SUBSTANCE EVALUATION CONCLUSION

as required by REACH Article 48

and

EVALUATION REPORT

for

Ethylene dinitrate

EC No 211-063-0

CAS RN 628-96-6

Evaluating Member State: Italy

Dated: 6 July 2021

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Evaluating Member State Competent Authority

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Year of evaluation in CoRAP: 2016

Before concluding the substance evaluation a Decision to request further information was issued on 29 June 2018.

Further information on registered substances here:

http://echa.europa.eu/web/guest/information-on-chemicals/registered-substances

DISCLAIMER

This document has been prepared by the evaluating Member State as a part of the substance evaluation process under the REACH Regulation (EC) No 1907/2006. The information and views set out in this document are those of the author and do not necessarily reflect the position or opinion of the European Chemicals Agency or other Member States. The Agency does not guarantee the accuracy of the information included in the document. Neither the Agency nor the evaluating Member State nor any person acting on either of their behalves may be held liable for the use which may be made of the information contained therein. Statements made or information contained in the document are without prejudice to any further regulatory work that the Agency or Member States may initiate at a later stage.

Foreword

Substance evaluation is an evaluation process under REACH Regulation (EC) No. 1907/2006. Under this process the Member States perform the evaluation and ECHA secretariat coordinates the work. The Community rolling action plan (CoRAP) of substances subject to evaluation, is updated and published annually on the ECHA web site[1].

Substance evaluation is a concern driven process, which aims to clarify whether a substance constitutes a risk to human health or the environment. Member States evaluate assigned substances in the CoRAP with the objective to clarify the potential concern and, if necessary, to request further information from the registrant(s) concerning the substance. If the evaluating Member State concludes that no further information needs to be requested, the substance evaluation is completed. If additional information is required, this is sought by the evaluating Member State. The evaluating Member State then draws conclusions on how to use the existing and obtained information for the safe use of the substance.

This Conclusion document, as required by Article 48 of the REACH Regulation, provides the final outcome of the Substance Evaluation carried out by the evaluating Member State. The document consists of two parts i.e. A) the conclusion and B) the evaluation report. In the conclusion part A, the evaluating Member State considers how the information on the substance can be used for the purposes of regulatory risk management such as identification of substances of very high concern (SVHC), restriction and/or classification and labelling. In the evaluation report part B the document provides explanation how the evaluating Member State assessed and drew the conclusions from the information available.

With this Conclusion document the substance evaluation process is finished and the Commission, the Registrant(s) of the substance and the Competent Authorities of the other Member States are informed of the considerations of the evaluating Member State. In case the evaluating Member State proposes further regulatory risk management measures, this document shall not be considered initiating those other measures or processes. Further analyses may need to be performed which may change the proposed regulatory measures in this document. Since this document only reflects the views of the evaluating Member State, it does not preclude other Member States or the European Commission from initiating regulatory risk management measures which they deem appropriate.

[1] http://echa.europa.eu/regulations/reach/evaluation/substance-evaluation/community-rolling-action-plan

Contents

Part A. Conclusion

1. CONCERN(S) SUBJECT TO EVALUATION

Ethylene dinitrate was originally selected for substance evaluation in order to clarify concerns about:

- suspected reprotoxic
- suspected sensitiser
- potential endocrine disruptor
- suspected PBT/vPvB
- wide dispersive use
- high (aggregated) tonnage

During the evaluation an additional concern was identified:

- suspected carcinogenic

2. OVERVIEW OF OTHER PROCESSES / EU LEGISLATION

Not applicable.

3. CONCLUSION OF SUBSTANCE EVALUATION

The evaluation of the available information on the substance has led the evaluating Member State (eMSCA) to the following conclusions, as summarised in the table below.

Table 1

CONCLUSION OF SUBSTANCE EVALUATION Conclusions	Tick box
Need for follow-up regulatory action at EU level	
Harmonised Classification and Labelling	
Identification as SVHC (authorisation)	
Restrictions	
Other EU-wide measures	
No need for regulatory follow-up action at EU level	X

4. FOLLOW-UP AT EU LEVEL

4.1. Need for follow-up regulatory action at EU level

Not applicable.

4.1.1. Harmonised Classification and Labelling

Not applicable.

4.1.2. Identification as a substance of very high concern, SVHC (first step towards authorisation)

Not applicable.

4.1.3. Restriction

Not applicable.

4.1.4. Other EU-wide regulatory risk management measures

Not applicable.

5. CURRENTLY NO FOLLOW-UP FORESEEN AT EU LEVEL

5.1. No need for regulatory follow-up at EU level

Table 2

REASON FOR REMOVED CONCERN The concern could be removed because	Tick box
Clarification of hazard properties/exposure	
Actions by the registrant(s) to ensure safety, as reflected in the registration dossiers (e.g. change in supported uses, applied risk management measures, etc.)	X

The eMSCA has performed the evaluation of the substance ethylene dinitrate for both human health and environmental aspects.

Ethylene dinitrate was originally selected for substance evaluation in order to clarify specific concerns such as suspected reprotoxic, suspected sensitiser, potential endocrine disruptor, suspected PBT/vPvB, wide dispersive use, high (aggregated) tonnage. An additional concern of suspected carcinogenic was raised during the evaluation. However, since this substance is used in explosives products, because the Substance is characterized by extremely high explosive properties, performing laboratory studies with this substance is extremely dangerous.

The eMSCA requested the Registrant(s) to provide appropriate documentation from a CRO (Contract Reasearch Organisation) stating that testing is not possible because of the explosive properties of the substance. Moreover, a documentation for the exposure to professional and to the environment was provided by the Registrant(s), where the strictly controlled conditions are declared to apply also to professional uses ensuring that neither human nor environmental exposure occurs. The eMSCA considers that the documentation provided is acceptable and concludes that no further data are needed following the substance evaluation.

5.2. Other actions

Not applicable.

