Annex XV dossier

PROPOSAL FOR IDENTIFICATION OF A SUBSTANCE AS A CMR CATEGORY 1A OR 1B, PBT, vPvB OR A SUBSTANCE OF AN EQUIVALENT LEVEL OF CONCERN

Substance Name(s): 1**,3,5-Tris(oxiran-2-ylmethyl)-1,3,5-triazinane-2,4,6-trione**

EC Number(s): 219-514-3

CAS Number(s): 2451-62-9 (TGIC, a combination of two isomers)

Submitted by: CA of the Netherlands

PUBLIC VERSION: *This report does not include the Confidential Annex referred to in Part II.*

CONTENTS

PROPOSAL FOR IDENTIFICATION OF A SUBSTANCE AS A CMR CAT 1 OR 2, PBT, VPVB OR A SUBSTANCE OF AN EQUIVALENT LEVEL OF CONCERN

Substance Name(s): 1,3,5-Tris(oxiran-2-ylmethyl)-1,3,5-triazinane-2,4,6-trione

EC Number(s): 219-514-3

CAS Number(s): 2451-62-9

- The substance is proposed to be identified as substance meeting the criteria of Article 57 (b) of Regulation (EC) 1907/2006 (REACH) owing to its classification as mutagen category 1B[1], which corresponds to classification as mutagen category 2[2].

1,3,5-Tris(oxiran-2-ylmethyl)-1,3,5-triazinane-2,4,6-trione (TGIC, a combination of two isomers) (EC number: 219-514-3, CAS number: 2451-62-9, index number for the Annex VI entry i.e. 615-021-00-6) is listed in Annex VI, part 3, Table 3.1 of Regulation (EC) No. 1272/2008 (list of harmonized classification and labeling of hazardous substances). as mutagen category 1B (H340; May cause genetic defects) This corresponds to a classification in Annex VI, part 3, Table 3.2 (the list of harmonized and classification and labeling of hazardous substances from Annex I to Directive 67/548/EEC) of Regulation (EC) No 1272/2008 as mutagen category 2 (R46; May cause heritable genetic damage).

Therefore, this classification of the substance in Regulation (EC) No 1272/2008 means that it meets the criteria for classification in the hazard class germ cell mutagenicity category 1B in accordance with Article 57 (b) of REACH.

Two Annex XV dossiers will be prepared, for:

- 2451-62-9 (a combination of two isomers), and
- 59653-74-6 (ß-TGIC)

These two substances are listed in Annex VI of the CLP. α-TGIC (CAS number 59653-73-5), is not listed on Annex VI, and therefore no Annex XV dossier will be prepared for this chemical. If industry would register α-isomer at some point, first step should be to include α-TGIC (with appropriate justification in an Annex VI dossier) to Annex VI of the CLP, and then to put it to the Candidate List.

Registration dossiers have been submitted for this substance: Yes

[1] Classification in accordance with Regulation (EC) No 1272/2008 Annex VI, part 3, Table 3.1 List of harmonised classification and labelling of hazardous substances.

[2] Classification in accordance with Regulation (EC) No 1272/2008, Annex VI, part 3, Table 3.2 List of harmonised classification and labelling of hazardous substances (from Annex I to Council Directive 67/548/EEC).

PART I

JUSTIFICATION

1 IDENTITY OF THE SUBSTANCE AND PHYSICAL AND CHEMICAL PROPERTIES

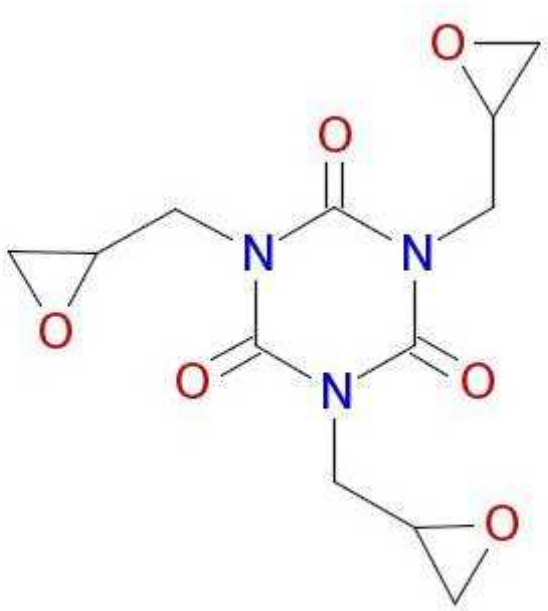
1.1 Name and other identifiers of the substance

