December 2017

How to gather information to register a multi-constituent or a UVCB substance - toxicological information

Contents

List of figures

List of tables

1. Introduction

The substance is a liquid organic substance, consisting of several constituents. Some of the constituents are isomers with similar structures.

The company that wants to register produces the substance in a volume between 10 and 100 tonnes per year. Therefore, the information requirements from Annexes VII and VIII of REACH are relevant.

This example will illustrate:

- The difference between a multi-constituent substance and a substance of unknown or variable composition, complex reaction products or biological materials (UVCB)
- How to identify a substance
- How to name a substance
- How to use information from the individual constituents (read-across) to fulfil the information requirements for this substance

Methods to gather missing information, such as weight-of-evidence approach, read-across or testing[1].

In the example there are multiple scenarios where existing information leads to different routes of further data gathering. Not all routes will be completely described. For some routes only a limited description of the next steps and relevant issues will be provided in this example.

More information is available in chapters I and II of the Practical guide for SME managers and REACH coordinators – How to fulfil your information requirements at tonnages 1-10 and 10-100 tonnes per year.

All the Guidance documents referred to in this document can be found on a dedicated web page.

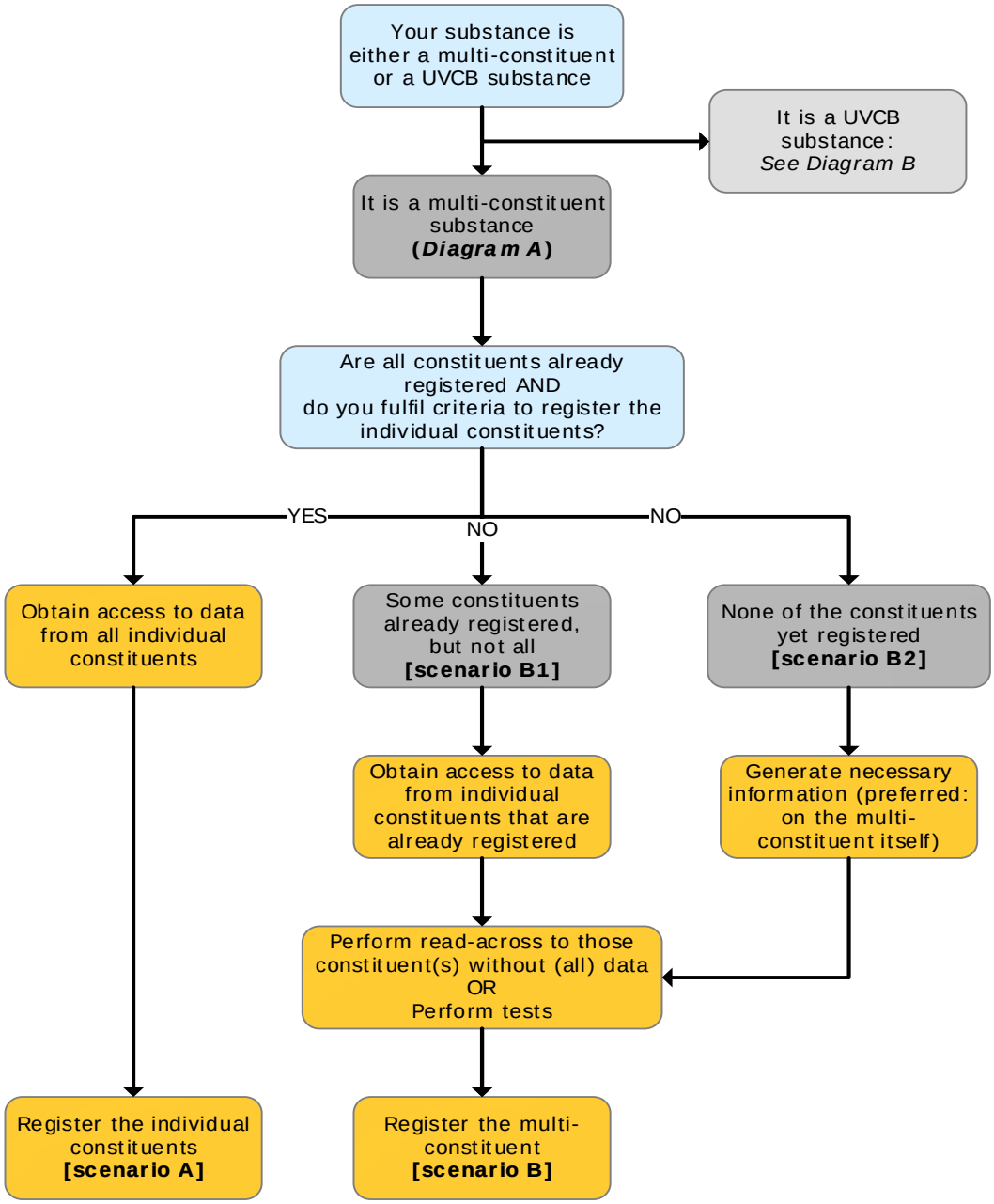
The flow chart of this example is illustrated in Figure 1.