6. TENTATIVE PLAN FOR FOLLOW-UP ACTIONS (IF NECESSARY)

Not applicable.

Part B. Substance evaluation

7. EVALUATION REPORT

The Substance evaluation started in March 2016 and aimed to evaluate the following endpoints:

Suspected sensitising properties:
Read-across based on study for nitroglycerin (EC number 200-240-8; CAS RN 55-63-0) has been used in the documentation of skin sensitisation (moderate effect in guinea pig maximisation test). Some cases of skin sensitisation induced by ethylene dinitrate in human were reported by Kanerva (1991).

Suspected reproductive toxicity/suspected ED properties:

Read-across based on study for nitroglycerin has been used in the documentation of developmental toxicity (NOAEL: 0.6 mg/kg bw/day). Nitroglycerin has not been evaluated yet in any legal processes for chemicals in the EU, except C&L harmonisation (classification for reprotoxicity not harmonised, no self-classification notified). The study used in read-across has been published in 1978. No self-classification has been proposed for reproductive toxicity and the only study presented is old pre-glp study.

Suspected PBT properties:

Toxic properties of the substance needs to be clarified regarding reproductive toxicity concern. Although estimated aquatic BCF is 8.9 L/kg (QSAR), the estimated (KOAWIN) Log KOA is 5.78, this value has to be further clarified to assess bioaccumulation potential in air-breathing organisms. Read-across based on study for Nitroglycerin has been used in the documentation of persistency (DT50(water) > 1 year).

The Substance presents a high aggregate tonnage and the uses by professional workers are described by ERC 8f: wide dispersive outdoor use resulting in inclusion into or onto a matrix.

Additional concern

Additional concern for carcinogenicity was raised by eMSCA during the evaluation of the ethylene dinitrate. The concern was based on the data set for the read-across substance nitroglycerin presented by Registrant(s).

7.1. Overview of the substance evaluation performed

Ethylene dinitrate was originally selected for substance evaluation in order to clarify concerns about:

- suspected reprotoxic
- suspected sensitiser
- potential endocrine disruptor
- suspected PBT/vPvB
- wide dispersive use

- high (aggregated) tonnage

During the evaluation also other concern was identified. The additional concern was:
- suspected carcinogenic

Table 3

EVALUATED ENDPOINTS	
Endpoint evaluated	**Outcome/conclusion**
Suspected reprotoxic	**Unresolved:** The Registrant(s) provided documents confirming that all identified uses are under strictly controlled conditions, ensuring that neither human nor environmental exposure occurs. The Registrant(s) provided a declaration from a CRO that testing the substances according to the relevant test guidelines is technically not possible due the explosive properties of the substance. eMSCA considers the documentation provided acceptable. No further action.
Suspected sensitiser	**Unresolved:** The Registrant(s) provided documents confirming that all identified uses are under strictly controlled conditions, ensuring that neither human nor environmental exposure occurs. The Registrant(s) provided a declaration from a CRO that testing the substances according to the relevant test guidelines is technically not possible due the explosive properties of the substance. eMSCA considers the documentation provided acceptable. No further action.
Potential endocrine disruptor	**Unresolved:** The Registrant(s) provided documents confirming that all identified uses are under strictly controlled conditions, ensuring that neither human nor environmental exposure occurs. The Registrant(s) provided a declaration from a CRO that testing the substances according to the relevant test guidelines is technically not possible due the explosive properties of the substance. eMSCA considers the documentation provided acceptable. No further action.
Suspected PBT/vPvB	**Unresolved:** Registrant(s) provided documents confirming that all identified uses are under strictly controlled conditions, ensuring that neither human nor environmental exposure occurs. The Registrant(s) provided a declaration from a CRO that testing the substances according to the relevant test guidelines is technically not possible due the explosive properties of the substance. eMSCA considers the documentation provided acceptable. No further action (see sections below).
Suspected carcinogenic	**Unresolved:** The Registrant(s) provided a documentation for the exposure to professional and to the environment where the strictly controlled condition are declared to apply also to professional use ensuring that neither human nor environmental exposure occurs. The Registrant(s) provided a declaration from a CRO that the shipment of the substance is forbidden and testing the substances according the relevant test guidelines is technically not possible due the explosive properties of the substance. eMSCA considers the documentation provided acceptable. No further action.
Wide dispersive use	The concern is refuted based on SCC: The Registrant(s) provided documents confirming that all identified uses are under strictly controlled conditions, ensuring that neither human nor environmental exposure occurs. No further action.
high (aggregated) tonnage	Registrant(s) provided documents confirming that all identified uses are under strictly controlled conditions, ensuring that neither human nor environmental exposure occurs. No further action.

7.2. Procedure

On the basis of an opinion of the ECHA Member State Committee and due to initial grounds for concern relating to suspected Reprotoxic, suspected sensitiser, potential endocrine disruptor, suspected PBT/vPvB, wide dispersive use, high (aggregated) tonnage, ethylene dinitrate (EC No 211-063-0, CAS RN 628-96-6) was included in the Community rolling action plan (CoRAP) for substance evaluation to be evaluated in 2016. The updated CoRAP was published on the ECHA website on 22 March 2016. The competent authority of Italy was appointed to carry out the evaluation.

In accordance with Article 45(4) of the REACH Regulation, the eMSCA carried out the evaluation of the above substance based on the information in the registration dossier(s) and other relevant and available information.

In the course of the evaluation, the eMSCA identified additional concerns regarding carcinogenicity.

The eMSCA considered that further information was required to clarify the above mentioned concerns, and prepared a draft decision under Article 46(1) of REACH to request further information. The eMSCA subsequently submitted the draft decision to ECHA on 22 March 2017.

The decision making followed the procedure of Articles 50 and 52 of the REACH Regulation. The Member State Committee reached a unanimous agreement on the draft decision in its MSC-60 written procedure and ECHA adopted the decision according to Article 51(6) of the REACH Regulation. The Substance Evaluation decision requested the Registrant(s) to provide additional information on exposure (exposure scenarios, uses and assessments) by July 2019.

