~~Confidential~~

Helsinki, 8 September 2022

Addressees
Registrant(s) of JS_3195-78-6 as listed in Appendix 3 of this decision

Date of submission of the dossier subject to this decision
22/12/2017

Registered substance subject to this decision ("the Substance")
Substance name: N-methyl-N-vinylacetamide
EC number: 221-698-5

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 ***16 December 2024***.

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

Information required from all the Registrants subject to Annex VII of REACH

1. Ready biodegradability (Annex VII, Section 9.2.1.1.; test method: EU C.4. A/B/C/D/E/F/OECD TG 301A/B/C/D/E/F or EU C.29./OECD TG 310)

Information required from all the Registrants subject to Annex VIII of REACH

2. Short-term repeated dose toxicity (28 days; Annex VIII, Section 8.6.1.) to be combined with the Screening for reproductive/developmental toxicity below

3. Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.; test method: EU B.64/OECD TG 422) by oral route, in rats

The reasons for the decision(s) are explained in Appendix 1.

Information required depends on your tonnage band

You must provide the information listed above for all REACH Annexes applicable to you in accordance with Articles 10(a) and 12(1) of REACH. The addressees of the decision and their corresponding information requirements based on registered tonnage band are listed in Appendix 3.

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 requirements for testing and reporting new tests under REACH, see Appendix 4.

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

Appendix 1: Reasons for the decision
Appendix 2: Procedure
Appendix 3: Addressees of the decision and their individual information requirements
Appendix 4: Conducting and reporting new tests under REACH

[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 1: Reasons for the decision

Contents

Reasons related to the information under Annex VII of REACH

1. Ready biodegradability – Annex VII

1 Ready biodegradability is an information requirement in Annex VII to REACH (Section 9.2.1.1.).

1.1. Information provided

You have provided an OECD TG 301B study on the Substance (2015)

1.2. Assessment of information provided

2 We have assessed this information and identified the following issue:

3 To fulfil the information requirement, a study must comply with the OECD TG 301 or 310 (Article 13(3) of REACH). Therefore, for a study according to OECD TG 301, the following requirements must be met:

4 Reporting of the methodology and results

a) The inoculum concentration in the test is adequately reported to verify that the specifications of OECD TG 301B are met;
b) The results of measurements at each sampling point in each replicate is reported in a tabular form;
c) The inorganic carbon content (IC) and total carbon content (TC) of the test material suspension in the mineral medium at the beginning of the test is reported.

5 Your registration dossier provides an OECD TG 301B showing the following:

6 Reporting of the methodology and results

a) The concentration of the inoculum is reported as "30 mg/L dry weight". You have not provided information on cell density (in cells/mL) in the test bottles;
b) The results of measurements at each sampling point in each replicate is not reported;
c) The inorganic carbon content (IC) and total carbon content (TC) of the test material suspension in the mineral medium at the beginning of the test is not reported.

7 Based on the above, the reporting of the study is not sufficient to conduct an independent assessment of its reliability. More,specifically,

- as you have not provided adequate reporting of the inoculum density in the test, it is not possible to verify that the inoculum density met the specification of OECD TG 301B (i.e., 10^7 to 10^8 cells/L in the test vessel);
- as you have not provided adequate reporting of the study results, it is not possible to conduct an independent assessment of whether the validity criteria of the test guideline were met.

8 Therefore, the requirements of OECD 301B are not met.

9 On this basis, the information requirement is not fulfilled.

10 In the comments to the draft decision, you have attached a copy of a robust study summary (RSS). The RSS includes the information listed above as missing in the dossier. You have proposed to update your dossier with the modified RSS.

11 The information provided as part of your comments addresses the incompliances identified above. However, as the information is currently not available in your registration dossier,

the data gap remains. You should submit this information in an updated registration dossier by the deadline set in the decision.

Reasons related to the information under Annex VIII of REACH

2. Short-term repeated dose toxicity (28 days)

12 A short-term repeated dose toxicity study (28 days) is an information requirement under Annex VIII to REACH (Section 8.6.1.).