[1] For explanation of terms, see https://echa-term.echa.europa.eu/home

Figure 1: Flow chart on how to decide whether to register a multi-constituent substance, individual constituents or a UVCB substance

Diagram A: *You have a multi-constituent substance*

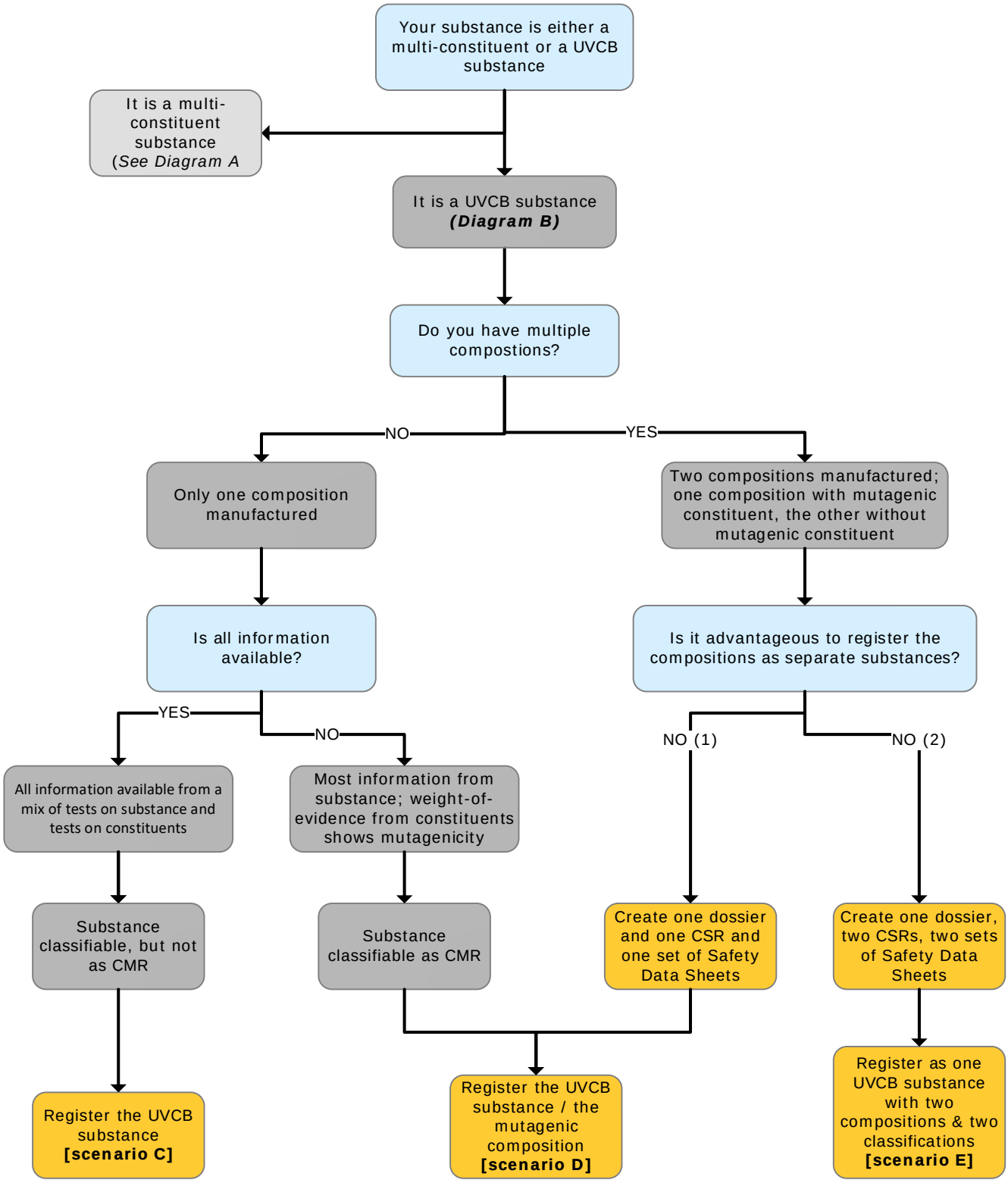
The scenarios identified in the diagram (scenario A, B [B1, B2]) are further developed in section 3 below.



