies conducted with the source substances (xii-xiii, xv-xxv, xxvii) do not have adequate and reliable coverage of the key parameters foreseen to be investigated in the corresponding test methods and/or do not cover an exposure duration comparable to or longer than the corresponding test method.

3. Conclusion

Based on the above, the information you provided does not fulfil the information requirement.

Information on the study design

Referring to the criteria provided in Annex IX, Section 8.6.2, Column 2, the oral route is the most appropriate route of administration to investigate repeated dose toxicity, because the Substance is a liquid with low vapour pressure, and as stated above, the inhalation and dermal routes are not the most appropriate route.

Therefore the sub-chronic toxicity study must be performed according to the OECD TG 408, in rats and with oral administration of the Substance.

2. Pre-natal developmental toxicity study in one species

A Pre-natal developmental toxicity (PNDT) study (OECD TG 414) in one species is a standard information requirement under Annex IX to REACH.

In your dossier, you have provided the following key and supporting studies conducted with the Substance[10]:

i. Supporting - VDF_diesel_ARCO_1994
ii. Supporting - straight_run_diesel_ARCO_1994
iii. Supporting - straight_run_diesel_ARCO_1993
iv. Key - PNDT PetroleumHPV CAS 68334-30-5
v. Supporting - 68334-30-5_API_1979b;

You have also adapted the standard information requirement by applying read-across adaptation in accordance with Annex XI, Section 1.5. You have provided the following key and supporting studies conducted with the source substances[11]:

vi. Key - VTO_Mobil_1989a
vii. Supporting - for test proposal - White mineral oil inhalation [redacted] 1987;
viii. Supporting - No. 2 heating oil_API_1979c;
ix. Supporting - for test proposal - White mineral oil [redacted] 1987b

[10] ECHA notes that the naming of the studies included in the list reflects the naming provided by the Registrant in IUCLID.
[11] *Ibid*.

We have assessed this information and identified the following issue(s):

1. Information provided with the Substance

1.1 Route of administration

The pre-natal developmental toxicity study must be conducted by the most appropriate route of administration, having regard to the likely route of human exposure (Annex IX, Section 8.7.2, Column 1). The selection of the "most appropriate route of administration" focuses on identification of hazards, and the oral route is the 'default' route[12]. In practice, testing via the oral route is usually performed with liquids and dusts and testing via inhalation route is usually performed with gases and liquids with very high vapour pressure. Testing via dermal route might be necessary under specific circumstances, for example for substances with high dermal penetration and indications for a specific toxicity following dermal absorption[13]. According to OECD TG 414, if another route of administration other than oral is used, the registrant should provide justification and reasoning for its selection.

a. Dermal route

The studies (i-iv) were performed by the dermal route, and you have also provided a justification for the use of the dermal route [redacted]). You refer to the column 2 criteria of Annex IX, 8.6.2 [sub-chronic toxicity study] and provide arguments to support the dermal route as described above for the Sub-chronic toxicity study (90-day) (Appendix A.1, Section 1.1, Route of administration).

As described under Appendix A.1, while ECHA agrees that human exposure is expected principally via dermal route, you have not demonstrated that the Substance would have a high dermal penetration. Rather, the physico-chemical properties of constituents of the Substance suggest that many constituents will be poorly absorbed across the skin. In addition, you have not demonstrated that there would be a specific toxicity following dermal absorption that would not be evident following oral absorption.

The scientific considerations regarding the most appropriate route of administration for the sub-chronic toxicity (as set out in Appendix A.1, Section 1.1, Route of administration) also apply for the developmental toxicity.Therefore, you have not justified a specific circumstance that the dermal route would be the most appropriate route and hence, the 'default' oral route is considered the most appropriate route.

In your comment on the draft decision numbered 5, you comment on the column 2 criteria of Annex IX, 8.6.2 in respect of the route of administration, although such criteria are not present in Annex IX, 8.7.2. In respect of the arguments you raise in your comments, the responses provided for the sub-chronic toxicity (Appendix A, section 1.1) also apply for the developmental toxicity.

In your comment on the draft decision numbered 5, you argue that the '2012 studies' (of which the only PNDT study is study (iv)) are modern studies conducted by the dermal route, and the fact that they have not been conducted via the oral route is insufficient reason to reject them. You further argue that insufficient consideration is given to the weight of evidence of these studies (and other non-oral route studies). Furthermore, you refer to the future studies that are planned to substantiate the read-across for the VHGO category, including OECD 422 studies by the oral route and some dermal 422 studies to justify the historical

[12] ECHA Guidance R.7.a, section R.7.6.2.3.2 (pages 436 and 482 in version 6.0 – July 2017)
[13] ECHA Guidance R.7.a, section R.7.6.2.3.2 (pages 436 and 482 in version 6.0 – July 2017)

dermal studies, as well as testing proposals for some other substances in the VHGO category and consider that there is no need to request a PNDT study via oral route on the Substance.

