Helsinki, 29 May 2017

Addressee: [redacted]

Decision number: TPE-D-2114360580-54-01/F
Substance name: 2,4,6-trinitrotoluene
EC number: 204-289-6
CAS number: 118-96-7
Registration number: [redacted]
Submission number: [redacted]
Submission date: 29.09.2015
Registered tonnage band: 1000+T

## DECISION ON A TESTING PROPOSAL

Based on Article 40 of Regulation ((EC) No 1907/2006) (the REACH Regulation), ECHA examined your testing proposal(s) and decided as follows.

Your testing proposal is accepted and you are requested to carry out:

1. **Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.; test method: EU B.31./OECD TG 414) in a first species (rat or rabbit), oral route using the registered substance (composition TNT)**

You are requested to perform:

2. **Pre-natal developmental toxicity study (Annex X, Section 8.7.2.; test method: EU B.31./OECD TG 414) in a second species (rabbit or rat), oral route using the registered substance (composition TNT).**

While your originally proposed test for Reproduction/developmental toxicity screening test (OECD TG 421) using the registered substance is rejected, you are requested to perform:

3. **Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.; test method: EU B.56./OECD TG 443) in rats, oral route with the registered substance (composition TNT) specified as follows:**
   - **Ten weeks premating exposure duration for the parental (P0) generation;**
   - **Dose level setting shall aim to induce some toxicity at the highest dose level;**
   - **Cohort 1A (Reproductive toxicity);**
   - **Cohort 1B (Reproductive toxicity) without extension to mate the Cohort 1B animals to produce the F2 generation; and**
   - **Cohorts 2A and 2B (Developmental neurotoxicity)**

You may adapt the testing requested above according to the specific rules outlined in Annexes VI to X and/or according to the general rules contained in Annex XI to the REACH Regulation.

To ensure compliance with the respective information requirement, any such adaptation will need to have a scientific justification, referring and conforming to the appropriate rules in the respective annex, and an adequate and reliable documentation.

You have to submit the requested information in an updated registration dossier by **9 December 2019**. You also have to update the chemical safety report, where relevant. The timeline has been set to allow for sequential testing.

The reasons for this decision are set out in Appendix 1. The procedural history is described in Appendix 2 and advice and further observations are provided in Appendix 3.

**Appeal**

This decision can be appealed to the Board of Appeal of ECHA within three months of its notification. An appeal, together with the grounds thereof, has to be submitted to ECHA in writing. An appeal has suspensive effect and is subject to a fee. Further details are described under: http://echa.europa.eu/regulations/appeals.

Authorised[1] by Claudio Carlon, Head of Unit, Evaluation E2

[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**

The decision of ECHA is based on the examination of the testing proposals submitted by you.

1. **Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.) in a first species**

Pursuant to Article 40(3)(a) of the REACH Regulation, ECHA may require the Registrant to carry out the proposed test.

A pre-natal developmental toxicity study for a first species is a standard information requirement as laid down in Annex IX, Section 8.7.2. of the REACH Regulation. The information on this endpoint is not available for the registered substance but needs to be present in the technical dossier to meet the information requirements. Consequently there is an information gap and it is necessary to provide information for this endpoint.

You have submitted a testing proposal for a pre-natal developmental toxicity study according to EU B.31/OECD 414.

ECHA considers that the proposed study is appropriate to fulfil the information requirement of Annex IX, Section 8.7.2. of the REACH Regulation.

You proposed testing in rat or rabbit, oral route. According to the test method EU B.31/OECD 414, the rat is the preferred rodent species, the rabbit the preferred non-rodent species and the test substance is usually administered orally. ECHA considers these default parameters appropriate and testing should be performed by the oral route with the rat or the rabbit as a first species to be used.

The registration dossier covers three different compositions, one being the pure form, the other two with the same impurities at different concentrations. Due to the known hazard classification of the impurities, ECHA considers that the pure form of the registered substance, the composition TNT, should be tested.

b) Outcome

Therefore, pursuant to Article 40(3)(a) of the REACH Regulation, you are requested to carry out the proposed study with the registered substance (composition TNT) subject to the present decision: Pre-natal developmental toxicity study in rats or rabbits, oral route (test method: EU B.31/OECD 414).