2.1. Information provided

13 You have provided:

(i) GLP DRF study according to OECD 412 (2015) with the Substance.

(ii) GLP screening study according to OECD 422 via inhalation in rats (2017) with the Substance.

2.2. Assessment of the information provided

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

2.2.1. Study not adequate for the information requirement

15 To fulfil the information requirement, the short-term toxicity study (28 days) must meet the requirements of OECD TG 412. Therefore, the following specifications must be:

a. testing of at least three dose levels (unless conducted at the limit dose) with concurrent controls;

b. highest dose level should aim to induce toxicity or reach the limit dose.

c. at least 5 male and 5 female animals for each dose and control group;

d. dosing of the test material for a minimum of 6h/day, on a 5 day per week basis for a period at least 28 day

e. histopathology as specified in the test guideline;

16 The study is described as according to OECD TG 412 (study i) and OECD TG 422 (study ii). However, the following specifications are not according to the requirements of OECD TG 412:

a. no concurrent controls (study i);

b. no justification for the dose setting while the highest dose level tested was 50 mg/m^3 (study ii), which is below the limit dose of the test guideline, and only caused local effects in the nasal cavity of parental animals;

In your comments to the draft decision, you explain that the DRF study (study i) identified a LOAEC of 100 mg/m^3, based on "*effects on liver, kidney and respiratory tract*." You continue by stating that the findings were "*clearly dose dependent and an exacerbation with prolonged exposure time and higher susceptibility of pregnant females could not be excluded. Thus, due to significant prolonged exposure duration* […] *and treatment of pregnant females in the subsequent OECD 422 inhalation study, 50 mg/m³ was selected as high concentration*". This reasoning however does not resolve the remaining concern that, in study (ii), the top dose (50 mg/m³) did not cause any notable adverse effects.

c. no males the dose and control groups (study i);

d. an exposure duration of 14 days (study i);

e. no data on histopathology findings: incidence and severity. In particular, the following investigations are missing: spleen, adrenals and heart (study i).

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

18 In your comments to the draft decision, you state that "[…] local and systemic toxicity was observed after 14 days of vapor exposure, which led to labelling as STOT RE cat. 1 (target organs: liver, kidney, respiratory tract) […] and illustrates the importance of inhalation as a relevant route of exposure". In addition, you have attached a copy of a robust study summary (RSS) with an updated dose level justification. You have proposed to update your dossier with the modified RSS.

19 ECHA acknowledges that you have self-classified as STOT RE cat. 1 based on the outcome of an inhalation DRF study (study i). However, as you have not addressed the concerns listed under 2.2.1., the information provided in your comments does not change the assessment outcome.

2.3. Specification of the study design

20 When there is no information available neither for the 28-day repeated dose toxicity endpoint (EU B.7, OECD TG 407), nor for the screening study for reproductive/developmental toxicity (OECD TG 421 or TG 422), the conduct of a combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (OECD TG 422) is preferred to ensure that unnecessary animal testing is avoided. Such an approach offers the possibility to avoid carrying out a 28-day study according to OECD TG 407, because the OECD TG 422 can at the same time fulfil the information requirement of REACH Annex VIII, 8.6.1 and that of REACH Annex VIII, 8.7.1. (Guidance on IRs and CSA, Section R.7.6.2.3.2.).

21 The studies (i and ii) you submitted were performed with the inhalation route. However, according to the criteria in Annex VIII, Section 8.6.1, Column 2, ECHA considers that the inhalation route is not appropriate for this substance, because exposure of humans via inhalation is unlikely. More specifically, the Substance is a liquid of low vapour pressure (1.73 hPa at 20 °C) and according to your Chemical Safety Report, risk management measures are in place to prevent inhalation exposure.

22 Referring to the criteria in Annex VIII, Section 8.6.1, Column 2, the oral route is the appropriate route of administration to investigate repeated dose toxicity.