ECHA considers that if there are studies for the PNDT information requirement which are not performed by the most appropriate route, the studies have to be rejected as they do not fulfil the legal requirements, for the reasons already described above. Consequently, there is a data gap for the Substance and a study by the most appropriate route must be generated and provided. In addition, while you have contested that insufficient consideration has been given to a weight of evidence for these studies, ECHA notes that you have not provided an adaptation according to Annex XI, 1.2, or any argumentation that could be interpreted as such, neither in the dossier nor in your comments. Furthermore, the results of any studies which may become available in the future do not provide a basis for compliance of the existing dossier or substantiate the read-across which is currently rejected for the reasons set out under appendix on Reasons common to several requests.

Finally, you note in your comments that *'as ECHA acknowledge the robustness of this study, and the appropriateness of the route when modelling human exposure, it is likely that Concawe will refer to this study when conducting human risk assessment, as there would be no need for theoretical route-to-route.'* ECHA notes that this decision addresses incompliance with the information requirement and the appropriateness of the study for human risk assessment is not the subject of the assessment made in this decision.

To conclude, your comments do not affect the original conclusion that the information requirement is not fulfilled.

b. Inhalation route

The study (v) was performed by the inhalation route, and no justification for the use of the inhalation route is provided.

The vapour pressure of the Substance is 0.4kPa at 40°C, indicating a low propensity for exposure by this route. The testing via inhalation route is usually performed with gases and liquids with very high vapour pressure. The Substances is a gas and in view of the physico-chemical properties of the Substance, not considered to have a very high vapour pressure. Therefore, there are strong reasons that inhalation is not the most appropriate route, and the default presumption that the oral route is most appropriate for liquids is maintained.

Therefore, the studies (i-v) conducted with the Substance are not performed by the most appropriate route, and hence do not fulfil the information requirement.

1.2 Study not meeting the key parameters of the guideline

In order to be considered compliant and enable assessing if the Substance is a developmental toxicant, the study has to meet the requirements of OECD TG 414. The criteria of this test guideline include e.g.

- testing of at least three dose levels and a concurrent control,
- 20 female animals with implantation sites for each test and control group,
- examination of the foetuses for external, skeletal and soft tissue alterations (variations and malformations).

The study (v) does not cover the expected dose levels as only two test dose levels (not indicated as limit dose) and a control were reported.

You indicate that study (i) was conducted using between 14 and 19 pregnant females per test group, and study (ii) had 14 or 15 presumed pregnant females per test group. Therefore, the statistical power of the information provided is not sufficient.

In the studies (i, ii), the key parameters of foetal measurements have not been performed as required in OECD TG 414. Specifically, studies (i) and (ii) report that "No skeletal or visceral exams were conducted."

Based on above, the studies (i,ii, and v) conducted with the Substance do not meet the requirements of the OECD TG 414, and hence, these studies with the Substance cannot be used to fulfil the information requirement.

1.3 Conclusion on the information provided with the Substance

Based on above, the information provided with the Substance has deficiencies in route of exposure used, details on test substance as well as coverage of key parameters. Therefore, the information requirement is not fulfilled.

Furthermore, although ECHA has not identified deficiencies in the test material characterisation of the Substance in studies in the dossier in 1.1-1.3 above, in your comment on the draft decision numbered 4, you provide information on the chemical characterisation of multiple samples of the Substance, and consider this relevant to the test materials of studies on the Substance. Further, ECHA notes that although you state that samples were "obtained from different registrants over time", there is no documentation of the time of sampling, nor analysis thereof in the 'Supporting analytical data' document. Under any circumstances, ECHA considers there is not a basis to extrapolate from the analysis of the samples analysed in this document to historically obtained samples.

2. <u>Adaptation under Annex XI, Section 1.5</u>

As explained in the Appendix on Reasons common to several requests, section 1, your adaptation is rejected. In addition, the following endpoint-specific deficiencies have been identified in your read-across adaptation:

2.1 Adequacy and reliability of source study

According to Annex XI, Section 1.5., if the grouping concept is applied then in all cases the results to be read across should

- be adequate for the purpose of classification and labelling and/or risk assessment; and
- have adequate and reliable coverage of the key parameters foreseen to be investigated in the corresponding test methods referred to in Article 13(3);

2.1.1 Route of administration

The pre-natal developmental toxicity (PNDT) study must be conducted with the most appropriate route of administration, having regard to the likely route of human exposure (Annex IX, Section 8.7.2, Column 1)

For your adaptation, you have provided three PNDT studies conducted with the source substances via dermal or inhalation routes (vi, dermal; vii-viii, inhalation). Your justification for the use of dermal and inhalation routes for grouping and read-across is the same as for the Substance.