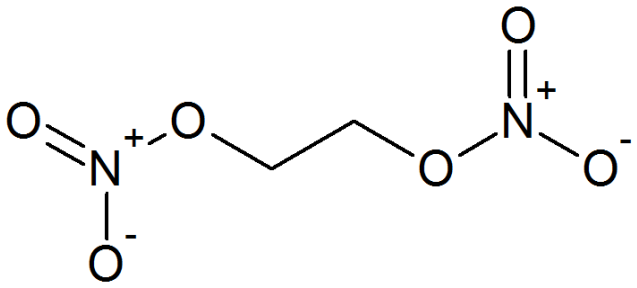
7.3. Identity of the substance

Table 4

SUBSTANCE IDENTITY	
Public name:	Ethylene dinitrate
EC number:	211-063-0
CAS number:	628-96-6
Index number in Annex VI of the CLP Regulation:	603-032-00-9
Molecular formula:	C2H4N2O6
Molecular weight range:	152.063
Synonyms:	Ethylene dinitrate Ethylene glycol dinitrate Ethanediol dinitrate Dinitroglycol Dinitroglicol Ethylene nitrate Ethylenglykoldinitrat Glycol (dinitrate de) Glycol dinitrate Glycoldinitraat Glykoldinitrat Nitroglycol Nitroglykol 1,2-Bis(nitrooxy)ethane 1,2-Ethanediol dinitrate EGDN ethane-1,2-diyl dinitrate

Type of substance ☒ Mono-constituent ☐ Multi-constituent ☐ UVCB

Structural formula:



7.4. Physico-chemical properties

Table 5

OVERVIEW OF PHYSICOCHEMICAL PROPERTIES	
Property	**Value**
Physical state at 20°C and 101.3 kPa	Liquid
Vapour pressure	6 Pa at 20C
Water solubility	5.2 g/L at 25 °C.
Partition coefficient n-octanol/water (Log Kow)	ca. 1.16 at 20 °C
Flammability	The study is technically not feasible
Explosive properties	Explosive - explodes at 114-116 °C
Oxidising properties	The study is technically not feasible
Granulometry	Not relevant, the substance is a liquid
Stability in organic solvents and identity of relevant degradation products	soluble in carbon tetrachloride, benzene, toluene, and acetone.
Dissociation constant	The study is technically not feasible

7.5. Manufacture and uses

7.5.1. Quantities

Table 6

AGGREGATED TONNAGE (PER YEAR)				
☐ 1 – 10 t	☐ 10 – 100 t	☐ 100 – 1000 t	☒ 1000- 10,000 t	☐ 10,000-50,000 t
☐ 50,000 – 100,000 t	☐ 100,000 – 500,000 t	☐ 500,000 – 1000,000 t	☐ > 1000,000 t	☐ Confidential

For this substance, six Registrant(s) provided the information on the total tonnage manufactured in their CSRs. The reported total tonnages are different and referred to different year ranges.

The eMSCA notes that the provided CSRs are not harmonised and the Lead Registrant(s) does not cover the manufactured quantities of the co-Registrants.

7.5.2. Overview of uses

This substance is manufactured and/or imported in the European Economic Area in 1000 – 10.000 tonnes per year. The Substance is used in the following products: explosives. The Substance is used in the following areas: mining and building & construction work. Release to the environment is therefore likely to occur from industrial use: formulation of mixtures and manufacturing of the substance.

Uses by professional workers are described by ERC 8f: Wide dispersive outdoor use resulting in inclusion into or onto a matrix, as stated in the justification document based on IUCLID Registration file, entry 3.5: "life cycle description".

Table 7

USES	Use(s)
Uses as intermediate	-
Formulation	Manufacture of the substance Formulation or re-packing
Uses at industrial sites	Preparation for blasting
Uses by professional workers	Professional use; Explosive Preparation for blasting
Consumer Uses	-
Article service life	-

7.6. Classification and Labelling

7.6.1. Harmonised Classification (Annex VI of CLP)

The substance is currently listed on Annex VI of CLP Regulation ((EC) No 1272/2008).

Table 8

HARMONISED CLASSIFICATION ACCORDING TO ANNEX VI OF CLP REGULATION (REGULATION (EC) 1272/2008)							
Index No	**International Chemical Identification**	**EC No**	**CAS No**	**Classification**		**Spec. Conc. Limits, M-factors**	**Notes**
				Hazard Class and Category Code(s)	**Hazard statement code(s)**		
603-032-00-9	ethylene dinitrate ethylene glycol dinitrate	211-063-0	628-96-6	Unst. Expl. Acute Tox. 2 * Acute Tox. 1 Acute Tox. 2 * STOT RE 2	H200 H300 H310 H330 H373**		

7.6.2. Self-classification

In the registration(s): No deviations from harmonised classification.The following hazard classes are in addition notified among the aggregated self classifications in the C&L Inventory:no additional classification notified.

7.7. Environmental fate properties

7.7.1. Degradation

In the updated IUCLID file and CSRs, there are no experimental data on the substance for degradation/biodegradation testing. There are only read-across studies from a supporting substance Nitroglycerin (NG) for hydrolysis and for predicting ready biodegradability.

The results of the read-across study for hydrolysis (no guideline available, reliability 2, data published in Registration dossier) carried out at pH range 3-9 and at different temperatures (25°C, 37°C and 80°C), are: t0.5 > 1 year for pH 3-8 (25°C) and t0.5 > 1 month for pH 9 (25°C).

The OECD test guideline 111 states that if the results of the preliminary test are t0.5 > 1 year (at 50 ± 0.5°C and pH 4.0, 7.0 and 9.0), the test substance is considered hydrolytically stable and no additional testing is required.