23 For more information on the study design, see request for OECD TG 422 below.

3. Screening for reproductive/developmental toxicity

24 A screening for reproductive/developmental toxicity study (OECD 421 or OECD 422) is an information requirement under Annex VIII to REACH (Section 8.7.1.), if there is no evidence from analogue substances, QSAR or in vitro methods that the substance may be a developmental toxicant.

3.1. Information provided

25 You have provided:

(i) Screening study according to OECD 422 via inhalation in rats (2017) with the Substance.

3.2. Assessment of the information provided

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

3.2.1. Study not adequate for the information requirement

27 To fulfil the information requirement, the study must meet the requirements of EU B.63/OECD TG 421 or EU B.64/OECD TG 422. Therefore, the following specifications must be:

a. highest dose level should aim to induce toxicity or reach the limit dose.
b. at least 10 male and 12-13 female animals for each dose and control group;
c. an exposure duration of at least four weeks for males, including a minimum of two weeks prior to mating, and approx. 63 days for females to cover premating, conception, pregnancy and at least 13 days of lactation;
d. examination of parameters for sexual function and fertility such as parturition and lactation.

28 The study (i) is described as OECD TG 422 via inhalation. However, the following specifications are not according to the requirements of EU B.63/OECD TG 421 or EU B.64/OECD TG 422:

a. no justification for the dose setting while the highest dose levels tested was 50 mg/m^3, which is below the limit dose of the test guideline, and only caused local effects;

   In your comments to the draft decision, you explain that a DRF study identified a LOAEC of 100 mg/m^3, based on "*effects on liver, kidney and respiratory tract*." You continue by stating that the findings were "*clearly dose dependent and an exacerbation with prolonged exposure time and higher susceptibility of pregnant females could not be excluded. Thus, due to significant prolonged exposure duration* […] *and treatment of pregnant females in the subsequent OECD 422 inhalation study, 50 mg/m³ was selected as high concentration*." This reasoning however does not resolve the remaining concern that in study (i) the top dose (50 mg/m³) did not cause any notable adverse effects.
b. 10 males and 10 females in each dose and control group;
c. an exposure duration of 30 days for males and 56 day for females. No information was provided whether dosing included premating, conception, pregnancy and at least 13 days of lactation;

   In your comments to the draft decision, you have attached a copy of a robust study summary (RSS) wherein you describe the whole study period as "*The duration of treatment covered a 2-week premating and 2-week mating period in both sexes, one day postmating in males, and the entire gestation and lactation period (until PND 19) of the females.*" You have proposed to update your dossier with the modified RSS.

   The information provided as part of your comments addresses the incompliance regarding exposure duration.
d. no investigation of parturition and lactation was described.

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

30 In your comments to the draft decision, you have only partially addressed issues a and c listed above, and you have not provided any additional information regarding issues b and d. Therefore, the information provided in your comments does not change the assessment outcome.

3.3. Specification of the study design

31 When there is no information available neither for the 28-day repeated dose toxicity endpoint (EU B.7, OECD TG 407), nor for the screening study for reproductive/developmental toxicity (OECD TG 421 or TG 422), the conduct of a combined

repeated dose toxicity study with the reproduction/developmental toxicity screening test (OECD TG 422) is preferred to ensure that unnecessary animal testing is avoided. Such an approach offers the possibility to avoid carrying out a 28-day study according to OECD TG 407, because the OECD TG 422 can at the same time fulfil the information requirement of REACH Annex VIII, 8.6.1 and that of REACH Annex VIII, 8.7.1. (Guidance on IRs and CSA, Section R.7.6.2.3.2.).

32 A study according to the test method EU B.64/OECD TG 422 must be performed in rats.

33 The screening study (i) you submitted was performed with the inhalation route. However, according to the Guidance on IRs and CSA (Section R.7.6.2.3.2.), ECHA considers that the inhalation route is not appropriate for this substance, because exposure of humans via inhalation is unlikely. More specifically, the Substance is a liquid of low vapour pressure (1.73 hPa at 20 °C) and according to your Chemical Safety Report, risk management measures are in place to prevent inhalation exposure.