Note: regarding the registration of individual constituents, please refer to the relevant chapter of the Guidance for identification and naming of substances under REACH and CLP.

Diagram B: *You have a UVCB substance*

The scenarios identified in the diagram (scenario C, D and E) are further developed in section 4 below.



2. Identification and naming of substance

You manufacture an organic substance from a petrochemical stream by means of several fractionation and refinement steps. The exact composition of the petrochemical stream varies, according to the source of the material. You intend to deliver a substance useful for the client and the usefulness is largely dependent on a number of physico-chemical parameters and much less on the exact composition of the substance.

From experience, you know that the manufactured substance consists of at least three major constituents A, B and C. These constituents are isomers or they have similar chemical structures. Other constituents are also present in smaller amounts.

The first question you need to answer is: “Is my substance a multi-constituent substance or a UVCB?”

Definitions for a multi-constituent and UVCB substances:

!	**Multi-constituent**: Your substance contains more than one main constituent, and each main constituent is present between 10% and 80%. There can also be unintentional constituents present in your substance, which are the results of side reactions. They are called impurities and each impurity is below 10%. **UVCB**: Your substance is a UVCB (Unknown or Variable composition, Complex reaction product or Biological material) substance if it contains a high number of constituents in varying, and often not well-known amounts. It is made from a manufacturing process that may consist of several steps, or it is obtained from a biological source, such as a plant material or an animal material. See chapter 3 of the Practical guide for SME managers and REACH coordinators. For more information on how to decide between a multi-constituent or UVCB substance, see Guidance for identification and naming of substances under REACH and CLP.

Table 1 describes the expected conclusions after running a series of techniques leading to identify your substance.

Table 1: Information required and conclusions for the identification of the substance

Technique	Results	Conclusions
Scenario 1		
Gas chromatographic analysis with mass spectrometry (GCMS) of several batches	The substance consists of three aromatic constituents, respectively 25, 30 and 37.5%, four impurities of which you know the identity (5, 1, 0.5 and 0.5%) and a number of unknown impurities (0.5%, of which each impurity is <0.1%); limited variation in percentages	Substance is defined by its quantitative composition: more than one main constituent is present in between 10 and 80% (w/w) → Multi-constituent substance
Ultra-violet (UV), infra-red (IR) and nuclear magnetic resonance (NMR) spectroscopy	Substance consists of three aromatic constituents, with a very similar chemical structure, in a more or less fixed composition	Based on combined results from spectral and chromatographic data, constituents are identified as: Main constituent A: 25% Main constituent B: 30% Main constituent C: 37.5% Impurity D: 5% Impurity E: 1% Impurity F: 0.5% Impurity G: 0.5% Unknown impurities: 0.5% (each impurity < 0.1%
Scenario 2		
Gas chromatographic analysis with mass spectrometry (GCMS) of several batches	More than three constituents in varying percentages; three major constituents (10-50%, 20-70% and 5-50%); several other constituents are present too There are indications that the substance may have variable compostions, e.g. • variation in the source materials; • compostion is very dependent on process conditions; • chemistry of reaction may not fully be known in case of import	Substance is defined by its quantitative composition: largely variable → UVCB substance
UV, IR and NMR spectroscopy	Composition of the substance is variable and unpredictable, some components are unknown	Based on combined results from spectral and chromatographic data constituents are (mostly) identified as: Main constituents A (10-50%), B (20-70%) and C (5-50%); other constituents D (5-20%), E (1-10%), F (0-5%), G (0-1%), and H (0-10%) are aromatic and some aliphatic; not all are identified

Table 2 details how the corresponding naming of the substance is defined based on its identification.