The lead Registrant updated the Registration dossier providing a read-across justification document. Based on all available calculated and experimental data, the read-across between the source substance nitroglycerin and the target substance ethylene dinitrate allows a reliable assessment of the hazard for the environmental compartment covering the endpoints hydrolysis, biodegradation in water, short- and long-term toxicity to fish and long-term toxicity to aquatic invertebrates. This prediction is supported by physicochemical and ecotoxicological data on the substances. The approach is considered plausible. Therefore, accepting nitroglycerine as supporting substance, the eMSCA concludes that the target substance (Ethylene dinitrate) is considered hydrolytically stable.

Regarding screening readily biodegradability, the Registrant(s) conclusion is that the substance ethylene dinitrate is readily degradable.

The read-across Ready Biodegradability Studies on nitroglycerin utilised old tests (1978, 1980) without Guideline indications.

eMSCA raises doubts about the relevance and validity of supporting biodegradation studies on nitroglycerin. Indeed, based on the little information available, there is no sufficient evidence to conclude on persistency (e.g. no standard test guidelines, without evidence of the use of not pre-adapted inoculums, suitable concentration of test substance, etc.).

The eMSCA concludes that the biodegradation studies on read-across substance do not allow to conclude on the persistency of ethylene dinitrate. However, due to the explosive nature of ethylene dinitrate, performing laboratory studies would be extremely dangerous and is not recommended. The Registrant(s) provided a declaration from a CRO that testing the substances according the relevant test guidelines is technically not possible due the explosive properties of the substance. eMSCA considers the documentation provided acceptable. In addition, only industrial and professional uses are foreseen and the uses are under strictly controlled conditions, ensuring that neither human nor environmental exposure occurs.

For these reasons, the eMSCA concludes that no further information needs to be required under this substance evaluation to clarify the biodegradation potential of the substance.

7.7.2. Environmental distribution

For this substance in IUCLID file and CSRs there are no data on environmental distribution. As justification, Registrant(s) indicated that the information requirements under section 9.3.1 and 9.3.3 may be omitted since the log Kow value for the test substance is <3.0 (CSR sections 1.3 and 4.2.1) and has low potential for adsorption, as suggest from guideline Ch.R.7a - R.7.1.15.4 Adaptation of the standard testing regime). The eMSCA supports this conclusion.

7.7.3. Bioaccumulation

Aquatic Bioaccumulation

The Registrant(s) provided 4 reliable QSAR estimates, and the corresponding supporting documentation, conducted on the registered substance ethylene dinitrate (CAS number 628-96-6), indicating:

- BCF = 2.71 L/Kg (EPIWEB, BCFBAF v3.00, regression-based estimate);
- BAF = 1.69 L/Kg (EPIWEB, BCFBAF v3.00, Arnot-Gobas upper trophic);
- Biotransformation half-life = 0.03 days (EPIWEB, BCFBAF v3.00, Arnot-Gobas upper trophic);
- BCF = 8.9 L/Kg (OASIS, BCFmax-BCF).

Based on the available information, the Registrant(s), following a weight of evidence comparison of predicted BCFs and BAFs to B Criterion (BCF>2000 L/kg) and vB Criterion (BCF>5000 L/kg), came to the conclusion that ethylene dinitrate is likely not B or vB under REACH Regulation.

The eMSCA supports the conclusion on aquatic bioaccumulation.

Bioaccumulation in air-breathing organisms

Despite the conclusions regarding aquatic bioaccumulation, and a low value of log Kow (1.16 at 20°C, well below the triggering value of 4.5), the estimate of logKoa performed with KOAWIN v1.10 (EPIWEB) on the registered substance provided a value of 5.11. This value suggests a potential bioaccumulation in air-breathing organisms that has to be further explored (Gobas *et al.*, 2003, 2009).

Therefore, the information provided by the Registrant(s) is not sufficient to exclude that the substance is bioaccumulative in air-breathing-organisms.

However, due to the explosive nature of ethylene dinitrate, performing laboratory studies would be extremely dangerous and is not recommended. The Registrant(s) provided a declaration of CRO that testing the substances according the relevant test guidelines is technically not possible due the explosive properties of the substance. eMSCA considers the documentation provided acceptable. In addition, only industrial and professional uses are foreseen and the uses are demonstrated to be under strictly controlled industrial conditions.

For these reasons, the eMSCA concludes that no further information can be requested to clarify the concern on bioaccumulation potential in air-breathing organisms.

7.8. Environmental hazard assessment

7.8.1. Aquatic compartment (including sediment)

7.8.1.1. Fish

Short term toxicity

The Registrant(s) provided 2 reliable test results conducted on the read-across substance nitroglycerin, indicating an LC_{50} in the range of 1-10 mg/L for freshwater fish species.

The lowest 96h LC_{50} value of 1.9 mg/L (nominal concentration) was determined for the effects of the test substance on mortality of *Oncorhynchus mykiss* in accordance with ASTM E 729-80. This study was used for the purpose of CSA.
Based on the available information, the eMSCA supports the conclusion on this endpoint.

Long term toxicity

The Registrant(s) provided 2 reliable test results conducted on the read-across substance nitroglycerin, indicating a NOEC in the range of 0.01-1 mg/L for freshwater fish species.

The lowest 60d NOEC value of 0.03 mg/L (measured concentration) was determined for the effects of the test substance on the growth (dry weight) of *Oncorhynchus mykiss* in accordance with ASTM Draft 10 early life-stage toxicity test with fish. This study was used for the purpose of CSA.

Based on the available information, the eMSCA supports the conclusion on this endpoint.

7.8.1.2. Aquatic invertebrates

Short term toxicity

The Registrant(s) provided a reliable test result conducted on the registered substance ethylene dinitrate, indicating an EC_{50} (48h) >100 mg/L (based on nominal concentrations; mortality effect) for *Daphnia magna* (OECD 202 TG, static).

Based on the available information, the eMSCA supports the conclusion on this endpoint.

