BUREAU FOR CHEMICAL SUBSTANCES

SUBSTANCE EVALUATION CONCLUSION

as required by REACH Article 48

and

EVALUATION REPORT

For

1,3,5-tris(oxiranylmethyl) -1,3,5-triazine-2,4,6(1H,3H,5H)-trione

EC No 219-514-3

CAS No 2451-62-9

Evaluating Member State(s): Poland

Dated: September 2016

Evaluating Member State Competent Authority

MSCA name: Bureau for Chemical Substances
Dowborczykow 30/34 Str.
90 – 019 Lodz,
Tel: + 48 42 25 38 440
Fax: + 48 42 25 38 440
Email: evaluation@chemikalia.gov.pl

Year of evaluation in CoRAP: 2015

Member State concluded the evaluation without any further need to ask more information from the registrants under Article 46(1) decision.

Further information on registered substances here:

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

DISCLAIMER

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

1,3,5-tris(oxiranylmethyl) -1,3,5-triazine-2,4,6(1H,3H,5H)-trione hereafter referred to as triglycidyl isocyanurate (TGIC) was originally selected for substance evaluation in order to clarify concerns about:

- suspected CMR,

- suspected PBT,

- wide dispersive use.

During the evaluation an additional concern was identified. TGIC has been reported to cause signs of respiratory disorders as dyspnoea, rhinitis, cough, wheezing and slight obstruction during spirometry with accompanying elevated level of blood eosinophils and serum total IgE. These symptoms may be related to occupational asthma and the classification as respiratory sensitizer may be considered.

2. OVERVIEW OF OTHER PROCESSES / EU LEGISLATION

TGIC is included on the Candidate List of Substances of Very High Concern for Authorisation as mutagen category 1B.

3. CONCLUSION OF SUBSTANCE EVALUATION

Table 1

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

4. FOLLOW-UP AT EU LEVEL

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

4.1.1. Harmonised Classification and Labelling

TGIC has been reported to induce asthma in the exposed workers. People working mainly as spray painters demonstrated the following symptoms: dyspnoea, rhinitis, cough, wheezing, slight obstruction during spirometry, elevated level of blood eosinophils and serum total IgE. The occupational asthma was confirmed by bronchial provocation testing. TGIC is included in the list of chemicals associated with occupational asthma (http://www.haz-map.com/OA1.html). Based on the available information eMSCA considers that a classification as: Resp. Sens. 1, H334 - May cause allergy or asthma symptoms or breathing difficulties if inhaled is warranted for TGIC.

5. CURRENTLY NO FOLLOW-UP FORESEEN AT EU LEVEL

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

During the evaluation process particular emphasis was put on the concerns listed in the Justification document for the selection of the candidate CoRAP substance. TGIC is already identified as Substance of Very High Concern due to its classification as Muta 1B, H340 (May cause genetic defects) and included in the candidate list.

The information on toxicity and ecotoxicity submitted in the registration dossier was considered as relevant and adequate for the purpose of this substance evaluation. The analysis of data demonstrated no PBT properties.

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

During the evaluation an additional concern was identified regarding respiratory damage. The eMSCA proposes an additional classification and labelling of TGIC as Resp. Sens. 1, H334 - May cause allergy or asthma symptoms or breathing difficulties if inhaled.

Part B. Substance evaluation

7. EVALUATION REPORT

7.1. Overview of the substance evaluation performed

Triglycidyl isocyanurate (TGIC) was originally selected for substance evaluation in order to clarify concerns about:

- suspected CMR,

- suspected PBT,

- wide dispersive use.

TGIC has been reported to induce asthma in the exposed workers. People working mainly as spray painters demonstrated the following symptoms: dyspnoea, rhinitis, cough, wheezing, slight obstruction during spirometry, elevated level of blood eosinophils and serum total IgE. The occupational asthma was confirmed by bronchial provocation testing. TGIC is included in the list of chemicals associated with occupational asthma (http://www.haz-map.com/OA1.html). Based on the available information eMSCA considers that a classification as: Resp. Sens. 1, H334 - May cause allergy or asthma symptoms or breathing difficulties if inhaled can be warranted for TGIC.

Table 4

EVALUATED ENDPOINTS	
Endpoint evaluated	**Outcome/conclusion**
Carcinogenicity/reproductive toxicity	Concerns not confirmed.
Environmental fate properties	PBT properties not confirmed.
Classification and labelling	The current classification supported. Additional classification as Resp. Sens. 1, H334 is warranted.

7.2. Procedure

The evaluation was performed based on the registration dossier (IUCLID file) and Chemical Safety Report (CSR) as well as on the other additional information available in scientific databases and publications.

In the endpoints assessed there is a reference to the registration dossier and not to the specific reports included in the dossier, except for cases where data come from publically available scientific information.

The available information was assessed regarding the reliability for evaluation of the main grounds of concern. The particular emphasis was placed on the possible PBT properties of TGIC and its potential carcinogenicity and reproductive toxicity. Other aspects as physical and chemical properties have been checked and described in general.

The results of the evaluation are documented in this report.