34 Referring to the Guidance on IRs and CSA (Section R.7.6.2.3.2.), the oral route is the appropriate route of administration to investigate repeated dose toxicity.

35 The study must be conducted with oral administration of the Substance (Guidance on IRs and CSA, Section R.7.6.2.3.2.).

References

The following documents may have been cited in the decision.

Guidance on information requirements and chemical safety assessment (Guidance on IRs & CSA)

Chapter R.4 Evaluation of available information; ECHA (2011).
Chapter R.6 QSARs, read-across and grouping; ECHA (2008).
Appendix to Chapter R.6 for nanoforms; ECHA (2019).
Chapter R.7a Endpoint specific guidance, Sections R.7.1 – R.7.7; ECHA (2017).
Appendix to Chapter R.7a for nanomaterials; ECHA (2017).
Chapter R.7b Endpoint specific guidance, Sections R.7.8 – R.7.9; ECHA (2017).
Appendix to Chapter R.7b for nanomaterials; ECHA (2017).
Chapter R.7c Endpoint specific guidance, Sections R.7.10 – R.7.13; (ECHA 2017).
Appendix to Chapter R.7a for nanomaterials; ECHA (2017).
Appendix R.7.13-2 Environmental risk assessment for metals and metal compounds; ECHA (2008).
Chapter R.11 PBT/vPvB assessment; ECHA (2017).
Chapter R.16 Environmental exposure assessment; ECHA (2016).

Guidance on data-sharing; ECHA (2017).

All Guidance on REACH is available online: https://echa.europa.eu/guidance-documents/guidance-on-reach

Read-across assessment framework (RAAF)

RAAF, 2017 Read-across assessment framework (RAAF), ECHA (2017)
RAAF UVCB, 2017 Read-across assessment framework (RAAF) – considerations on multi- constituent substances and UVCBs), ECHA (2017).

The RAAF and related documents are available online:
https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across

***OECD Guidance documents* (OECD GDs)**

OECD GD 23 Guidance document on aquatic toxicity testing of difficult substances and mixtures; No. 23 in the OECD series on testing and assessment, OECD (2019).
OECD GD 29 Guidance document on transformation/dissolution of metals and metal compounds in aqueous media; No. 29 in the OECD series on testing and assessment, OECD (2002).
OECD GD 150 Revised guidance document 150 on standardised test guidelines for evaluating chemicals for endocrine disruption; No. 150 in the OECD series on testing and assessment, OECD (2018).
OECD GD 151 Guidance document supporting OECD test guideline 443 on the extended one-generation reproductive toxicity test; No. 151 in the OECD series on testing and assessment, OECD (2013).

Appendix 2: Procedure

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 02 June 2021.

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 or the deadline.

In your comments on the draft decision, you requested an extension of the deadline to provide information. More specifically, you requested to extend the deadline from 12 to 24 months. You support this request by stating that "*no oral repeated dose data are available, which makes it necessary to conduct further range finding studies*" and "*laboratories/CROs have limited capacities*". You did not provide any documentary evidence for the claimed CRO capacity issue including a testing schedule for the requested information.

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. This is independent of the extension of the deadline you requested in the comments to the draft decision, which at the time was not substantiated by documentary evidence, as explained above.

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 3: Addressees of this decision and their corresponding information requirements

In accordance with Articles 10(a) and 12(1) of REACH, the information requirements for individual registrations are defined as follows:

- the information specified in Annex VII to REACH, for registration at 1-10 tonnes per year (tpa), or as a transported isolated intermediate in quantity above 1000 tpa;
- the information specified in Annexes VII and VIII to REACH, for registration at 10-100 tpa.

Registrant Name	Registration number	Highest REACH Annex applicable to you
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

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.

Appendix 4: Conducting and reporting new tests for REACH purposes

1. Requirements when conducting and reporting new tests for REACH purposes

1.1. 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[2].

1.2. 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
- 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.
- The reported composition must include all constituents of each Test Material and their concentration values and other parameters relevant for the property to be tested.

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[3].

[2] https://echa.europa.eu/practical-guides
[3] https://echa.europa.eu/manuals