Long term toxicity

The Registrant(s) provided a reliable test result conducted on the read-across substance nitroglycerin, indicating a NOEC (7d) = 3.23 mg/L (based on measured concentrations; mortality effect) for *Ceriodaphnia dubia* (proposed ASTM method for 3-brood renewal toxicity test, Draft 3, static exposure).

Based on the available information, the eMSCA supports the conclusion on this endpoint.

7.8.1.3. Algae and aquatic plants

The Registrant(s) provided an experimental key study with reliability 1, static exposure of *Desmodesmus subspicatus,* according to OECD Guideline 201 (Alga, Growth Inhibition Test) and GLP compliant.

A 72h ErC50 value of 100 mg/L and a 72h NOEC of 10 mg/L have been determined for the effects of Ethylene dinitrate on growth rate of green algae. The study is adequately described and in accordance with the conditions for the validity of the test.

EMSCA supports the Registrant(s) conclusion, considering any further information on this endpoint not necessary.

7.8.1.4. Sediment organisms

There is no toxicity data on sediment organisms in the registration dossiers. The Registrant(s) provided the following justification for data waiving: "In accordance with column 2 of REACH annex X, further degradation testing does not need to be conducted as the chemical safety assessment does not indicate a need for further investigation".

Indeed, REACH Regulation in section 9.5.1 of Annex X, column 2, states that: "Long term toxicity testing shall be proposed by the Registrant(s) if the results of the chemical safety assessment indicates the need to investigate further the effects of the substance and/or relevant degradation products on sediment organisms. The choice of the appropriate test(s) depends on the results of the chemical safety assessment".Based on the available information (measured log Kow = 1.16 at 20 °C; log Koc = 1.39 at 20 °C), adsorption in sediment and soil compartment is considered unlikely by the eMSCA and consequently the eMSCA supports the justification for data waiving on this endpoint.

7.8.2. Terrestrial compartment

The Registrant(s) provided data waiving for toxicity on all three terrestrial taxonomic groups (soil macro-organisms, soil micro-organisms and terrestrial plants) with a justification based on exposure considerations. The Registrant(s) indicate that, according to Annex IX and X, terrestrial toxicity studies do not need to be performed as any significant direct and indirect exposure to soil is unlikely. Moreover, physicochemical data also indicate that ethylene dinitrate has a low adsorptive (log Koc = 1.39) and bioaccumulative (log Kow= 1.16) potential. Therefore, a relevant distribution into soil compartment and significant exposure of soil organisms are not expected.

Thus, the eMSCA concludes that no further information is needed to clarify the hazard to terrestrial organisms.

7.8.3. Microbiological activity in sewage treatment systems

The Registrant(s) provide a reliable test results conducted on the Substance ethylene dinitrate, indicating a NOEC (3h)=10 mg/L (based on nominal concentrations). The Registrant(s) report on the CSR, also, an EC10(3h): >5.6 -<23 mg/L (based on nominal concentrations) and an EC50(3h): >160-<530 mg/L (based on nominal concentrations). Based on the available information, the eMSCA supports the conclusion on this endpoint.

7.8.4. PNEC derivation and other hazard conclusions

Table 9

PNEC DERIVATION AND OTHER HAZARD CONCLUSIONS		
Hazard assessment conclusion for the environment compartment	**Hazard conclusion**	**Remarks/Justification**
Freshwater	PNEC aqua (freshwater): 0.003 mg/L	Assessment factor: 10 Extrapolation method: Reliable short-term and long-term effects data for ethylene dinitrate / nitroglycerin from three trophic levels are available. The lowest NOEC value was obtained for fish (60d NOEC = 0.03 mg/L), therefore an AF of 10 was applied

Marine water	PNEC aqua (marine waters): 0.0003 mg/L	Assessment factor: 100 Extrapolation method: applied the standard assumption of a 10x lower PNEC than PNECfreshwater
Intermittent releases to water	PNEC aqua (intermittent releases): 0.019 mg/L	Assessment factor: 100 Extrapolation method: based on the lowest short-term toxicity result obtained with ethylene dinitrate / nitroglycerin from the fish trophic level (96h LC50 = 1.9 mg/L)
Sediments (freshwater)	PNEC sediment (freshwater): 0.004 mg/Kg sediment ww	Extrapolation method: PNECs for the sediment compartment were derived using equilibrium partitioning. The approach consists of predicting the concentration in sediment based on the PNEC derived for the water compartment
Sediments (marine water)	PNEC sediment (marine water): 0.0004 mg/Kg sediment ww	Extrapolation method: PNECs for the sediment compartment were derived using equilibrium partitioning. The approach consists of predicting the concentration in sediment based on the PNEC derived for the water compartment
Sewage treatment plant	PNEC STP: 1.3 mg/L	Assessment factor: 10 Extrapolation method: One reliable study was available for evaluating the toxicity of EDGN to microorganisms involved in sewage treatment. A respiration inhibition test resulted in an EC10 of 13 mg/L and an EC50 of 260 mg/L. A PNEC was derived using each of the toxicity results and the lowest value was retained as the final PNEC for this compartment
Soil	PNEC soil: 0.0025 mg/Kg ww	Extrapolation method: partition coefficient. No toxicity data are available on soil organisms. Therefore, PNEC soil was derived using equilibrium partitioning method (EPM). (See text below)
Secondary poisoning		There are no indications of secondary poisoning according to the REACH Guidance on Information Requirements and Chemical Safety Assessment

PNEC soil

According to ECHA Guidance R.10, in absence of any ecotoxicological data on terrestrial organisms for Ethylene dinitrate, the PNEC soil was derived using equilibrium partitioning method (EPM).

Based on the data provided in the registration dossier, according to ECHA Guidance R7.c the registered substance would fall into soil hazard category 1 and, in this context, a screening assessment based on EPM for soil risk characterization can be applied. The resulting PNEC soil value is considered valid and, in this case, the EPM-based screening assessment is sufficient and acceptable for soil risk characterization.