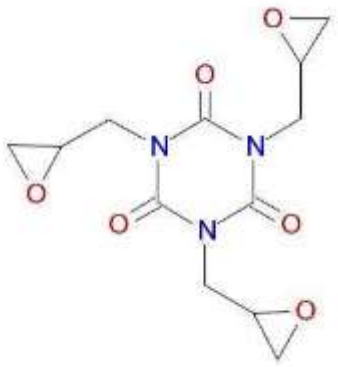
7.3. Identity of the substance

Table 5

SUBSTANCE IDENTITY	
Public name:	TGIC
EC number:	219-514-3
CAS number:	2451-62-9
Index number in Annex VI of the CLP Regulation:	615-021-00-6
Molecular formula:	C12H15N3O6
Molecular weight range:	297.264 g/mol
Synonyms:	TGIC; Teroxirone; TEPIC; Tris(2,3-epoxypropyl) isocyanurate; Tris(2,3-epoxypropyl)-s-triazine-2,4,6(1H,3H,5H)-trione; Isocyanuric Acid Triglycidyl Ester; 1,3,5-Triglycidylisocyanuric acid; Isocyanurate de triglycidyle (French); 1,3,5-tris(oxiranylmethyl)- 1,3,5-triazine-2,4,6(1H,3H,5H)-trione; Tris(epoxypropyl) isocyanurate; 1,3,5-tris(2,3-epoxypropyl)-s-triazine-2,4,6(1H,3H,5H)-trione; N,N',N''-Triglycidyl isocyanurate;

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

Structural formula:



Multiconstituent/UVCB substance/others

Table 6

Constituent			
Constituents	**Typical concentration**	**Concentration range**	**Remarks**
1,3,5-Triazine-2,4,6(1H,3H,5H)-trione, 1,3,5-tris[(2R)-2-oxiranyl methyl]-	< 11.9 % (w/w)	>= 11.75 — <= 12.5 % (w/w)	Theoretical value according to probability. A method for the quantitative separation of the isomer mixture is not known.
1,3,5-Triazine-2,4,6(1H,3H,5H)-trione, 1,3,5-tris[(2S)-2-oxiranyl methyl]-	< 11.9 % (w/w)	>= 11.75 — <= 12.5 % (w/w)	Theoretical value according to probability. A method for the quantitative separation of the isomer mixture is not known.
1,3,5-Triazine-2,4,6(1H,3H,5H)-trione, 1-[(2R)-2-oxiranylmethyl] -3,5-bis[(2S)-2-oxiranylmethyl]-	< 35.6 % (w/w)	>= 35.25 — <= 37.5 % (w/w)	Theoretical value according to probability. A method for the quantitative separation of the isomer mixture is not known.
1,3,5-Triazine-2,4,6(1H,3H,5H)-trione,	< 35.6 % (w/w)	>= 35.25 — <= 37.5 % (w/w)	Theoretical value according to probability. A

1,3-bis[(2R)-2-oxiranylmethyl]-5-[(2S)-2-oxiranylmethyl]-			method for the quantitative separation of the isomer mixture is not known.

Impurity			
Constituents	**Typical concentration**	**Concentration range**	**Remarks**
1,3-bis(oxiranylmethyl)-5-(2-hydroxy-3-chloropropyl)-1,3,5-triazine-2,4,6(1H,3H,5H)-trione	ca. 0.8 % (w/w)	> 0.0 — < 1.0 % (w/w)	
1,3-bis(oxiranylmethyl)-5-(2,3-dihydroxypropyl)-1,3,5-triazine-2,4,6(1H,3H,5H)-trione	ca. 1.8 % (w/w)	> 0.0 — < 3.0 % (w/w)	
5,5'-hydroxyisopropylidenedi((1,3-bis(oxiranylmethyl)-1,3,5-triazine-2,4,6(1H,3H,5H)-trione)	ca. 1.4 % (w/w)	> 0.0 — < 2.0 % (w/w)	

7.4. Physico-chemical properties

Table 7

OVERVIEW OF PHYSICOCHEMICAL PROPERTIES	
Property	**Value**
Physical state at 20°C and 101.3 kPa	Form: particulates Colour: white Odour: odourless
Vapour pressure	The vapour pressure of TGIC has been determined experimentally and by calculation. In the experimental study the value found was 0.0072 Pa at 20°C, and via calculation a lower value of 0.00091Pa (at 60°C) has been determined.
Water solubility	Two values have been reported for the water solubility of 9000 mg/l and 10'000 mg/l.
Partition coefficient n-octanol/water (Log Kow)	-0.8, at 20°C

Flammability	Non flammable
Explosive properties	Non explosive
Oxidising properties	Not an oxidizing
Granulometry	TGIC is sold as a granulate with an average particle size diameter of 4-8 mm. Smaller particles are possible due to a transport shaking and an abrasion between particles. However, this fraction generally remains negligible.
Stability in organic solvents and identity of relevant degradation products	From the measurements of its solubility over a certain period of time (5 days) it can be stated that TGIC is fully stable over this short period of time in organic solvents, contrary to the stability in water.
Dissociation constant	pKa is not applicable for TGIC. TGIC has no functional groups to dissociate, it remains in water as parent molecule or is hydrolyzed, depending on pH.

7.5. Manufacture and uses

7.5.1. Quantities

Table 8

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

7.5.2. Overview of uses

Table 9

USES	Use(s)
Uses as intermediate	-
Formulation	• Industrial formulation of powder coatings : Bending and extruding mixtures of resin, hardener(TGIC), pigments and additives and formation of pellets • Industrial packaging of solder mask ink • Formulation of molding resin application • Industrial formulation of solder mask inks • Manufacture of adhesive tape • Industrial packaging of powder coating
Uses at industrial sites	• Industrial application of Powder coatings: electrostatic application of powder to objects to be crosslinked at high temperature

	• Industrial application of Solder resist inks • Industrial application of electronic adhesive tape • Industrial application of solder resist inks
Uses by professional workers	-
Consumer Uses	-
Article service life	-

Table 10

Uses advised against	**Use(s)**
Uses as intermediate	-
Formulation	-
Uses at industrial sites	• Use as hardener in dental applications , application in house-hold products • Use as hardener in dental applications , application in house-hold products
Uses by professional workers	-
Consumer Uses	-
Article service life	-

7.6. Classification and Labelling

7.6.1. Harmonised Classification (Annex VI of CLP)

Table 11

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)**		
615-021-00-6	1,3,5-tris(oxiranylmethyl)-1,3,5-triazine-2,4,6(1H,3H,5H)-trione TGIC	219-514-3	2451-62-9	Acute Tox. 3 Skin Sens. 1 Eye Dam. 1 Acute Tox. 3 Muta. 1B STOT RE 2 Aquatic Chronic 3	H301 H317 H318 H331 H340 H373 H412		

7.6.2. Self-classification

Self-classification notifications for TGIC (EC Number: 219-514-3) are available in the C&L Inventory (http://echa.europa.eu/pl/information-on-chemicals/cl-inventory-database/-/cl-inventory/view-notification-summary/128251). In the following table the additional notified classification for TGIC is given (dating of October 2015).