As explained above under '*Route of administration*' for the studies conducted with the Substance, the chosen routes, i.e. dermal and inhalation, are not considered the most appropriate routes of administration. Therefore, the source studies (vi-viii) are not performed by the most appropriate route, and do not enable ECHA to conclude whether the Substance has dangerous properties, and the studies are not adequate for the purpose of classification and labelling or for the risk assessment.

2.1.2 Test material composition

Under Annex XI, Section 1.5., if the grouping concept is applied then in all cases the results to be read across must be adequate for the purpose of classification and labelling and/or risk assessment.

In order to predict the properties of the Substance, the test material used in the study on the source substance must be representative for the source substance (Article 10 and Recital 19 of REACH; Guidance on IRs and CSA, Section R.4.1.). Therefore, the unambiguous characterisation of the composition of the test material used to generate the source data is required to assess whether the test material is representative for the source substance.

A PNDT study is provided with the source material "[redacted] (ix). The justification document in the dossier [redacted] specifies that the source substances as well as the Substance are UVCBs with the composition varying in the quantitative profiles for different hydrocarbon classes including level and types of the PAH constituents. However, the information on the test material compositions of the source study provided in your dossier is limited to the name and numerical identifier (CAS No) and it does not contain information on the quantitative occurrence of the hydrocarbon classes.

ECHA agrees that the composition of the Substance may be linked to the hazardous properties of the Substance and considers that the compositional information is essential to characterise the relationship between the composition and the hazardous properties of the Substance, and to demonstrate that the test material is representative for the source substance and thereby also for the Substance.

Therefore, the provided PNDT study conducted with the source substance [redacted]" (ix) cannot be considered as adequate and reliable for the purpose of classification and labelling and/or risk assessment.

2.1.3 Coverage of the key parameters and study duration

According to the provisions of Annex IX, Section 8.7.2., information on pre-natal developmental toxicity (OECD TG 414) shall be provided. The key parameters foreseen to be investigated in OECD TG 414 PNDT study include but are not limited to

- testing of at least three dose levels and a concurrent control,
- 20 female animals with implantation sites for each test and control group,
- examination of the foetuses for external, skeletal and soft tissue alterations (variations and malformations).

For your adaptation, you have provided PNDT studies (studies vi-ix) conducted with the source substances.

The studies (vii, viii, ix) do not cover the expected dose levels. Specifically, only one test dose level (not indicated as limit dose) and a control was used in study (vii) and two test dose

levels (not indicated as limit dose) and a control in study (viii), while the study (ix) was conducted without a control group.
You indicate that the study (vi) was conducted using between 9 or 10 pregnant females for each test group. Therefore, the statistical power of the information provided is not sufficient.

In the study (ix), key parameters of foetal measurements have not been performed as required in OECD TG 414. Specifically, study (ix) reports that there is no data on soft tissue examination.

Based on above, ECHA concludes that the provided PNDT studies conducted with the source substances (vi-ix) do not have adequate and reliable coverage of the key parameters foreseen to be investigated in the OECD TG 414.

3. Conclusion

Based on the above, the information you provided does not fulfil the information requirement.

Information on the study design

A PNDT study according to the test method OECD TG 414 must be performed in rat or rabbit as preferred species with oral[14] administration of the Substance.

[14] ECHA Guidance R.7a, Section R.7.6.2.3.2.

Appendix B: Requirements to fulfil when conducting and reporting new tests for REACH purposes

A. Test methods, GLP requirements and reporting

1. Under Article 13(3) of REACH, all new data generated as a result of this decision must be conducted according to the test methods laid down in a European Commission Regulation or to international test methods recognised by the Commission or ECHA as being appropriate.
2. Under Article 13(4) of REACH, ecotoxicological and toxicological tests and analyses must be carried out according to the GLP principles (Directive 2004/10/EC) or other international standards recognised by the Commission or ECHA.
3. Under Article 10(a)(vi) and (vii) of REACH, all new data generated as a result of this decision must be reported as study summaries, or as robust study summaries, if required under Annex I of REACH. See ECHA Practical Guide on How to report robust study summaries[15].

B. Test material

Before generating new data, you must agree within the joint submission on the chemical composition of the material to be tested (Test Material) which must be relevant for all the registrants of the Substance.

1. *Selection of the Test material(s)*

   The Test Material used to generate the new data must be selected taking into account the following:
   - the variation in compositions reported by all members of the joint submission,
   - the boundary composition(s) of the Substance,
   - the impact of each constituent/ impurity on the test results for the endpoint to be assessed. For example, if a constituent/ impurity of the Substance is known to have an impact on (eco)toxicity, the selected Test Material must contain that constituent/ impurity.