Table 1: Substance identity

EC number:	219-514-3
EC name:	1,3,5-tris(oxiranylmethyl) -1,3,5-triazine-2,4,6(1H,3H,5H) -trione
CAS number (in the EC inventory):	2451-62-9
CAS number	414867-60-0
CAS name:	1,3,5-Triazine-2,4,6(1H,3H,5H)-trione, 1,3,5-tris(2-oxiranylmethyl)- (a combination of α and ß isomers of TGIC)
IUPAC name:	1,3,5-Tris(oxiran-2-ylmethyl)-1,3,5-triazinane-2,4,6-trione (a combination of α and ß-isomers)
Index number in Annex VI of the CLP Regulation	615-021-00-6
Molecular formula:	C12H15N3O6
Molecular weight range:	297.3 g/mol
Synonyms:	triglycidyl isocyanurate TGIC; 1,3,5-triglycidyl isocyanurate; 1,3,5-triglycidyl-s-triazinetrione; 1,3,5-tris(2,3-epoxypropyl)-s-triazine-2,4,6(1H,3H,5H)-trione; tris(2,3-epoxypropyl)isocyanurate 1,3,5-Triglycidyl-s-triazine-2,4,6-trione 1,3,5-Triglycidylhexahydro-1,3,5-triazine-2,4,6-trione 1,3,5-Triglycidylisocyanuric acid 1,3,5-Tris(2,3-epoxypropyl) isocyanurate 1,3,5-Tris(oxiran-2-ylmethyl)-1,3,5-triazine-2,4,6-trione 1,3,5-Tris(oxiranylmethyl)-1,3,5-triazine-2,4,6-trione Glycidyl isocyanurate N,N',N''-Triglycidyl isocyanurate NSC 269934 PTGIC TGT Triglycidyl isocyanurate Tris(2,3-epoxypropyl) isocyanurate Tris(epoxypropyl) isocyanurate TEPIC Araldite PT 810 TK 10622

(Registration Dossier 2010), (Nordic Council of Ministers 2001)

Structural formula:



1.2 Composition of the substance

The currently available Registration Dossiers refer to a substance with the α : ß ration of ca. 90 : 10 but this dossier should cover all possible combinations of isomers independent of their individual concentration in the substance.

Name: 1,3,5-Tris(oxiran-2-ylmethyl)-1,3,5-triazinane-2,4,6-trione

Description: epoxidized triazine

For further data on composition of the substance see confidential Annex 2.

1.3 Physico-chemical properties

Table 2: Overview of physicochemical properties

Property	Value	Remarks
Physical state at 20°C and 101.3 kPa	solid, which may occur as a white opaque powder or granules or as clear crystals	(Nordic Council of Ministers 2001)
Melting/freezing point	Melting point is 92 - 96 °C at normal pressure	**Value used for CSA in registration dossier:** 365 K at 1013 hPa Melting point was cited in NICNAS Chemical report (1994) from SDS data of data owner Ciba Geigy Ltd. The value measured with a particular batch was 92.8°C for TEPIC-G, and 94.6°C for Araldite PT810. Both values are within the range of 92 -96°C published by NICNAS[1]
Boiling point	Boiling Point > 240°C	Boiling point not determined as decomposition occurred starting at ca. 240°C and higher
Vapour pressure	The vapor 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.	**Value used for CSA in registration dossier:** 0.007 Pa at 293.15 K The measured vapor pressure of 0.0072 Pa (20°C) is probably more reliable than the calculated one which is almost 10 –times lower at a higher temperature (60°C). A vapor pressure of 0.0072 Pa is however quite high when comparing it to another triazine - Atrazine which has a VP=0.00003853 Pa (at 20°C), or Simazine with a VP=0.000002946 Pa (at 20°C), or Cyanuric acid with a VP=0.0000040 Pa (at 20°C). This means that the real vapour pressure is probably at least one order of magnitude lower than the existing value, namely in the order of 0.0001 - 0.0007 Pa (at 20 °C)
Water solubility	Two values have been reported for the water solubility of 9000 mg/l and 10,000 mg/l, namely by NICNAS (1994), a value derived from NISSAN, and by Budnowsky (1968)	**Value used for CSA in registration dossier:** 9000 mg/L at 25 °C The water solubility is relatively high in destilled water, but the solubility drops fast with increasing salt concentrations as used for environmental studies. The water solubility of 9000 mg/l has been confirmed by Ciba Specialty Chemicals Inc in 1996.
Partition coefficient n-octanol/water (log value)	The log Pow cited by NICNAS (1994) originates from NISSAN, and is a measured value (-0.8, at 20°C).	**Value used for CSA in registration dossier:** Log Kow (Pow): -0.8 at 20 °C QSAR value of ECOSAR coincides well with the measured value of -0.8
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.
Thermal stability	indirect photolysis half-life = 26 - 73 days in water	Photooxidation in sunlight and air is 7 hours.