Table 12

Classification		labelling		Number of Notifiers
Hazard Class and Category Codes	**Hazard Statement Codes**	**Hazard Statement Codes**	**Pictograms, Signal Word Code**	
Acute Tox. 4 Acute Tox. 4 Skin Irrit. 2	H302 H332 H315	H302 H332 H315	Dgr	3

7.7. Environmental fate properties

The data submitted in registration dossier are considered to be sufficient for evaluation of the environmental fate properties of TGIC. All other constituents listed in Section 7.3 represent a mixture of TGIC isomers, therefore it is expected that they have the same or even less unfavorable environmental fate properties than TGIC. Two of the three impurities reported in section 7.3 are structurally similar to TGIC and they have either two hydroxyl groups or hydroxyl group and chlorine in place of one epoxide ring. This suggests that these impurities have greater polarity and therefore they do not pose greater environmental concern in comparison to TGIC. The environmental fate of the impurity 5,5'-hydroxyisopropylidene di((1,3-bis(oxiranylmethyl)-1,3,5-triazine-2,4,6(1H,3H,5H)-trione, is further discussed in PBT assessment section.

7.7.1. Degradation

Abiotic degradation
Two studies in accordance with OECD Guideline No. 111 "Hydrolysis as a function of pH" conducted at different pH values and at different temperatures are available for TGIC. The test results indicate that the main products of hydrolysis are: dihydroxy, tetrahydroxy- and hexahydroxy-TGIC. On the basis of the studies, the longest half-time for TGIC is 6.6 days at 22ºC (pH 7).
Although the applicant did not provide any phototransformation study for TGIC, studies are available for other triazine herbicides (atrazine, simazine), which can be used as surrogates for TGIC. For example, half-life for atrazine is about 1 day. As TGIC is an epoxide, it can be assumed that its half-life should not be longer.

Biotic degradation
The key study in accordance with OECD Guideline 301 B, conducted with GLP, showed very low degradation level of TGIC. However, two other supporting studies, on ready biodegradability and inherent biodegradability, indicate that TGIC is inherently biodegradable, with the percentage of bio-degraded substance up to 48 %. It may be assumed that the variability of the results may be connected with the low solubility of TGIC in the buffered salt solution required for these tests. The test results indicate that the main product of biodegradation is 3,5-bis-carboxymethyl-2,4,6-trioxo[1,3,5]triazinan-1-yl)-acetic acid. Biodegradation in soil, water and sediment has not been experimentally tested.

7.7.2. Environmental distribution

Koc for TGIC is 31.7 (at 20°C), which corresponds to Log Koc of 1.5. Henry's law constant is 0.003 Pa m^3/mol. In line with model calculations (EQC Level I-III), when TGIC emission occurs via air, most of the substance gets to the water, while concurrent emission to air, water and soil leads to concentration of TGIC in soil, and to lesser extent in water.

7.7.3. Bioaccumulation

Based on a log Kow = -0.8 it can be stated that the bio-accumulation / bioconcentration potential is low.

7.8. Environmental hazard assessment

The data submitted in registration dossier are considered to be sufficient for evaluation of environmental hazard assessment of TGIC.

7.8.1. Aquatic compartment (including sediment)

Only limited ecotoxicological data for TGIC are available. The 96 h LC_{50} obtained in static studies on zebra fish (*Brachydanio rerio*) exceeded 77 mg/L (average of measured concentrations at 0 and 96 h). The 24 h EC_{50} in a static *Daphnia magna* immobilisation test was above 100 mg/L, with a NOEC of 58 mg/L. The 72 -hour toxicity in green algae (*Desmodesmus subspicatus*) showed an EC_{50} (growth rate of algae) of 29 mg/l and a NOEC = 6.3 mg/l. These results indicate that TGIC is moderately toxic to aquatic fauna under conditions of acute exposure. In addition, TGIC is rapidly hydrolized in water to 1,3,5-tris(hydroxypropyl) -1,3,5-triazine-2,4,6-(1H, 3H, 5H) -trion, an alcohol of rather low toxicity, as it can be expected from other alcohols characteristics (phloroglucinol, CAS no. 108-73-6).

Environmental exposure to TGIC is expected to be minimal as dust extractors and other pollution control devices will remove particulate waste for disposal. TGIC contained in such waste will be effectively immobile after consignment to landfill, particularly if most waste powder is heat cured beforehand. Any residues which remain free and enter the open environment will have limited persistence because of the lability of the epoxide substituents. As an example of release from a formulation plant, ICI Dulux estimates daily releases of TGIC to sewer of 15 kg. Passage through Werribee Treatment Complex (500 ML daily flow) would dilute that release to a concentration of 30 ppb, assuming that mixing is uniform and no removal takes place. That clearly provides an adequate safety margin for aquatic fauna, even if other waste streams containing TGIC are added, since the NOEC for daphnids is higher than this level more than 1000 times. The predicted environmental hazard is low. (NICNAS, (1994), Priority Existing Chemical No. 1 - Triglycidyl Isocyanurate, full Public Report, National Industrial Chemicals Notification and Assessment Scheme. Canberra, Australian Government Publishing Services, April 1994.)