2. **Pre-natal developmental toxicity study (Annex X, Section 8.7.2.) in a second species**

Pursuant to Article 40(3)(c) of the REACH Regulation, ECHA may require the Registrant to carry out one or more additional tests in case of non-compliance of the testing proposal with Annexes IX, X or XI of the REACH Regulation.

Pre-natal developmental toxicity studies (test method EU B.31./OECD TG 414) on two species are part of the standard information requirements for a substance registered for 1000 tonnes or more per year (Annex IX, Section 8.7.2., column 1, Annex X, Section 8.7.2., column 1, and sentence 2 of introductory paragraph 2 of Annex X of the REACH Regulation).

As outlined above under 1. ECHA has approved your testing proposal for a pre-natal developmental toxicity study in a first species according to EU B.31./OECD TG 414. ECHA notes that you registered your substance for 1000 tonnes or more per year and that your technical dossier does not contain information on a pre-natal developmental toxicity study in a second species (Annex X, Section 8.7.2.). Consequently there is an information gap and it is necessary to provide information for this endpoint.

According to the test method EU B.31./OECD TG 414, the rat is the preferred rodent species and the rabbit the preferred non-rodent species. On the basis of this default consideration, ECHA considers testing should be performed with rabbits or rats as a second species, depending on the species tested in the first pre-natal developmental toxicity study.

ECHA considers that the oral route is the most appropriate route of administration for substances except gases to focus on the detection of hazardous properties on reproduction as indicated in ECHA *Guidance on information requirements and chemical safety assessment* (version 4.1, October 2015) R.7a, chapter R.7.6.2.3.2. Since the substance to be tested is a solid, ECHA concludes that testing should be performed by the oral route.

The pure form of the registered substance, the composition TNT, should be tested (see Section 1 above).

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance (composition TNT) subject to the present decision: Pre-natal developmental toxicity study (test method: EU B.31./OECD TG 414) in a second species (rabbit or rat) by the oral route.

*Notes for your consideration*

Before performing a pre-natal developmental toxicity study in a second species you should consider the specific adaptation possibilities of Annex X, Section 8.7.2., column 2 and general adaptation possibilities of Annex XI. If the results of the test in the first species or any other new information enable such adaptation, testing in the second species should be omitted and the registration dossier should be updated containing the corresponding adaptation statement and underlying scientific justification.

For the selection of the appropriate species you are advised to consult ECHA *Guidance on information requirements and chemical safety assessment* (version 4.1, October 2015), Chapter R.7a, section R.7.6.2.3.2.

### 3. Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.)

Pursuant to Article 40(3)(d) and (c) of the REACH Regulation, ECHA may reject a proposed test and require the Registrant to carry out other tests in cases of non-compliance of the testing proposal with Annexes IX, X or XI.

The basic test design of an extended one-generation reproductive toxicity study (test method EU B.56./OECD TG 443 with Cohorts 1A and 1B, without extension of Cohort 1B to include a F2 generation, and without Cohorts 2A, 2B and 3) is a standard information requirement as laid down in column 1 of 8.7.3., Annex X. If the conditions described in column 2 of Annex X are met, the study design needs to be expanded to include the extension of Cohort 1B, Cohorts 2A/2B, and/or Cohort 3. Further detailed guidance on study design and triggers is provided in the ECHA *Guidance on information requirements and chemical safety assessment* R.7a, chapter R.7.6 (version 4.1, October 2015).

The information on this endpoint is not available for the registered substance but needs to be present in the technical dossier to meet the information requirements. Consequently there is an information gap and it is necessary to provide information for this endpoint.