	photo-oxidation half-life in sunlight and air is 7 hours. Thermal stability is guaranteed up to 70 °C for a short period of time, No data on metal compatibility are available.	Thermal stability is guaranteed up to 70 °C for a short period of time, No data on metal compatibility are available. Thus, in air and under UV-light influence TGIC is not stable

1. TEPIC-G is a combination of isomers, no further information given.

2 HARMONISED CLASSIFICATION AND LABELLING

2.1 Classification and labelling according to CLP / GHS

1,3,5-tris(oxiran-2-ylmethyl)-1,3,5-triazinane-2,4,6-trione (IUPAC) is listed by Index number 615-021-00-6 of Regulation (EC) No 1272/2008 in Annex VI, Part 3, Table 3.1 (list of harmonised classification and labelling of hazardous substances) as follows:

Table3: Classification according to Annex VI, Part 3, Table 3.1 (list of harmonised classification and labelling of hazardous substances) of Regulation (EC) No 1272/2008

Index No	International Chemical Identification	Classification		Labelling		
		Hazard Class and Category Code*	Hazard statement Code**	Pictogram, Signal Word Code	Hazard statement Code	Suppl. Hazard statement Code(s)
615-021-00-6	1,3,5-tris(oxiran-2-ylmethyl)-1,3,5-triazinane-2,4,6-trione	Muta. 1B Acute Tox. 3 * Acute Tox. 3 * STOT RE 2 * Eye Dam. 1 Skin Sens. 1 Aquatic Chronic 3	H340 H331 H301 H373 ** H318 H317 H412	GHS06 GHS08 GHS05 Dgr	H340 H331 H301 H373 ** H318 H317 H412	-

*# Hazard Class and Category Code:

Muta. 1B:	H340 (May cause genetic defects .)
Acute Tox. 3	H331 (Toxic if inhaled.)
Acute Tox. 3	H302 (Toxic if swallowed.)
STOT RE 2	H373 (May cause damage to organs through prolonged or repeated exposure.)
Eye Dam. 1	H318 (Causes serious eye damage.)
Skin Sens. 1	H317 (May cause an allergic skin reaction).
Aquatic Chronic 3	H412 (Harmful to aquatic life with long lasting effects.)

** Hazard statement code:

H317: May cause an allergic skin reaction. (by the oral and inhalation route)
H412: Harmful to aquatic life with long lasting aquatic environmental effects.
H340: May cause genetic defects .
H318: Causes serious eye damage
H301: Toxic if swallowed.
H331: Toxic if inhaled
H373: May cause damage to peripheral lymph system

2.2 Classification and labelling in Annex I of Directive 67/548/EEC

1,3,5-tris(oxiran-2-ylmethyl)-1,3,5-triazinane-2,4,6-trione (IUPAC) is listed by Index number 615-021-00-6of Regulation (EC) No 1272/2008 in Annex VI, Part 3, Table 3.2 (list of harmonised classification and labelling of hazardous substances from Annex I to Directive 67/548/EEC) as follows:

Table4: Classification according to Annex VI, Part 3, Table 3.2 (list of harmonised classification and labelling of hazardous substances from Annex I to Directive 67/548/EEC) of Regulation (EC) No 1272/2008