7.8.5. Conclusions for classification and labelling

The substance has a harmonized classification according to Regulation EC No 1272/2008 (CLP00/ATP01) in Annex VI as specific target organ toxicity after repeated exposure (STOT Rep. Exp. 2). The available data on registered substance, do not allow a classification for the environment: the toxicity results on invertebrates and algae are above the threshold values for classification. The fish ecotoxicity information (utilised for the $PNEC_{freswater}$ calculation) derived from read-across with nitroglycerin.

7.9. Human Health hazard assessment

7.9.1. Toxicokinetics

Metabolism and excretion studies submitted on ethylene dinitrate show that the substance is quantitatively metabolized to ethylene mononitrate and inorganic nitrate and nitrite. The parent compound is rapidly and completely metabolized, and nearly all is excreted as inorganic nitrate. The substance shows no bioaccumulation potential.

eMSCA agrees on the conclusion reported in the registration dossier.

7.9.2. Acute toxicity and Corrosion/Irritation

Not evaluated.

7.9.3. Skin sensitisation

Data submitted by the Registrant(s) on skin sensitisation focus on both human and animal studies.

The available human study using ethylene dinitrate is indicating that ethylene dinitrate has a low skin sensitising potential. Skin sensitization may be observed in some patients exposed to Ethylene dinitrate. However, the likelihood of occurrence among the exposed population appears to be low. The guinea pig study conducted with nitroglycerin (analogue substance) suggests that NG is sensitizing. The animal study submitted was conducted using guinea pigs (10 per group) that were first sensitized intradermally on day 0, and again topically on day 7. On day 21 the animals were challenged topically with a closed patch for 24 h and readings were taken 24 h and 48 h post-challenge. A control group received the same induction and challenge applications excluding the test agent (generic guinea pig maximization test description). Using a dermal application of 3.41% NG in lactose/peanut oil carrier, “moderate” skin sensitization was observed in 40% of guinea pigs in the treatment group. However, the study is not valid (Klimisch 3) since there is no information on the animal strain used, no information on the induction and elicitation concentrations and information is lacking on the reactions of control animals. This evaluation on the reliability of the study is in line with the assessment of the German MAK commission, which also considered the guinea pig test as not reliable and not valid (MAK Value Documentation - Glycerintrinitrat, 2006).

Therefore, even if there are indications that ethylene dinitrate could be weakly sensitizing, the available data is not strong enough to warrant classification for skin sensitization. Moreover, a documentation for the exposure to professional and to the environment was provided by Registrant(s) where the strictly controlled condition are declared to apply also to professional use ensuring that neither human nor environmental exposure occurs.

eMSCA considers the documentation provided acceptable and concludes that no further data can be requested to clarify the concern on skin sensitisation.

Conclusion: The initial concern has not been clarified and is unresolved.

7.9.4. Repeated dose toxicity

Not evaluated.

7.9.5. Mutagenicity

No data are available on ethylene dinitrate. The *in vitro* genotoxicity data set presented by Registrant(s) is based on the read-across substance nitroglycerin.

For the *in vivo* genotoxicity assessment read-across with the substance nitroglycerin is applied, but the read-across justification document is missing.

Although the proposed read-across approach is considered scientifically acceptable by eMSCA, the reasoning and associated supporting evidence must be justified and documented thoroughly.

eMSCA considers the read-across proposal not in accordance with the requirements of Annex XI, 1.5 of REACH and therefore not acceptable in its current form.

Therefore, eMSCA is of the opinion that the available information is not sufficient to draw a conclusion on this endpoint and requested an up-date of the justification document. In line with the request made in the decision, eMSCA adopted a stepwide approach for this substance asking the Registrant(s) firstly to provide reliable information on the risk management measures (RMMs) and Operational Conditions (OCs) adopted in order to prevent exposure of the workers and release to the environment of ethylene dinitrate.

In case the provided information on exposure and uses would indicate release to the environment and exposure to workers, the eMSCA could consider a second decision to clarify the concern on genotoxicity/mutagenicity.

Following the decision, the Registrant(s) provided a documentation for the exposure to professional and to the environment where the strictly controlled conditions are declared to apply also to professional use ensuring that neither human nor environmental exposure occurs. eMSCA considers the documentation provided acceptable and concludes that no data requests are needed following SEV to clarify the concern on genotoxicity/mutagenicity

Conclusion: The endpoint mutagenicity has not been clarified.

7.9.6. Carcinogenicity

No data are available for carcinogenicity or repeated dose toxicity on ethylene dinitrate. The registration dossier contained chronic toxicity study using the read-across substance nitroglycerin that was administered to rats by feeding. The study was conducted equivalent or similar to the OECD 452 with reliability 2 and deemed not GLP compliant. The result indicated the incidence of neoplastic changes at the highest dose group in males (363 mg/kg/day) and females (434 mg/kg/day). These were hepatocellular carcinoma and cholangiofibrosis in the liver, and cell tumors in the testis (pressure on the tubules, aspermatogeneis).

eMSCA rejected the read-across and adopted a stepwise approach to address the concern on carcinogenicity and genotoxicity by requesting firstly reliable information on the risk management measures (RMMs) and Operational Conditions (OCs) adopted in order to prevent exposure of the workers and release to the environment of ethylene dinitrate.

Due the declared use in strictly contolled condition also to professional use ensuering that neither human nor environmental exposure occurs, no further action is requested. See also above on mutagenicity.

Conclusion: The additional concern has not been clarified and is unresolved

7.9.7. Toxicity to reproduction (effects on fertility and developmental toxicity)

The Read-across based on a 3-generation study published in 1978 on nitroglycerin has been used in evaluating developmental toxicity in the registration dossier. No self-classification has been proposed for reproductive toxicity and the only study presented is old and the reliability cannot be assessed. Additionally, the substance activates DART (Developmental And Reproductive Toxicity) alerts for developmental/reproductive toxicity and ED properties.