Table 2: Naming of the substance in relation to the identification results

Identity of Substance	Naming convention	Resulting name
Multi-constituent with three main constituents	Reaction mass of [names of main constituents]	Reaction mass of main constituent A and main constituent B and main constituent C
UVCB substance from petroleum	Naming is based either on the refinery process and source of the petroleum substance or, if further refined, on the carbon chain length, in case of hydrocarbon solvents.[2]	Source, refinery process, carbon chain length

For more detail on the conventions regarding naming of multi-constituent and UVCB substances, see the Guidance for identification and naming of substances under REACH and CLP.

!	If your substance is a UVCB coming from a petroleum source, you use a name from the standard naming conventions of the petrochemical industry. In general, it is common that you indicate the source and the process in the name of the UVCB substance. For further refined substances, such as hydrocarbon solvents you use the naming convention as described in the OECD Guidance for Characterisation Hydrocarbon Solvents for Assessment Purposes.

3. Information gathering for a multi-constituent substance

In this part, we make the following assumptions:

- Your substance is a multi-constituent substance (Diagram A), and
- You may produce a number of multi-constituent substances consisting of the same three constituents A, B and C in varying concentrations.

[2] For sector-specific support for substance identification, see “Petroleum products” on ECHAs support pages (http://echa.europa.eu/support/substance-identification/sector-specific-support-for-substance-identification/petroleum-products) and “Hydrocarbon solvents” http://echa.europa.eu/support/substance-identification/sector-specific-support-for-substance-identification/hydrocarbon-solvents.

3.1. Scenario A: multi-constituent – registering individual constituent(s)

We assume that you do not have any data for your multi-constituent substance(s) but you know that all constituents have been registered. Table 3 lists the steps to gather all information. You fulfil the criteria for registration of individual constituents.

Table 3: Steps to gather all information for the registration of individual constituents of a multi-constituent substance (scenario A)

Steps to register individual constituents of a multi-constituent substance		
What you know	**What you need to do**	**Remarks**
You produce a number of multi-constituent substances that consist of the same three constituents A, B and C, but in varying concentrations. The volume of each multi-constituent substance is between 10 and 100 tonnes per year. *Examples* Multi-constituent I: Constituent A 5% Constituent B 32% Constituent C 63% Multi-constituent II: Constituent A 18% Constituent B 37% Constituent C 45% Multi-constituent III: Constituent A 49% Constituent B 3% Constituent C 48% Multi-constituent IV: Constituent A 59% Constituent B 34% Constituent C 7% Note: the above examples represent four different multi-constituent substances with constituents ≥10% and <80%	Check if either the multi-constituent substances or the individual constituents are already registered by another registrant. This can be done on ECHA's Search for Chemicals webpage.	As a general rule, the multi-constituent substance itself has to be registered. However, in some situations you may be allowed to register the individual constituents provided that all of the following conditions are met: • For each of the individual constituents, you need to fulfil the information requirements corresponding to the volume of your multi-constituent substance • Sufficient information is already available for all constituents and there is no need to perform additional animal tests • Registration of the individual constituents is more efficient than registration of various multi-constituent substances consisting of the same constituents • You must provide the composition of the multi-constituent substance(s) in your registration dossier More information can be found in section 4.2.2 of the Guidance for identification and naming of substances under REACH and CLP