You have submitted a testing proposal for a reproduction/developmental toxicity screening test (OECD TG 421). ECHA notes that this study would not provide the information required by Annex X, Section 8.7.3. because it does not cover key elements, such as exposure duration, life stages and statistical power of an extended one-generation reproductive toxicity study. In addition there is a particular concern for developmental neurotoxicity according to column 2 of Annex X, Section 8.7.3. Therefore, your testing proposal for a reproduction/developmental toxicity screening test (OECD TG 421) is rejected and an extended one-generation reproductive toxicity study according Annex X, Section 8.7.3. is required. The following refers to the specifications of this required study.

*a) The specifications for the study design*

*Premating exposure duration and dose-level setting*

To ensure that the study design adequately addresses the fertility endpoint, the duration of the premating exposure period and the selection of the highest dose level are key aspects to be considered. According to ECHA Guidance, the starting point for deciding on the length of premating exposure period should be ten weeks to cover the full spermatogenesis and folliculogenesis before the mating, allowing meaningful assessment of the effects on fertility.

Ten weeks premating exposure duration is required because there is no substance specific information in the dossier supporting shorter premating exposure duration as advised in the ECHA *Guidance on information requirements and chemical safety assessment* R.7a, chapter R.7.6 (version 4.1, October 2015).

The highest dose level shall aim to induce some toxicity to allow comparison of effect levels and effects of reproductive toxicity with those of systemic toxicity. The dose level selection should be based upon the fertility effects with the other cohorts being tested at the same dose levels.

If there is no existing relevant data to be used for dose level setting, it is recommended that results from a conducted range-finding study (or range finding studies) are reported with the main study. This will support the justifications of the dose level selections and interpretation of the results.

*Cohorts 2A and 2B*

The developmental neurotoxicity Cohorts 2A and 2B need to be conducted in case of a particular concern on (developmental) neurotoxicity as described in column 2 of 8.7.3., Annex X. When there are triggers for developmental neurotoxicity, both the Cohorts 2A and 2B are to be conducted as they provide complementary information.

ECHA notes that according to the harmonised classification and labelling approved by the European Union, this substance may cause damage to organs through prolonged or repeated exposure (STOT RE 2). The technical dossier lists liver, eyes, nervous system and circulatory system as target organs.

In this respect, ECHA notes that as reported in the toxicokinetics study (OECD TG 417) in the technical dossier, the registered substance is (bio)transformed to a nonpolar metabolite which accumulates in the brain. It has also been shown that workers having long contact with the registered substance showed disorders of the nervous system, mainly in the motor and sensory neurons, and also a disorder in the thermoregulating reactions to heat and cold was observed (Hoek 2010[2]).

ECHA concludes that the developmental neurotoxicity Cohorts 2A and 2B need to be conducted because there is a particular concern on (developmental) neurotoxicity based on the registered substance's harmonised classification for STOT RE 2 with the nervous system as target organ; the *in vivo* toxicokinetics study showing that a metabolite of the registered substance accumulates in the brain; and human data reporting adverse effects on the nervous system.

The study design must be justified in the dossier and, thus, the existence/non-existence of the conditions/triggers must be documented.

*Species and route selection*

According to the test method EU B.56./ OECD TG 443, the rat is the preferred species. On the basis of this default assumption, ECHA considers that testing should be performed in rats.

ECHA considers that the oral route is the most appropriate route of administration for substances except gases to focus on the detection of hazardous properties on reproduction as indicated in ECHA *Guidance on information requirements and chemical safety assessment* (version 4.1, October 2015) R.7a, chapter R.7.6.2.3.2. Since the substance to be tested is a solid, ECHA concludes that testing should be performed by the oral route.

*Tested material*

The pure form of the registered substance, the composition TNT, should be tested (see Section 1 above).