Index No	Chemical name	Classification*	Labelling**
615-021-00-6	1,3,5-tris(oxiran-2-ylmethyl)-1,3,5-triazinane-2,4,6-trione	Muta. Cat. 2; R46 T; R23/25 Xn; R48/22 Xi; R41 R43 R52-53	T R: 46, 23/25, 41, 43, 48/22, 52/53, S: 53, 45, 61

*. Classigfication: Muta. Cat. 2; R46 May cause heritable genetic damage.
T; R23/25: Toxic, Toxic by inhalation and if swallowed.
Xn; R48/22: Harmful, Harmful: danger of serious damage to health by prolonged exposure if swallowed.
Xi; R41: Irritant; Risk of serious damage to eyes
R43: May cause sensitisation by skin contact
R52-53: Harmful to aquatic organisms, may cause long-term adverse effects in the aquatic environment.

** Labelling: T - toxic

R41 - risk of serious damage to eyes
R23/25 - toxic by inhalation and if swallowed
R43 - may cause sensitisation by skin contact
R48/22 - harmful: danger of serious damage to health by prolonged exposure if swallowed
R46 - may cause heritable genetic damage
R52/53 - harmful to aquatic organisms, may cause long-term adverse effects in the aquatic environment
S45 - in case of accident or if you feel unwell, seek medical advice immediately (show the lable where possible)
S61 - Avoid release to the environment. Refer to special instructions/Safety data sheets
S53 - avoid exposure - obtain special instructions before use

3 ENVIRONMENTAL FATE PROPERTIES

Not relevant for this type of dossier.

4 HUMAN HEALTH HAZARD ASSESSMENT

See section 2 on harmonised classification and labelling.

For details on the relevant Human Health endpoints see Annex 1.

5 ENVIRONMENTAL HAZARD ASSESSMENT

Not relevant for this type of dossier.

6 CONCLUSIONS ON THE SVHC PROPERTIES

6.1 PBT, vPvB assessment

Not relevant for this type of dossier.

6.2 CMR assessment

1,**3,5-Tris(oxiran-2-ylmethyl)-1,3,5-triazinane-2,4,6-trione** (TGIC, a combination of two isomers) (EC number: 219-514-3, CAS number: 2451-62-9, index number for the Annex VI entry i.e. 615-021-00-6) is listed in Annex VI, part 3, Table 3.1 of Regulation (EC) No. 1272/2008 (list of harmonized classification and labeling of hazardous substances). as mutagen category 1B (H340; May cause genetic defects). This corresponds to a classification in Annex VI, part 3, Table 3.2 (the list of harmonized and classification and labeling of hazardous substances from Annex I to Directive 67/548/EEC) of Regulation (EC) No 1272/2008 as mutagen category 2 (R46; May cause heritable genetic damage).

Therefore, this classification of the substance in Regulation (EC) No 1272/2008 means that it meets the criteria for classification in the hazard class germ cell mutagenicity category 1B in accordance with Article 57 (b) of REACH.

6.3 Substances of equivalent level of concern assessment.

Not relevant for this dossier.

PART II

INFORMATION ON USE, EXPOSURE, ALTERNATIVES AND RISKS

General Remark: General information on use TGIC (mainly, but not exclusively, a combination of isomers, as this is a substance used by the industry) is given. In open sources literature it is referenced usually as TGIC, without further specification. It could be assumed, that TGIC (a combination of isomers, 90% α and 10% β isomer) is meant.

Therefore in this chapter "TGIC" will be used as a substance name. However, part of the data is taken from TGIC (a combination of isomers, 90% α and 10% β isomer) dossier, and this will be clearly indicated.