The Registrant(s) provided documents confirming that all identified uses are under strictly controlled conditions, ensuring that neither human nor environmental exposure occurs. Moreover, the Registrant(s) provided a declaration from a CRO that testing the substances according to the relevant test guidelines is technically not possible due the explosive properties of the substance. eMSCA considers the documentation provided acceptable.

Conclusion: Overall, the initial concern has not been clarified and is unresolved.

7.9.8. Hazard assessment of physico-chemical properties

Not evaluated.

7.9.9. Conclusions of the human health hazard assessment and related classification and labelling

Not relevant for this evaluation.

7.10. Assessment of endocrine disrupting (ED) properties

As described in Section 7.9.7, the substance activates DART alerts for both developmental/reproductive toxicity and ED properties. To conclude on such hazards and to fill the related gaps of knowledge, further studies should be to overcome both i) the nitroglycerin-based read-across relying on the obsolete 1978 3-generation study, and ii) the overall absence of studies (either *in silico* or *in vitro* or *in vivo*) dealing with ED-related outcomes.

Registrant(s) provided documents confirming that all identified uses are under strictly controlled conditions, ensuring that neither human nor environmental exposure occurs. Moreover, the Registrant(s) provided a declaration from a CRO that testing the substances according to the relevant test guidelines is technically not possible due the explosive properties of the substance. eMSCA considers the documentation provided acceptable.

Conclusion: Overall, the initial concern has not been clarified and is unresolved.

7.11. PBT and VPVB assessment

In the updated CSR, Lead Registrant(s) applied a weight of evidence approach that implied recent testing data and QSAR model predictions for Ethylene dinitrate, read-across by empirical data for nitroglycerine. According to the Registrant(s) the PBT conclusions were as follows:

- Not P (based on read-across from nitroglycerine);

- Not B ((based on QSAR); and,

- Not T (based on empirical testing and read-across from nitroglycerine).

The eMSCA however did not accept the Registrant(s) conclusion providing the following considerations:

7.11.1. Persistence

No testing data are available on ethylene dinitrate biodegradation. The read-across study from NG indicates that the substance is stable to hydrolysis. Results by read-across with NG do not allow to confirm the ready biodegradability.

Read-across studies

Despite claiming uncertainties on the results, Registrant(s) proposed a Weight of evidence approach for P evaluation, based on the above mentioned NG read-across information (3 studies), concluding that ethylene dinitrate is not persistent (P) according to the REACH Regulation (Annex XIII) criteria and applicable guidance. The study on nitroglycerin is based on old tests (1978, 1980) without Guideline indications.

eMSCA raises doubts about the relevance and validity of supporting biodegradation studies on NG. In fact, based on the little information available, there is not sufficient evidence to conclude on persistency (e.g. no standard test guidelines, without evidence of the use of not pre-adapted inoculums, suitable concentration of test substance, etc.).

Summarising, there are no biodegradation studies on the Substance ethylene dinitrate; and the screening results on biodegradation by read-across with NG do not allow to confirm the ready biodegradability of ethylene dinitrate.

Therefore, the Persistence of ethylene dinitrate cannot be excluded according to Annex XIII criteria of REACH.

7.11.2. Bioaccumulation

Regarding information on Aquatic Bioaccumulation, a measured value of log Kow =1.16 at 20°C (Hansch et al. 1995) is available. Registrant(s) provided an additional log Kow = 2.1, estimated by QSAR application. Both values are well below the screening trigger value of 4.5. Although estimated aquatic BCF is lower than 2000, there is concern for potential bioaccumulation in air-breathing organisms due to an estimated (KOAWIN) Log $K_{OA=}$ 5.78 (see section 7.7.3).

Therefore, the bioaccumulation potential of the Substance cannot be excluded according to Annex XIII criteria of REACH.

7.11.3. 3) Toxicity

Based on ecotoxicity data set for ethylene dinitrate / nitroglycerine that includes acute and chronic effect values for all three trophic levels, the substance does not meet the criteria to be identified as T.

The substance has a harmonised classification according to Regulation EC No 1272/2008 (CLP00/ATP01) in Annex VI, as specific target organ toxicity after repeated exposure (STOT Rep. Exp. 2).

Therefore, according to Annex XIII of REACH regulation, the Substance meets the Toxicity criteria.

7.11.4. Overall eMSCA conclusion

- potential P/vP;

- potential B/vB;

- T (STOT RE 2).

The Registrant(s) provided a declaration from a CRO that testing the Substances according to the relevant test guidelines is technically not possible due to the explosive properties of the Substance. Moreover, the Registrant(s) provided documents confirming that all the

identified uses are under strictly controlled conditions. The eMSCA considers the documentation provided acceptable.

Summarising, the information available does not allow to conclude on PBT/vPvB properties of ethylene dinitrate.

7.12. Exposure assessment

7.12.1. Human health

7.12.1.1. Worker

For all the identified uses (Manufacture of substance; End use of substance in a preparation (explosive)), exposure scenarios have been developed and a quantitative estimation of the exposure levels has been carried out. The exposure levels have been estimate by using the ECETOC TRA worker v2.3.

Risk management measures (RMMs), such as Local Exhaust Ventilation and Personal Protective Equipments (gloves) are proposed to adequate control the risk.

Registrant(s) are requested to provide refinement of the exposure assessment as to lower the RCRs (see Section 7.13 Risk characterisation).

7.12.1.2. Consumer

Not applicable.

7.12.2. Environment

The used tool for environmental exposure by all Registrants is EUSES v2.1.2.