Steps to register individual constituents of a multi-constituent substance		
What you know	**What you need to do**	**Remarks**
Your multi-constituent substance(s) do(es) not appear to be registered by another registrant. All the individual constituents are registered by other registrants, and because of the variation in composition of your multi-constituent substance(s), it is more efficient to register the individual constituents. You also know that you fulfil the criteria for "registration of the individual constituents of a multi-constituent substance" as stipulated in section 4.2.2 of the Guidance for identification and naming of substances under REACH and CLP.	First, you need to find the Lead Registrant of each of the constituents. You can find this information in REACH-IT. As you want to use information that was generated by others (data sharing), you will need to pay the Substance Information Exchange Forum (SIEF) for access to the information.	More information on SIEF and data sharing can be found on the Get organised with your co-registrants web page. **NB:** You only have to pay for the information that is needed for your registration, even if the joint registration was done for a higher volume. In your case information requirements are for the volume 10-100 tonnes per year, i.e. Annex VII and VIII of the REACH Regulation. If the information you require was submitted more than 12 years ago to an EU authority, for instance as part of a notification of a new substance prior to REACH, you do not need to compensate the data owner.
You have reached an agreement with the SIEF, and for each of the constituents you have received access to the joint registrations.	You now have to create your company specific parts including the information on use(s) in the registration dossiers in IUCLID, for each of the constituents. In REACH-IT you have to confirm that you are a member of the joint submissions, and after that you can submit your registration dossiers.	Registration of the individual constituents of a multi-constituent substance requires a specific approach for filling in the information in the registration dossiers in IUCLID. More information can be found in the manual on How to prepare registration and PPORD dossiers[3].

3.2. Scenario B: Registering a multi-constituent substance

We assume that you don't have any data for your multi-constituent substance. However, you know that:

- Scenario B1: some constituents have been registered;
- Scenario B2: none of the constituents have been registered.

You do not fulfil the criteria for registration of individual constituents.

Table 4 indicates the steps to take to gather all information.

[3] See http://echa.europa.eu/manuals

Table 4: Steps to to gather all information for the registration of a multi-constituent substance (scenario B)

Steps to register a multi-constituent substance		
What you know	**What you need to do**	**Remarks**
You produce a multi-constituent substance that consists of three constituents A, B and C, which are isomers with a similar structure. The volume of your substance is between 10 and 100 tonnes per year.	Check if either the multi-constituent substance or the individual constituents are already registered by another registrant. This can be done on ECHA's Search for Chemicals webpage.	The multi-constituent substance itself has to be registered, but in some situations you may be allowed to register the individual constituents (see details in Table 3 above). More information can be found in section 4.2.2 of the Guidance for identification and naming of substances under REACH and CLP.
Scenario B1: Some constituents of your multi-constituent are registered by other registrants		
Your multi-constituent substance consists of three constituents which are isomers with a similar structure. It does not appear to be registered by another registrant. Only two of the individual constituents are registered by other registrants. Therefore you do not see an advantage in fulfilling the criteria for registration of the individual constituents. You know that in REACH animal testing is the last choice, so you will further investigate if you can apply the read-across[4] approach and use the data from the two constituents for the registration dossier of your multi-constituent substance	To assess whether you can apply the read-across approach: • you create an overview of all available physicochemical, environmental and human health information for each of the constituents; • you use this overview to decide (preferably with a scientific expert) whether you can conclude that all constituents can be regarded as similar; • based on all available data and if you decide to apply read-across, you have to develop a strong and scientific justification and submit it in your registration dossier • you need to contact the SIEF and request access to data of the individual constituents (i.e. buy a Letter of Access for the studies).	Advanced scientific expertise is required (i) to decide that experimental data from the two constituents can be used (read-across) for the registration dossier of your multi-constituent and (ii) to build the read-across justification. **NB:** You only have to pay for the information that is needed for your registration. There is no formal obligation to share data of similar substances. However it is strongly encouraged in order to not perform unnecessary animal testing. If the information you require was submitted more than 12 years ago to an EU authority, you do not need to compensate the data owner.