1 INFORMATION ON MANUFACTURE, IMPORT/EXPORT AND USES – CONCLUSIONS ON EXPOSURE

1.1 Production processes

TGIC is produced batchwise by adding first in the addition reactor epichlorohydrin (CAS- no. 106-89-8, EU-no. 203-439-8) to cyanuric acid (CAS-no. 108-80-5, EU-no. 203-618-0) in the presence of a catalyst. Epichlorohydrin is used as a reactive solvent.
A second step is performed in the presence of caustic soda (CAS-no. 7542-12-3, EU-no. 231-420-4) to facilitate ring closure. The salt is removed by filtration, and the resin solution is washed, dried, and concentrated by evaporation, then precrystallized and flaked on a cooling belt.
(Nordic Council of Ministers 2001)

1.2 Production and use volumes

The worldwide production of triglycidyl isocyanurate in the past was approximately 7000–8000 tonnes per year. The United Kingdom imported approximately 400 tonnes of triglycidyl isocyanurate per year for use in powder coatings. In the United Kingdom, approximately 30 tonnes of solder "mask" inks containing triglycidyl isocyanurate are manufactured per year by four or five companies (CICAD 1998). These amounts are by far outdated and current manufacture and use has been declined considerably.

The actual global production volume is not known. The total current use of TGIC in Europe is estimated to be around the lower end of the 100-1,000 tons per year range. There are no manufacturing sites in the EU. The estimates for current use of TGIC in the EU for solder mask and in powder coating applications are about 20% and 80% (Industry, personal communication).

For current data on production and use of TGIC see confidential Annex 2.

1.3 Uses of the substance:

TGIC is an epoxy compound that is used as a hardener in resins and coatings. The main use is in polyester powder coatings for metal finishing and such coatings typically contain between 4 and 10% TGIC. In Europe it is has been used in weather-resistant powder coatings since the 1970s for coating articles such as steel garden furniture, car parts, metal fencing, window and door frames. It is also used for powder coating electrical equipment, refrigerators, washing machines and ovens. The substance may also be used in inks in the printed circuit board industry, for example two-part inks used for solder-masking can contain up to around 60% TGIC in the hardener component. Other uses of the substance reported include in electrical insulation materials, resin moulding systems, laminated sheeting, silk-screen printing coatings, tools, adhesives, lining materials and stabilisers for plastics. The technical grade substance is supplied under the trades names TEPIC, Araldite PT 810 or TK 10622 (NICNAS 1994).

The main function of triglycidyl isocyanurate is as a three-dimensional cross-linking or curing agent in polyester powder coatings, hardener in the thermosetting one-component polyester powder coatings (paints). In the manufacture of powder coatings, TGIC granules are mixed with resin, pigments (if pigmented powder coatings), fillers and additives. The mixture is heated until melting occurs and the melt is mixed to ensure homogeneity. It is then extruded into a thin sheet, which cools and solidifies. The solid material is chipped, milled, sieved and packed as a fine powder. Generally, the particle size of 90–95% of the powder coating is >10 μm.
TGIC is partially cross-linked to the polyester resin. The powder coatings (4-10% TGIC) are sprayed onto metal objects by an electrostatic process. The spray guns charge the powder with a positive or negative charge depending on the spray equipment used. The electrostatically charged powder particles are sprayed onto earthed metal objects. The coated metal objects are then placed in an oven. At a temperature of about 200°C the resin melts, flows, and chemically cross-links to form a paint film. The TGIC in powder coatings after application to metal particles is fully cross-linked and is bound in a solid matrix. The coatings are durable and resist ultraviolet damage and are therefore typically used in out-door applications. (Nordic Council of Ministers 2001) (NICNAS 1994)

TGIC is also used in solder “mask” inks in the printed circuit board industry. The two-part inks contain approximately 25% TGIC in the hardener component. The inks are applied primarily by screen printing, to a lesser extent by curtain coating and also has a niche application method is via electrostatic spraying. The coated circuit board is finally passed through an oven at 150 °C to complete the curing process.

(Industry, personal communication)

In addition, TGIC is used in electrical insulation materials, resin-moulding systems, laminated sheetings, silk-screen printing coatings, tools, inks, adhesives, lining materials, and stabilizers for plastics. (Nordic Council of Ministers 2001)

2 INFORMATION ON EXPOSURE

2.1 Occupational exposure

Occupational exposure to TGIC may occur during the manufacture of TGIC and the manufacture and use of products containing TGIC. The most likely routes of occupational exposure are

inhalational and dermal. A fraction of the inhaled material will be swallowed, and there may also be some oral ingestion. Activities likely to cause high levels of exposure during the manufacture of TGIC powder coatings are weighing out of TGIC, filling hoppers, mixing, transfer of powder mixes in open vessels, extrusion, milling, bagging, cleaning-up spills and cleaning equipment. The highest level of exposure to TGIC will occur when handling technical grade TGIC. However, particle size data on technical grade TGIC as granules indicate that only very small fractions are respirable. Of TEPIC particles, 99.6% are >400 μm and only 0.003% are <10 μm.