[2] Bart Hoek (2004) Military Explosives and Health: Organic Energetic Compound Syndrome?, Medicine, Conflict and Survival, 20:4, 326-333

b) Outcome

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance (composition TNT) subject to the present decision: Extended one-generation reproductive toxicity study (test method EU B.56./OECD TG 443), in rats, oral route, according to the following study-design specifications:

- Ten weeks premating exposure duration for the parental (P0) generation;
- Dose level setting shall aim to induce some toxicity at the highest dose level;
- Cohort 1A (Reproductive toxicity);
- Cohort 1B (Reproductive toxicity) without extension to mate the Cohort 1B animals to produce the F2 generation; and
- Cohorts 2A and 2B (Developmental neurotoxicity)

*Notes for your consideration*

The conditions to include the extension of Cohort 1B are currently not met. Furthermore, no triggers for the inclusion of Cohort 3 (developmental immunotoxicity) were identified. However, you may expand the study by including the extension of Cohort 1B and/or Cohort 3 if new information becomes available after this decision is issued to justify such an inclusion. Inclusion is justified if the new information shows triggers which are described in column 2 of Section 8.7.3., Annex X and further elaborated in ECHA *Guidance on information requirements and chemical safety assessment* R.7a, chapter R.7.6 (version 4.1, October 2015). You may also expand the study to address a concern identified during the conduct of the extended one-generation reproduction toxicity study and also due to other scientific reasons in order to avoid a conduct of a new study. The justification for the expansion must be documented. The study design must be justified in the dossier and, thus, the existence/non-existence of the conditions/triggers must be documented.

## Appendix 2: Procedural history

ECHA received your registration containing the testing proposals for examination in accordance with Article 40(1) on 11 April 2013.

These initial testing proposals (submission number UX472467-86) included, among others, testing proposals for a 90-day study, a pre-natal developmental toxicity and a two-generation reproductive toxicity.

ECHA held a third party consultation for these testing proposals from 4 April 2014 until 19 May 2014. This public consultation called for information on the substance subject to this decision on the endpoints for which you had submitted testing proposals in your dossier with the submission number UX472467-86, i.e. sub-chronic toxicity, pre-natal developmental toxicity and reproductive toxicity. ECHA received information from third parties regarding the sub-chronic toxicity endpoint. ECHA has sent you a draft decision on these testing proposals on 24 July 2014. You have subsequently updated your dossier with the submission subject to this decision. However, you removed the original testing proposal for the sub-chronic toxicity endpoint, while you did not modify the endpoints for which you have proposed further testing, i.e. pre-natal developmental toxicity and reproductive toxicity. The latter endpoints were covered by the public consultation, which are the same as those addressed in this decision. Therefore, ECHA considers that the initial public consultation for these two endpoints still applies.

This decision does not take into account any updates after **6 March 2017**, 30 calendar days after the end of the commenting period.

The decision making followed the procedure of Articles 50 and 51 of the REACH Regulation, as described below:

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

ECHA did not receive any comments by the end of the commenting period.

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

As no amendments were proposed, ECHA took the decision according to Article 51(3) of the REACH Regulation.

## Appendix 3: Further information, observations and technical guidance

1. This decision does not imply that the information provided in your registration dossier is in compliance with the REACH requirements. The decision does not prevent ECHA from initiating a compliance check on the registration at a later stage.

2. Failure to comply with the requests in this decision, or to otherwise fulfil the information requirements with a valid and documented adaptation, will result in a notification to the enforcement authorities of the Member States.

3. In relation to the information required by the present decision, the sample of the substance used for the new tests must be suitable for use by all the joint registrants. Hence, the sample should have a composition that is suitable to fulfil the information requirement for the range of substance compositions manufactured or imported by the joint registrants.

   It is the responsibility of all joint registrants who manufacture or import the same substance to agree on the appropriate composition of the test material and to document the necessary information on their substance composition. In addition, it is important to ensure that the particular sample of the substance tested in the new tests is appropriate to assess the properties of the registered substance, taking into account any variation in the composition of the technical grade of the substance as actually manufactured or imported by each registrant.

   If the registration of the substance by any registrant covers different grades, the sample used for the new tests must be suitable to assess these grades. Finally there must be adequate information on substance identity for the sample tested and the grades registered to enable the relevance of the tests to be assessed.