7.8.1.1. Fish

The results of key study (reliability 2) performed according to OECD guideline 203 in *Danio rerio* indicated that 96 h LC_{50} value is > 77 mg/l. Only a single dose was tested with a nominal concentration of 100 mg/l and a measured concentration of 77 mg/l. No mortality occurred and no signs of toxicity were recorded.

No long-term fish toxicity studies have been performed, as in the acute toxicity study the LC_{50} was > 77 mg/l and because the environmental concentrations are expected to be low due to rather fast hydrolysis of TGIC in water.

TGIC is considered to have a moderate toxic potential towards fresh water fish.

7.8.1.2. Aquatic invertebrates

The results of the key study (reliability 2) performed according to OECD guideline 202 in *Daphnia magna*, with the major deviation of a shorter exposure time, indicated that 24 h EC50 is > 100 mg/L. In the high dose of 100 mg/l 4/20 animals were immobilized (20%), in the second dose of 58 mg/l 0/20 animals were immobilized (0%). The nominal concentrations were in the range, namely 90 - 112 % of the nominal concentrations as average of 0 and 24 hours. However, the short exposure period (24 instead of 48 hrs) may be taken with caution. The value for 48 hrs could be significantly lower. TGIC is considered to have a moderate toxic potential towards fresh water invertebrates.

7.8.1.3. Algae and aquatic plants

The results of key study (reliability 2) performed according to OECD guideline 201 *Desmodesmus subspicatus* indicated that 72 h EC50 is at 29 mg/L. The tested dose levels were 0, 0.21, 0.72, 2.1, 6.3, 19.4, and 63.4 mg/l. The EC_{50} was determined based on the growth rate of algae (number of cells).

TGIC is considered to have a moderate toxic potential towards fresh-water algae.

7.8.2. Terrestrial compartment

No terrestrial toxicity studies have been performed.

Environmental exposure to TGIC is expected to be minimal as dust extractors and other pollution control devices will remove particulate waste for disposal. TGIC contained in such waste will be effectively immobile after consignment to landfill, particularly if waste powder is heat cured beforehand. Any residues which remain free and enter the open environment will have limited persistence because of the lability of the epoxide substituents (NICNAS (1994) Priority Existing Chemical No. 1- Triglycidyl Isocyanurate, full public report, National Industrial Chemicals Notification and Assessment Scheme. Canberra, Australian Government Publishing Service, April).

The results of aquatic toxicity tests indicate that TGIC is considered to have a moderate toxic potential towards aquatic fauna under conditions of acute exposure. Chronic effects would not be expected because of limited persistence, both in water as well as in soil.

7.8.3. Microbiological activity in sewage treatment systems

Activated Sludge, Respiration Inhibition Test (key study, reliability 2) with TGIC was performed according to OECD guideline 209. The EC_{50} of > 100 mg/l and the $EC_{20}/10$ > 100 mg/l can be considered as practically non-toxic and no damage of sewage treatment plants is to be expected.

No further test have been conducted as environmental concentrations of TGIC are extremely low.

Based on the results the toxicity of TGIC towards sludge bacteria is considered to be low.

7.8.4. PNEC derivation and other hazard conclusions

Table 11

PNEC DERIVATION AND OTHER HAZARD CONCLUSIONS		
Hazard assessment conclusion for the environment compartment	**Hazard conclusion**	**Remarks/Justification**
Freshwater	PNEC aqua (freshwater): 0.029 mg/L	Assessment factor: 1000 Extrapolation method: assessment factor The PNEC is based on the lowest short-term test with algae with an EC50 = 29 mg/l, and an assessment factor = 1000 is applied. This AF is justified by the fact that three aquatic species have been tested, but only in short-term

		tests. All other NOECs were higher and are not used for the calculations.
Marine water	PNEC aqua (marine water): 0.0029 mg/L	Assessment factor: 10000 Extrapolation method: assessment factor No marine aquatic species have been tested, but it is assumed that in the marine environment TGIC is quickly hydrolysed, and thus, shows even less toxicity. This will lead to higher PNEC-values. However, for worst case assumptions, for the marine environment the same values were taken, but an additional AF=10 was applied.
Intermittent releases to water	PNEC aqua (intermittent releases): 0.29 mg/L	Assessment factor: 100 Extrapolation method: assessment factor For the intermittent exposure a PNEC of 0.29 was assumed to be reasonable, using the EC50 of the short term test and applying an AF=100, as indicated in the Guidance.
Sediments (freshwater)	PNEC sediment (freshwater): 0.196 mg/kg sediment dw	Extrapolation method: partition coefficient No studies on sediment dwelling organisms have been conducted, and therefore, the PNEC sediment was derived using the equilibrium partitioning method. Regarding the calculations given in the guidance, the PNEC sediment was calculated as followed: PNEC sediment (wet weight) = Ksusp-water/RHOsusp * PNECwater * 1000 with Ksusp-water = 1.69 m3.m-3 and RHOsusp = 1150 kg.m-3. And a conversion factor of PNECsediment as wet weight to dry weight of 4,6 was applied.
Sediments (marine water)	PNEC sediment (marine water): 0.0196 mg/kg sediment dw	Extrapolation method: partition coefficient The PNEC marine-sediment was derived using the equilibrium partitioning method. Regarding the calculations given in the guidance, the PNEC marine-sediment was calculated as followed : PNECmarine sed (wet weight) = Ksusp-water/RHOsusp * PNECsalt water * 1000 with Ksusp-water = 1.69 m3.m-3 and RHOsusp = 1150 kg.m-3. And a conversion factor of