[4] See https://echa-term.echa.europa.eu/home and https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across

Steps to register a multi-constituent substance		
What you know	**What you need to do**	**Remarks**
You have reached an agreement with the lead registrants, and for the two constituents you have received access to the all available information for your registration volume.	You now have to create your substance registration dossier in IUCLID; that means company specific parts including the information on use(s) as well as the information that is available for the two constituents. In REACH-IT you can submit your dossier.	Information on how to fill in the substance information in IUCLID can be found in the manual on How to prepare a registration and PPORD dossier[5]
Scenario B2: None of the constituents of your multi-constituents is registered by other registrants		
Your multi-constituent substance does not appear to be registered by another registrant. As none of the individual constituents (as mono-constituent substance) are registered by other registrants, you do not see an advantage in fulfilling the criteria for registration of the individual constituents of your multi-constituent substance.	To fulfil the information requirements for your multi-constituent substance, you need to gather information for all REACH Annex VII and VIII properties (you produce 10 to 100 tonnes per year) for your multi-constituent substance.	Scientific expertise and advanced scientific expertise is required to make a plan for gathering of all information. For detailed guidance on information gathering see chapters I and II of the Practical Guide for SMEs on information requirements.
You have gathered all information required for the registration of your multi-constituent substance.	You now have to create your registration dossier in IUCLID; that means company specific parts including the information on use(s) as well as the study- and endpoint summaries, derivation of DNELs[6] and PNECs[7] and PBT[8] assessment. If your multi-constituent substance has a property that leads to unwanted effects and classification is needed, you will have to develop an exposure assessment and risk characterisation in your chemical safety report. In REACH-IT you can submit your dossier.	Information on how to fill in the substance information in IUCLID can be found in the manual on How to prepare registration and PPORD dossiers. For guidance on classification and labelling, PBT assessment, DNELs and PNECs and the chemical safety report see chapters 4, 5 and 6 of the Practical Guide for SME managers and REACH coordinators.

[5] See https://echa.europa/manuals
[6] DNEL= Derived no-effect level
[7] PNEC= Predicted no-effect concentration
[8] PBT= Persistent, bioaccumulative and toxic
See also https://echa-term.echa.europa.eu/home

!	The use of data from other substances, i.e. read-across, is only possible if (i) there is sufficient scientific justification that the other substances will have the same properties as the substance you want to register and (ii) if you have legal access to the data. The chemical structure is indicative, but small changes in structure may lead to significant changes in properties. Therefore, you have to justify the read-across with multiple layers of evidence, also taking into account different routes of exposure. Information from studies on toxicokinetics can be very useful to support a read-across. See chapter R.2 of the Guidance on Information Requirements and Chemical Safety Assessment, for more details on read-across. You can also check how ECHA assesses read-across approaches (Read-across Assessment Framework) on the Grouping and Read-Across web page.

4. Toxicological information on the UVCB substance

In this part, we make the following assumption:

Your substance is a UVCB substance (scenario 2 of Table 1).

- As per Figure 1, Diagram B, you may produce a UVCB substance where the main constituents fully determine the hazard of the substance (scenario C) and where no constituent is of very high concern.
- As per Figure 1, Diagram B, you may also have a UVCB substance where there is one constituent with a very hazardous property, which would in itself be a substance of very high concern (scenario D).
- As per Figure 1, Diagram B, the final possibility is that you produce two compositions of the UVCB substance, i.e. one with a constituent of very high concern and one without a constituent of very high concern (scenario E).

4.1. Scenario C: UVCB substance without constituent of very high concern

We assume that you have reliable data for all relevant toxicological tests, and also that physicochemical information and information on environmental fate and eco-toxicological properties are available (not further discussed below).

Table 5 indicates the results of the tests performed with the full (UVCB) substance or its constituents.

Table 5: Results of human toxicology testing and conclusions for a UVCB substance (scenario C)