The Lead Registrant updated the Registration dossier (nov. 2019) providing documents confirming that exposure to the environment does not occur due to its extreme explosiveness. In particular:
- ethylene dinitrate is fixed in the blasting gel which is sealed in cartridges preventing any direct contact of ethylene dinitrate with the environment,
- cartridges are only handled by authorized professionals at blasting zones eliminating any non-foreseen use which might result in environmental exposure,
- no ethylene dinitrate remains after explosion, since it is completely converted into carbon dioxide, nitric oxides and water vapour.

7.12.2.1. Aquatic compartment (incl. sediment)

No releases to aquatic compartment (incl. sediment) are claimed, consequently for all Exposure Scenarios, the release factors is fixed = 0%.

Indeed the substance is completely converted into carbon dioxide, nitric oxide and water during professional use. Thus, in some case, the used ERCs are misleading as exposure of the substance during professional use can be regarded as not relevant. Cartridges not exploding as foreseen will always be brought to explosion for safety reasons. Thus, no "unexploded cartridges" exist which could accidently lead to a release of the substance to the environment.

7.12.2.2. Terrestrial compartment

An exposure to soil can be excluded due to the applied strictly controlled conditions.

Registrant(s) state that the A-table of the TGD (2003) Industrial Category (IC)=2/ Use Category (UC)=18 (explosive) are used to calculate the fraction of tonnage released to

soil. The local PECs in soil and groundwater are calculated taking into account the air deposition.

In general Registrant(s) claim a Biological site specific STP with an effectiveness of ca. 87 %. The Registrant(s) state that the sludge is not applied in agricultural soil.

7.12.2.3. Atmospheric compartment

An exposure of air cannot be totally excluded just for one scenario, during transfer of the substance. Thus, exposure calculations for the air compartment were included to assess the chemical safety. The Fraction released to air is estimated as 0.05%, according to Technical Guidance Document on Risk Assessment, Part II (2003), section IC 2 Chemical Industry: Basic Chemicals (Formulation), table A2.1 Main Category (MC) = 1b, Isolated intermediates stored on site.

7.12.3. Combined exposure assessment

Some Registrants, having only one manufacture site, state that the combined for all relevant emission/release sources is not applicable, as each exposure scenario occurs at different sites.

The other Registrants, having more than one manufacture sites, state that the combined for all relevant emission/release sources is not applicable for environmental exposure at local level. Combined exposure for two sites was taken into consideration for estimating environmental exposure at regional level.

7.13. Risk characterisation

7.13.1. Human Health

7.13.1.1. Workers

For all the relevant scenarios identified (Manufacture of substance; End use of substance in a preparation (explosive)) a quantitative risk assessment has been carried out. The exposure levels have been estimated by using the ECETOC TRA worker v2.3. DNELs were derived for workers for long-term exposure *via* both the dermal and inhalative route of exposure.

Although a safe use has been identified for each Exposure Scenario (ES), and Risk Management Measures have been identified demonstrating an adequate risk control, eMSCA makes some remarks regarding the outcome of the risk assessment.

First of all, in the ES 1 (*i.e.*, Manufacture of substance), risk characterization ratios (RCRs) calculated for the individual contributing scenario (*i.e.*, PROC), combining contributes from the different routes of exposure, result to be lower than the trigger value. Nevertheless, in the event worker is involved in more than one tasks during the shift, the cumulative RCR calculated results to be higher than 1, and a potential unacceptable risk can occur.

Secondly, in the ES 2 (*i.e.*, End use of substance in a preparation (explosive)) the RCR, derived by combining the exposure levels estimated for all the routes of exposure, results are very close to the trigger value. So that, the eMSCA believes that a safe use cannot be fully guaranteed under the conditions established in the scenario.

In consideration of all the above, Registrant(s) should refine the risk characterization. However, Registrant(s) provided documents confirming that all identified uses are under strictly controlled conditions, ensuring that neither human nor environmental exposure occurs. eMSCA considers the documentation provided acceptable.

7.13.1.2. Consumers

Not relevant.

7.13.1.3. Indirect exposure of humans via the environment.

No risk has been identified.

7.13.2. Environment

7.13.2.1. Aquatic compartment (incl. sediment).

The risk is considered to be controlled (RCR<1).

7.13.2.2. Terrestrial compartment

The risk is considered to be controlled (RCR<1).

7.13.2.3. Atmospheric compartment

PEC local for air is not compared with the PNEC air because this latter was not available.

7.13.2.4. Microbiological activity in sewage treatment systems

The risk is considered to be controlled (RCR<1).

7.13.3. Overall risk characterization

Human health (combined for all exposure routes): no risks have been identified for all the scenarios considered. Additional RMM could be envisaged by the Registrant(s) in case the workers are involved in different tasks during the shift.
Environment (combined for all exposure routes): no risks have been identified for all the scenarios considered.

7.14. References

Aside from the registration dossier(s), no other additional sources were used. Registration dossier for Ethylene dinitrate, European Chemicals Agency.

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7.15. Abbreviations

AF	Assessment factor
BW	Body weight
CAS	Chemical abstracts service
C&L	Classification and labelling
CLP	Classification, labelling and packaging (Regulation (EC) No1272/2008)
CMR	Carcinogenicity, mutagenicity and toxicity to reproduction
CRO	Contract Reasearch Organisation
CSR	Chemical Safety Report
DART	Developmental and Reproductive Toxicity
DNEL	Derived no effect level
eMSCA	Evaluating Member State Competent Authority
ES	Exposure Scenario
IC	Industrial Category
MC	Main Category
NG	Nitroglycerin
NOAEL	No Observed Adverse Effect Level
NOEC	No Observed Effect Concentration
OECD	Organisation for Economic Co-operation and Development
OC	Operational Conditions
PBT	Persistent, Bioaccumulative, Toxic
PEC	Predicted Environmental Concentration
PNEC	Predicted No Effect Concentration
QSAR	Quantitative structure–activity relationship
RCR	Risk characterization ratio
RMMs	Risk Management Measures
STP	Sewage Treatment Plant
UC	Use Category
vPvB	Very Persistent and very Bioaccumulative