		PNECsediment as wet weight to dry weight of 4.6 was applied.
Sewage treatment plant	PNEC STP: 10 mg/L	Assessment factor: 10 Extrapolation method: assessment factor A concentration of 100 mg/l of TGIC was the NOEC or EC10, and did not inhibit significantly bacterial respiration measured by CO2 production over a period of 3 hours. The bacteria were from municipal sludge, and showed no signs of toxicity. The assessment factor (AF) =10 was taken according to the guidance.
Soil	PNEC soil: 0.022 mg/kg soil dw	Extrapolation method: partition coefficient No tests have been performed on soil living animals, bacteria or plants. Therefore, the PNEC Soil was derived using the equilibrium partitioning method. Regarding the calculations given in the guidance, the PNEC soil was calculated as followed: PNECsoil (wet weight) = Ksoil-water/RHOsoil * PNECwater * 1000 with Ksoil-water = 1.15 m3.m-3 and RHOsoil = 1700 kg.m-3. And a conversion factor of PNECsoil as wet weight to dry weight of 1,13 was applied.
Air	-	-
Secondary poisoning	No potential for bioaccumulation	

7.8.5. Conclusions for classification and labelling

According to CLP requirements TGIC is classified for the environment: Aquatic chronic 3, H412.

7.9. Human Health hazard assessment

TGIC is an epoxide resin containing approximately 76-80% of the alfa isomer and approximately 20-24% of the beta isomer (Screening-level hazard characterization, Triglycidyl isocyanurate. U.S. Environmental Protection Agency, 2009). The data refer to α-TGIC are used as an indicative values for β-TGIC.

7.9.1. Toxicokinetics

The human data indicates that TGIC does not bioaccumulate in the organism. Following intravenous infusions plasma concentration of the substance rapidly reached plateau value and remained constant during infusion. The mean plasma elimination half-time ranged between 0.9-10 min. dependently on the dose (study reports in the registration dossier, The Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals 128. Triglycidyl isocyanurate Lindell B. and Montelius J., 2001). The other available toxicokinetic data come from the animal studies (rats) following oral and intraperitoneal administration of TGIC. The studies show that metabolism of TGIC involves hydrolysis of the epoxy group catalysed by microsomal epoxide hydrolase (Toxicological evaluation and limit values for 2-ethylexyl acryate, propylene carbonate, quaternary ammonium compounds, triglycidyl isocyanurate and tripropyleneglycol diacrylate. Berthelsen P., Beltoft V., Thorup I., Soborg I. and Nielsen N. Environmental Project No 555, 2000). Excretion of TGIC is expected to be primarily in urine.

7.9.2. Acute toxicity and Corrosion/Irritation

The eMSCA supports classification of TGIC as:
Acute Tox 3 H301 (Toxic if swallowed),
Acute Tox 3, H331 (Toxic if inhaled),
Eye Dam. 1, H318 (Causes serious eye damage).

7.9.3. Sensitisation

Skin sensitisation

The eMSCA supports classification of TGIC as Skin Sens. 1 (May cause an allergic skin reaction).

Respiratory sensitisation - human data

According to the case report (reliability 2) the exposure to TGIC in a polyester powder paint containing 4% of TGIC can cause asthma symptoms. TGIC has been reported to induce asthma. The exposed workers can become sensitised to TGIC and may then develop an asthmatic reaction.

The available information on asthma cases following exposure to TGIC is shown in the table below:

Case description	**Symptoms**	**Reference (publically available)**
28-year-old female exposed to powder paint containing 2.5-10% TGIC.	4 months after beginning work developed recurrent episodes of cough, dyspnea, shortness of breath and wheezing. Physical examination, blood tests and spirometry results were normal. Skin prick test were negative. During nasal provocation testing with 4% TGIC, a 20% decrease of forced	Sastre et al, 2011, Quirce and Sastre, 2011

	expiration volume (FEV) was observed accompanied by symptoms such as cough and wheezing. These symptoms were reversible within 24 hours. The analysis revealed no IgE in ELISA testing.	
Six workers exposed as bystanders to heated TGIC	Following TGIC exposure, 3 subjects had dual asthmatic reaction and 1 had an isolated late reaction. Most of the subjects suffer from upper airway soreness and headache. The occupational asthma was confirmed by peak expiratory flow measurements (consistently lower PEF at work with no discernible significant early or late reaction).	Anees et al, 2011
38-year-old man employed in the air-spraying of metal frames with polyester powder pigments containing TGIC.	Respiratory symptoms (rhinitis, cough, dyspnea and wheezing) appeared after of the cutaneous symptoms. They decreased during weekends and cleared completely on vacations. The contact dermatitis was confirmed by patch testing (TGIC 0.5% and 5%)and the occupational asthma was confirmed by bronchial provocation testing: two challenges to an aerosol containing 0.05% and 0.1% of TGIC. No immunologic evidence of specific IgE-mediated reaction was observed.	Meuleman et al, 1999
38-year-old man working as a spray painter using a polyester powder paint containing 4% TGIC.	Occupational asthma was diagnosed based on the inhalation challenge tests with a paint containing 4% of TGIC. A dual reaction in PEF and a late 23% fall in FEV was observed.	Pirilla et al, 1997 (abstract)

TGIC is included in the list of chemicals associated with occupational asthma (http://www.haz-map.com/OA1.html)

According to Workplace Hazardous Materials Information System (WHMIS) TGIC is classified as respiratory sensitizer Cat. 1B.
(http://www.csst.qc.ca/en/prevention/reptox/Pages/information-sheet-whmis.aspx?langue=a&no_produit=204438).