Human health properties – tests, results and conclusions			
Endpoint	**Test done on**	**Result**	**Conclusion and next step**
Skin irritation	Full substance	Irritating	Classify as irritating; Exposure assessment required
Eye irritation	Full substance	Not irritating	Conclusive but not sufficient for classification
Skin sensitisation	Full substance	Not sensitising	Conclusive but not sufficient for classification
In vitro mutagenicity	Full substance	Not mutagenic	Conclusive but not sufficient for classification
In vivo mutagenicity	Full substance	Not mutagenic	Conclusive but not sufficient for classification
Acute toxicity: oral	Full substance	Oral LD50 in rats > 4000 mg/kg body weight (bw) for males and females	Conclusive but not sufficient for classification
Acute toxicity: inhalation	Full substance	Inhalation LC50 in male rats > 6000 ppm (26000 mg/m^3)	Conclusive but not sufficient for classification
Acute toxicity: dermal	Full substance	Dermal LD50 in male rats > 4000 mg/kg bw	Conclusive but not sufficient for classification
Short-term repeated dose toxicity	Full substance	Oral effect level (lowest observable adverse effect): 250 mg/kg bw for male and female rats	Basis for DNELs in risk characterisation
Screening for reproductive/developmental toxicity	Majority of constituents (up to > 95% of the composition)	No reproductive or developmental effects at doses at which parental effects occur; no indication that any of the other constituents is toxic to reproduction	Conclusive but not sufficient for classification

!	If tests were performed before 2016, properties for skin/eye irritation and skin sensitisation were likely assessed *in vivo*. As of end of 2016, this data must be performed *in vitro* first[9]. Only if you cannot perform the test *in vitro* or if you cannot classify your substance based on the *in vitro* results, you are then allowed to perform the test *in vivo* - as a last resort.

To conclude:

- The data, generated on the registered substance, are available and reliable for all properties at Annex VIII (tonnage 10-100 tonnes per year): No further information gathering needed, as there is no data gap.
- The UVCB substance shows some toxic effect in short-term repeated dose toxicity test, but it is not mutagenic or toxic to reproduction. Therefore, there is no indication of very high concern.
- However, as the substance is classified for some properties. Therefore, exposure assessment and risk characterisation are required.

!	Since your substance has a human health property which may lead to unwanted effects (irritation of the skin), you will have to develop an exposure assessment and risk characterisation and document it in your chemical safety report (CSR). For guidance on the CSR see chapter 6 of the Practical guide for SME managers and REACH coordinators.

4.2. Scenario D: UVCB substance with a constituent of very high concern

We assume that you have reliable data for all relevant toxicological tests, partly on the registered substance and partly on its constituents.

We also assume that physicochemical information and information on environmental fate and eco-toxicological properties are available (not further discussed below).

Table 6 indicates the results of the tests, conclusions and whether they were performed with the full (UVCB) substance or with one of its constituents.

[9] https://echa.europa.eu/-/new-advice-on-using-non-animal-test-methods

Table 6: Results of human toxicology testing and conclusions for a UVCB substance (scenario D)

Human health properties – tests, results and conclusions			
Endpoint	**Test done on**	**Result**	**Conclusion and next step**
Skin irritation	Full substance	Irritating	Classify as irritating; Exposure assessment required
Eye irritation	Full substance	Not irritating	Conclusive but not sufficient for classification
Skin sensitisation	Full substance	Not sensitising	Conclusive but not sufficient for classification
In vitro mutagenicity[1]	Majority of constituents (up to > 95% of the composition)	Not mutagenic	The substance is mutagenic, based on weight-of-evidence from the different constituents[2]
In vitro mutagenicity[1]	One constituent (> 0.1% of substance)	Mutagenic	
In vivo mutagenicity[1]	Majority of constituents (up to > 95% of the composition)	Not mutagenic	
In vivo mutagenicity[1]	One constituent (> 0.1% of substance)	Mutagenic	
Acute toxicity: oral	Full substance	Oral LD50 in rats > 4000 mg/kg bw for males and females	Conclusive but not sufficient for classification
Acute toxicity: inhalation	Full substance	Inhalation LC50 in male rats > 6000 ppm (26000 mg/m^3)	Conclusive but not sufficient for classification
Acute toxicity: dermal	Full substance	Dermal LD50 in male rats > 4000 mg/kg bw	Conclusive but not sufficient for classification
Short-term repeated dose toxicity	Full substance	Oral effect level (lowest observable adverse effect): 250 mg/kg bw for male and female rats	Basis for DNELs in risk characterisation
Screening for reproductive/developmental toxicity[1]	Majority of constituents (up to > 95% of the composition)	No reproductive or developmental effects at doses at which parental effects occur	Conclusive but not sufficient for classification
Screening for reproductive/developmental toxicity[1]	Other constituents (partly from literature)	No reproductive or developmental effects at doses at which parental effects occur	Conclusive but not sufficient for classification