2. *Information on the Test Material needed in the updated dossier*

   a) You must report the composition of the Test Material selected for each study, under the "Test material information" section, for each respective endpoint study record in IUCLID.

   b) The reported composition must include the careful identification and description of the characteristics of the Tests Materials in accordance with OECD GLP (ENV/MC/CHEM(98)16) and EU Test Methods Regulation (EU) 440/2008 (Note, Annex), namely all the constituents must be identified as far as possible as well as their concentration. Also any constituents that have harmonised classification and labelling according to the CLP Regulation must be identified and quantified using the appropriate analytical methods.

This information is needed to assess whether the Test Material is relevant for the Substance and whether it is suitable for use by all members of the joint submission.

Technical instructions on how to report the above is available in the manual on How to prepare registration and PPORD dossiers[16].

[15] https://echa.europa.eu/practical-guides
[16] https://echa.europa.eu/manuals

Appendix C: Procedure

The information requirement for an Extended one-generation reproductive toxicity study (EOGRTS; Annexes IX or X, Section 8.7.3.) is not addressed in this decision. This may be addressed in a separate decision once the information from the Sub-chronic toxicity study (90-day) requested in the present decision is provided; due to the fact that the results from the 90-day study is needed for the design of the EOGRTS. Similarly the information requirement for a Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.) is not addressed in this decision; as the EOGRTS will cover the same parameters.

This decision does not prevent ECHA from initiating further compliance checks at a later stage on the registrations present.

ECHA followed the procedure detailed in Articles 50 and 51 of REACH.

The compliance check was initiated on 22 September 2020.

ECHA notified you of the draft decision and invited you to provide comments.

ECHA took into account your comments and did not amend the requests.

In your comments on the draft decision, you requested an extension of the deadline to provide information from 12 to 24 or 30 months from the date of adoption of the decision, for the reasons that CROs do not have the capacity to perform the studies more quickly, that there are specific issues associated with agreement amongst Registrants, scientific issues associated with performing the tests on the Substance and a need for sequential testing. You provided supporting documentation from CROs, which supports up to a maximum of 24 months to perform the studies.

ECHA notes the intention to perform dose range-finding studies, and the time required for these studies. However, ECHA considers that there is no need for the 90-day and PNDT study to be performed sequentially.

ECHA took into account this information and the provided documentary evidence. The deadline of the decision is set based on standard practice for carrying out OECD TG tests. It has been exceptionally extended by 12 months from the standard deadline granted by ECHA to take into account currently longer lead times in contract research organisations.

On this basis, ECHA has extended the deadline to 24 months.

ECHA notified the draft decision to the competent authorities of the Member States for proposals for amendment.

As no amendments were proposed, ECHA adopted the decision under Article 51(3) of REACH.

Appendix D: List of references - ECHA Guidance[17] and other supporting documents

Evaluation of available information
Guidance on information requirements and chemical safety assessment, Chapter R.4 (version 1.1., December 2011), referred to as ECHA Guidance R.4 where relevant.

QSARs, read-across and grouping
Guidance on information requirements and chemical safety assessment, Chapter R.6 (version 1.0, May 2008), referred to as ECHA Guidance R.6 where relevant.

Read-across assessment framework (RAAF, March 2017)[18]

RAAF - considerations on multiconstituent substances and UVCBs (RAAF UVCB, March 2017)[18]

Physical-chemical properties
Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Toxicology
Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7c (version 3.0, June 2017), referred to as ECHA Guidance R.7c in this decision.

Environmental toxicology and fate
Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7b (version 4.0, June 2017), referred to as ECHA Guidance R.7b in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7c (version 3.0, June 2017), referred to as ECHA Guidance R.7c in this decision.

PBT assessment
Guidance on information requirements and chemical safety assessment, Chapter R.11 (version 3.0, June 2017), referred to as ECHA Guidance R.11 in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.16 (version 3.0, February 2016), referred to as ECHA Guidance R.16 in this decision.

Data sharing
Guidance on data-sharing (version 3.1, January 2017), referred to as ECHA Guidance on data sharing in this decision.

OECD Guidance documents[19]
Guidance Document on aqueous–phase aquatic toxicity testing of difficult test chemicals – No 23, referred to as OECD GD 23.

[17] https://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment
[18] https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across
[19] http://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm

Guidance document on transformation/dissolution of metals and metal compounds in aqueous media – No 29, referred to as OECD GD 29.

Guidance Document on Standardised Test Guidelines for Evaluating Chemicals for Endocrine Disruption – No 150, referred to as OECD GD 150.

Guidance Document supporting OECD test guideline 443 on the extended one-generation reproductive toxicity test – No 151, referred to as OECD GD 151.

Appendix E: Addressees of this decision and their corresponding information requirements

You must provide the information requested in this decision for all REACH Annexes applicable to you.

Registrant Name	Registration number	Highest REACH Annex applicable to you
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Where applicable, the name of a third party representative (TPR) may be displayed in the list of recipients whereas ECHA will send the decision to the actual registrant.