There are other evidence that the substance can cause occupational asthma in humans. In people working mainly as spray painters the following symptoms were observed: dyspnoea, rhinitis, cough, wheezing, slight obstruction during spirometry, elevated level of blood eosinophils and serum total IgE. The occupational asthma was confirmed by bronchial provocation testing (Meuleman et al, 1999, Sastre et al, 2011, Anees et al, 2011).

Based on the available information the eMSCA considers that classification of TGIC as: Resp. Sens. 1, H334 - May cause allergy or asthma symptoms or breathing difficulties if inhaled may be needed.

7.9.4. Repeated dose toxicity

The main effects observed following oral, inhalation and intravenous exposure to different concentrations of TGIC were haematological effects as reduced number of leucocyte and lymphocyte, effects on the mesenteric lymph system and depletion of lymphocytes in the thymus and spleen. In dogs following intravenous injection some signs interpreted as neurological effects were observed at high dose level.

Based on the results of repeated oral and inhalation toxicity studies the eMSCA supports classification of TGIC as STOT RE 2, H373 (May cause damage to organs through prolonged or repeated exposure) due to its peripheral lymph system effect.

7.9.5. Mutagenicity

The mutagenicity of TGIC has been investigated in a wide range of in vitro and in vivo assays. TGIC was mutagenic in most of Salmonella typhimurium strains in bacterial reverse mutation assay, in the mouse lymphoma cells with and without metabolic activation (key study), DNA-alkylation type assay and in vitro mammalian chromosome aberration test with and without activation. It also caused micronuclei and sister chromatid exchange in mammalian cell systems. In vivo TGIC was positive in a variety of rodent assays chromosomal aberrations in somatic and germinal tissues.

Based on the available information, the eMSCA supports the classification of TGIC as Muta 1B, H340 – May cause genetic defects.

TGIC as Muta 1B, H340 meets the criteria of Article 57(b) of Regulation (EC) 1907/2006 (REACH). The substance is therefore included in the Candidate List for inclusion in Annex XIV.

7.9.6. Carcinogenicity

The carcinogenic potential of TGIC was examined in a study performed in compliance with OECD guideline 451 (reliability 1).
Animals were given by dietary admixture either 0, 10, 30, 100 or 300 ppm TGIC (principal group). In addition, a satellite group were exposed for 26 weeks to 0, 100, and 300 ppm TGIC.
Microscopic examination was performed in all tissues, macroscopic lesions and palpable masses from control and high-dose (300 ppm) animals at the end of the treatment period in the principal and satellite groups. Additionally, similar examination of the intermediate dosed (100 ppm) animals of the principal study group was conducted at the end of the treatment period.

In principal group the only positive trend for neoplastic lesions was pituitary adenomas, however this was mainly due to a higher incidence at 30 ppm.

At 100 ppm, terminal body weight was lower as well as mean food consumption in treated animals compared to controls, however the differences were not statistically significant. A slight increase in hepatocellular adenoma (6/50 vs. 4/50 for controls) and carcinomas (3/50 vs. 0/50 for controls) was noted, however the incidence was not dose-related and was within the range of historical controls.
At 300 ppm group lower food consumption and a decrease in body weight gain was observed as well as poor clinical condition. Histopathological investigations revealed a significantly higher incidence of mastocitosis haemosiderosis and haemorrhage in the lymph nodes and depletion of the spleen lymphoid cells in 300 ppm group. In addition, a higher incidence of hyposecretion and small tubulo-alveolar units in the prostate was found. The authors concluded that mastocytosis related to a histamine-related hypotension might have been responsible for the increased mortality observed in this group.

Haematological changes as a higher neutrophil count and monocyte count, lower lymphocyte count and lower total leukocyte count were noted. These findings were attributed to treatment. No indication of treatment-related non-neoplastic changes was seen in the 10, 30 and 100 ppm.

No treatment-related clinical signs or mortality were observed in the satellite toxicity group, and no adverse effects were observed at 100 ppm. High dose (300 ppm) treated animals revealed the following alterations: decrease in body weight and slightly marked haematological changes (lower total leukocyte count and higher thrombocyte count. The other accompanying effects were increased relative mesenteric lymph nodes, lower absolute weights of thymus and spleen, lymphoid depletion and lower absolute weights of prostate and seminal vesicles.

In conclusion, there were no dose-related carcinogenic effect in animals treated up to 100 ppm. At the highest dose (300 ppm) the principal effects were decrease of body weight, mastocystosis in the lymph nodes and depletion of the spleen lymphoid cells.

It should be noted that TGIC was considered as an anti-tumour agent.
The anti-tumour properties of α- and ß-TGIC have been investigated in various transplantable mouse tumour systems. Both stereoisomers displayed a high therapeutic activity, but α-TGIC was superior to the ß-isomer in prolonging the lifespan of treated animals and in inducing long-term survival, probably due to a higher water solubility. In vitro studies measuring cells killed by the drug indicated that neoplastic cells were more susceptible to α-TGIC than non-neoplastic cells. α-TGIC has also been available as an experimental anti-neoplastic agent and was used in human clinical trials in the early 1980s.

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

The reproductive toxicity of TGIC was examined in the studies performed in compliance with OECD guidelines 408 (Repeated dose toxicity and fertility study) and 478 (Rodent dominant lethal assay), both with reliability 1.

In the study on fertility the male rats were exposed to TGIC at the dose of 0, 0.72, 2.08 or 7.32 mg/kg body weight/day for 13 weeks. After 64 days of treatment each male was placed with two untreated females for mating. Decreases in the mean number of spermatozoa in treated groups were reported, but without any statistical analysis.