1 For mutagenicity and reproductive/developmental screening, only studies on separate constituents are available. Based on the combination of data from separate constituents, it is concluded that the substance is mutagenic, but not toxic to reproduction.
2 You assess the substance as if it were a mixture according to the mixture criteria of the CLP Regulation. If a mixture contains > 0.1% of a mutagenic substance (Cat. 1B), the mixture should be classified as Cat. 1B mutagenic substance. See Guidance on the Application of the CLP Criteria, chapter 3.5.

!	If tests were performed before 2016, properties for skin/eye irritation and skin sensitisation, were likely assessed *in vivo*. Since the end of 2016, this data must be performed *in vitro* first[10]. Only if you cannot perform the test *in vitro* or if you cannot classify your substance based on the *in vitro* results, you are then allowed to perform the test *in vivo*, as a last resort.

To conclude:

- The data generated on the registered substance or its constituents is available and reliable for all properties at Annex VIII (tonnage 10-100 tonnes per year). No further information gathering is needed, as there is no data gap.
- The UVCB substance is considered to be mutagenic, based on data from one constituent, and there is no threshold for human health effects. Therefore, a qualitative or semi-quantitative risk characterisation is done, with a Derived Minimal Effect Level[11] as a threshold for the semi-quantitative assessment.
- Exposure assessment and risk characterisation are required.

!	Since your substance has a human health property that may lead to unwanted effects (mutagenicity), you will have to develop an exposure assessment and risk characterisation and document it in your chemical safety report (CSR). For guidance on the CSR see chapter 6 of the Practical guide for SME managers and REACH coordinators.

4.3. Scenario E: UVCB substance produced in two compositions: one with a mutagenic constituent and one without a mutagenic constituent

We assume that you produce two compositions of the substance, the only difference being that one has slightly more than 0.1% of known mutagenic constituents, while the other, based on a slightly different process (such as different distillation temperature), has a lower concentration of the known mutagenic constituents (clearly < 0.1%). You therefore wonder whether you can register both purities as one substance.

Once you have decided, according to the options presented in Table 7, you can follow the steps presented in Table 6, to conclude on the classification per property, based on the data you have (will generate) on the properties of the test material.

[10] https://echa.europa.eu/-/new-advice-on-using-non-animal-test-methods
[11] See https://echa-term.echa.europa.eu/home

Table 7: Option to register a UVCB substance produced in two compositions : mutagenic constituent < 0.1% and > 0.1% (scenario D and E)

Produced substance	Options	Result	Conclusion and next step
Two compositions of a UVCB substance: one has > 0.1% of a Cat. 1B mutagenic constituent and the other has < 0.1% of Cat. 1B mutagenic constituent	Option 1: register as one substance, assume the substance is mutagenic	One registration for the mutagenic composition which also covers the non-mutagenic composition	Include the classification as mutagenic for both compositions in your dossier One dossier, one CSR, one safety data sheet (SDS)
	Option 2: register as one substance, but with relevant classification for each composition	One registration including the composition containing > 0.1% of the mutagenic constituent and the composition containing < 0.1% of the mutagenic constituent	Classify one composition as mutagenic, the other as not mutagenic* One dossier, two CSRs, two sets of safety data sheets
* It is considered acceptable to submit a registration dossier with different classifications, depending on the various levels of impurities in the substance			

! Since your substance has a human health property that may lead to unwanted effects (mutagenicity), you will have to develop an exposure assessment and risk characterisation and document it in your chemical safety report (CSR).

For guidance on the CSR see chapter 6 of the Practical guide for SME managers and REACH coordinators.

! If the manufacturer cannot control the variability of the substance composition, where one or more constituents can present carcinogenic, mutagenic properties and/or is toxic to reproduction (CMR), the substance should be considered as CMR.

If the manufacturer can control the level of CMR constituents and can ensure that the substance of one composition is not considered a CMR, while another composition of the same substance is considered a CMR, there is the option to submit one dossier with the different compositions and relevant classifications.