According to the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) the decreases were not significant when analysed by analysis of variance. Re-assessment of the raw data, performed by the Nordic Expert Group confirmed that there was no statistically significant difference between the dose groups.
The mean spermatozoa viability in treated groups was similar to that in the control group and the decrease in the number of spermatozoa did not impact fertility outcomes or embryonic and pup development.

No changes were seen compared to controls in a number of parameters studied (pre- and post-implantation losses, number of live foetuses, foetal body weights, sex ratios, number of live born, viability 4 and 21 days postpartum, pup weight day 1-21, external anomalies, malformations, physical and reflex development of pups).

In a dominant lethal assay, male mice were exposed to TGIC via inhalation at the concentration of 0, 2.5, 10 or 50 mg/m^3 for 6 hours for 5 days. General toxicity was observed at 50 mg/m^3 and included death, reduction in body weight, ocular discharge and swelling. No dominant-lethal effect was associated with TGIC exposure. TGIC had no significant effect on foetal parameters over 8 mating periods but caused reduced male and female mating rates during the first three mating periods and reduced female mating rate during mating period 6.

The results of supporting study following oral exposure (dose levels: 0, 137.5, 275 and 550 mg/kg bw, single exposure) did not indicate dominant-lethal effects induced by TGIC in mice. Females mated to TGIC-exposed males had only background numbers of dead implants as compared to the control group. Fertility index, number of pregnant females, total number of implants, and mean implant number per female was similar in all dose groups.

In conclusion, despite the presence of some effects as reduced sperm counts and sperm motility overall reproductive performance of rat males was not affected following exposure to TGIC. In females exposed chronically to TGIC no histopathological effects were observed. No changes in pregnancy rates, pre- and post-implantation losses, number of live foetuses, foetal body weights, sex ratios, number of live born, viability, pup weight, external anomalies, malformations, physical and reflex development of pups were seen. Therefore, the eMSCA concludes that there is no concern for reproductive toxicity of TGIC.

7.9.8. Hazard assessment of physico-chemical properties

TGIC is not explosive, not highly flammable in contact with water and has no oxidizing properties.

7.9.9. Selection of the critical DNEL(s)/DMEL(s) and/or qualitative/semi-quantitative descriptors for critical health effects

The most important route of exposure to TGIC is inhalatory tract. TGIC is classified as Muta. 1B, based on the genetic toxicity endpoint. The DNEL for dermal long-term exposure = 0.43 mg/kg bw is derived from a chronic oral toxicity study and thus is very conservative, as the dermal exposure route is less important than the oral route. The lowest short-term repeated-dose inhalation DMEL is calculated from a 5 -day inhalation mouse study, with special emphasis on mutagenic effects in the spermatogonial cells.
No long-term dermal or long-term inhalation experiments have been conducted with TGIC, and neither local nor systemic effects have been determined with the exception of the extrapolation from the long-term oral to long-term dermal study endpoints.

However, a long-term inhalation DNEL can be calculated from the oral one assuming an equal absorption rate of 100%. The value of 0.43 mg/kg bw (determined for the oral route) is multiplied by 60 (average minimal body weight of workers) and divided by 10 (m^3 air consumed during a 8 -hour workshift), an additional Safety Factor of 50 for change of exposure route and change from carcinogenic to mutagenic effects is added and that results in a DMEL = 0.052 mg/m^3 air.

Table 12

CRITICAL DNELS/DMELS					
Endpoint of concern	**Type of effect**	**Critical study(ies)**	**Corrected dose descriptor(s) (e.g. NOAEL, NOAEC)**	**DNEL/ DMEL**	**Justification/ Remarks**
WORKERS					
Inhalation	Systemic effects-long-term	Genetic toxicity	NOAEC	DMEL=0.052 mg/m^3	Overall Assessment Factor=500
Inhalation	Systemic effects-short-term	Genetic toxicity	NOAEC	DMEL=0.052 mg/m^3	Overall Assessment Factor=500
Inhalation	Local effects-short-term	Respiratory tract irritation	LOAEC	DNEL=0.1 mg/m^3	Overall Assessment Factor=100
Dermal	Systemic effects-long-term	Repeated dose toxicity	NOAEL	DNEL=0.43 mg/kg/bw/d	Overall Assessment Factor=10
Dermal	Systemic effects-short-term	Skin sensitisation	LOAEL	DNEL=0.16 mg/kg/bw/d	Overall Assessment Factor=100
Dermal	Local effects-short-term	Skin irritation	LOAEL	DNEL=0.43 mg/kg/bw/d	Overall Assessment Factor=100
GENERAL POPULATION					
Inhalation	Systemic effects-long-term	Genetic toxicity	NOAEC	DMEL=0.005 mg/m^3	Overall Assessment Factor=5000
Inhalation	Systemic effects-short-term	Genetic toxicity	NOAEC	DMEL=0.002 mg/m^3	Overall Assessment Factor=1000
Inhalation	Local effects-short-term	Respiratory tract irritation	LOAEC	DNEL=0.01 mg/m^3	Overall Assessment Factor=1000
Dermal	Systemic effects-long-term	Repeated dose toxicity	NOAEL	DNEL=0.043 mg/kg/bw/d	Overall Assessment Factor=100
Dermal	Systemic effects-short-term	Skin sensitisation	LOAEL	DNEL=0.016 mg/kg/bw/d	Overall Assessment Factor=1000
Dermal	Local effects-short-term	Skin sensitisation	LOAEL	DNEL=0.04 mg/kg/bw/d	Overall Assessment Factor=1000
Oral	Systemic effects-long-term	Repeated dose toxicity	NOAEL	DNEL=0.043 mg/kg/bw/d	Overall Assessment Factor=100

Oral	Systemic effects-short-term	Genetic toxicity	NOAEL	DNEL=0.096 mg/kg/bw/d	Overall Assessment Factor=1000

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

According to HH CLP criteria, TGIC is classified as:
Acute Tox. 3 H301
Skin Sens. 1 H317
Eye Dam. 1 H318
Acute Tox. 3 H331
Muta. 1B H340
STOT RE 2 H373

Following the evaluation an additional concern was identified regarding respiratory damage. The eMSCA proposes an additional classification and labelling of TGIC as Resp. Sens. 1, H334 - May cause allergy or asthma symptoms or breathing difficulties if inhaled.

7.10. Assessment of endocrine disrupting (ED) properties

Not evaluated.

7.11. PBT and VPVB assessment

Persistence

The TGIC hydrolysis half-life is approximately 6.6 days in water. Although no phototransformation study for TGIC is available, assumed photolysis half-life is 1 day or less on the basis of the study for surrogate atrazine herbicides. TGIC is not readily biodegradable, but it shows inherent biodegradability up to 48% in active sludge. TGIC molecule has three epoxide rings and degradation leads to formation of more polar metabolites.

The results of analysis of the structural similarity of TGIC and other constituents and impurities listed in Section 7.3 suggest that persistency of 5,5'-hydroxyisopropylidene di((1,3-bis(oxiranylmethyl)-1,3,5-triazine-2,4,6(1H,3H,5H)-trione may be higher than persistency of TGIC.

On the basis of above mentioned data, persistency of TGIC cannot be excluded.

Bioaccumulation

TGIC has a log Pow = -0.8, indicating a very low bio-concentration and bioaccumulation potential. Although no studies have been conducted concerning the bioaccumulation, epoxides are rapidly metabolized in higher organisms by epoxide hydrolases to form the respective hydroxylates which are rapidly glucuronidated and excreted. Based on the ECOSAR model calculation presented in CSR, the bioconcentration factor (BCF) is 18.

The results of analysis of the polarity of molecules of TGIC and other constituents and impurities listed in Section 7.3 suggest that bioaccumulation potential of these substances is lower than for TGIC, with the only exception of impurity 5,5'-hydroxyisopropylidene di((1,3-bis(oxiranylmethyl)-1,3,5-triazine-2,4,6(1H,3H,5H)-trione.

However, modelling results from different models (EPI Suite ™, PBT Profiler, OECD (Q)SAR Toolbox) show that estimated log Kow is lower than 1. Therefore bioaccumulation potential of 5,5'-hydroxyisopropylidene di((1,3-bis(oxiranylmethyl)-1,3,5-triazine-2,4,6(1H,3H,5H)-trione is expected to be low.

On the basis of above mentioned data, TGIC is not considered as bioaccumulative.

Toxicity

The substance is classified as Mutagenic Category 1B.

On the basis of above mentioned data, TGIC is considered as toxic.

Overall conclusion

The data submitted in registration dossier are considered to be sufficient for evaluation of PBT / vPvB potential of TGIC.

TGIC was selected as CoRAP candidate i.a. as potential PBT/vPvB substance. The reasons for this selection were as follows:

(1) the data on persistency of TGIC and other constituents and impurities of TGIC was regarded not fully sufficient,
(2) the data on bioaccumulation of other constituents and impurities of TGIC was not fully addressed in the CSR**.**

Thus, in the justification document it was indicated that the substance is potentially persistent and toxic in the environment.

After in-depth evaluation of available data, even if the final conclusion on persistency is still not possible, TGIC and other constituents and impurities listed in Section 7.3 do not show accumulation potential. Additionally, hydrolysis seems to be more significant than biodegradation with respect to loss of toxicity and bioaccumulation potential.
Thus, on the basis of the conducted evaluation, TGIC is not considered to fulfil PBT or vPvB criteria.

7.12. Exposure assessment

7.12.1. Human health

7.12.1.1. Worker

The Polish CA analysed whether all identified uses reported in the registration dossier were considered in the Chemical Safety Assessment as well as in exposure scenarios.

7.12.1.2. Consumer

There are no identified consumer uses.

7.12.2. Environment

Not relevant for evaluation.

7.12.3.

7.13. Risk characterisation

The exposure scenarios as provided in the updated Chemical Safety Reports (2014) were carefully reviewed.

Worker Exposure

With the proposed operational conditions and risk management measures the risks to workers (based on worst case modelled data) are under control for the identified uses of 1,3,5-tris(oxiranylmethyl)-1,3,5-triazine-2,4,6(1H,3H,5H)-trione.

Consumer Exposure

At the time of finalising this report, there were no registered consumer uses of 1,3,5-tris(oxiranylmethyl)-1,3,5-triazine-2,4,6(1H,3H,5H)-trione.

Environment

Predicted concentrations calculated for the affected compartments are below threshold values for aquatic and terrestrial organisms for all identified uses, indicating that there is no relevant risk for all assessed compartments caused by the substance.

7.14. References

Study reports included in registration dossier for TGIC.

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7.15. Abbreviations

CLP – Classification, Labelling and Packaging
CoRAP – Community Rolling Action Plan
CSR – Chemical Safety Report
DMEL - Derived Minimal Effect Level
DNEL – Derived No Effect Level
EPA – Environmental Protection Agency
LOAEL – Lowest Adverse Observed Effect Level
LOAEC - Lowest Adverse Observed Effect Concentration
MSCA – Member State Competent Authority
NOAEC - No Observed Adverse Effect Concentration
NOAEL – No Observed Adverse Effect Level
PBT – Persistent, Bioaccumulative, Toxic
SVHC – Substance of Very High Concern
TGIC - Triglycidyl isocyanurate
vPvB – very Persistent, very Bioaccumulative