Exposure to TGIC during the use of products containing TGIC may occur in factories and paint shops, where TGIC powder coatings are sprayed onto metal objects prior to curing in ovens. There is a considerable potential for airborne dust generation during decanting of the powder in preparation for spraying (filling hoppers). The method of application (spraying) also provides considerable potential for exposure to powder coatings, especially if the area is not fully enclosed and the objects are manually sprayed. Furthermore, certain cleaning operations (cleaning-up spills, cleaning equipment, cleaning spray booths) may lead to exposure to large amounts of TGIC.
(Nordic Council of Ministers 2001)

For current uses of TGIC and processes involved see confidential Annex 2.

In NICNAS, 1994, occupational exposure for manufacture and use of powder coatings were described in details:

Manufacture of powder coatings:

- **Transport and storage of raw material:** TGIC is packaged in 25kg lots and sealed in a plastic bag inside a fibreboard box. Under normal transport and storage conditions, exposure is unlikely to occur unless the boxes are damaged and spillages occur.
- **Formulation process:** Plant operators work an eight hour shift. The highest level of exposure to TGIC will be when handling technical grade TGIC. Operators transfer TGIC granules into the mixing hopper by using metal scoops or by pouring from bags. This operation is performed in a weigh-booth equipped with local exhaust ventilation ducted to a central bag-house. Operators wear full protective clothing and a filtered air hood or powered air respirator with integral visors during weighing and transfer processes. After weighing, the raw materials are dry blended in a sealed mixer which is fitted with an exhaust extraction system. The premixed raw materials are transferred to the extruder. Local dust extraction is provided in areas where TGIC dust may be generated during the operation, such as at transfer points, mixing and extruding processes. Personal protective clothing and respirators are also worn by workers who may come into contact with TGIC powder coatings during extrusion, milling and filling processes.
- **Quality control:** Quality control testing is performed on extrudate, either in the form of solid flakes or finely milled powder from the plant. The quality control personnel mill the flaked extrudate into a fine powder for testing. The powders are then sprayed onto test panels for curing and evaluation. Spraying and cleaning is carried out in a spray booth with an exhaust air-flow to confine and extract any residual dust. The exhaust ventilation is ducted to a central bag house. Personnel use either powered air respirators or disposable dust masks and personal protective clothing as required, such as when weighing, spraying or when cleaning equipment.
- **Research and development:** Test spraying of TGIC powder is carried out in an enclosed spray booth with the exhaust ventilation ducted to a central bag house. Impervious rubber gloves, overalls or laboratory coats and disposable dust masks are used where and when

required. Occasionally respirators are used during some research and development activities, such as when weighing, spraying or cleaning equipment.

- **Maintenance and clean-up** Maintenance personnel are likely to be exposed to TGIC or TGIC powder coatings during regular cleaning and maintenance. Workers may also be exposed during the clean-up of accidental spills. Maintenance and clean-up is usually done by either vacuuming, wet scrubbing, water washing or sweeping/scooping. Disposable dust masks and gloves are worn during the clean-up of spills and during maintenance work. Any activity capable of producing airborne dust, such as sweeping, increases exposure.

Exposure during use - spray application

The method of application (spraying) provides considerable potential for exposure to powder coatings. The quality of equipment used and the level of exposure control in these establishments is variable. In general, assembly lines in the larger establishments use enclosed spray booths which contain most of the powder spray. Many of the smaller establishments use walk-in booths or booths which are not fully enclosed.

- **Transport and storage of powder coating:** TGIC powder coatings are packaged in 20-25 kg plastic bags inside fibreboard boxes. Under normal transport and storage conditions, exposure is unlikely to occur unless the boxes are damaged and spillages occur.
- **Decanting:** Spray paint operators fill the hopper from the powder containers. There is considerable potential for airborne dust generation during decanting of the powder from the containers in which it is transported to hoppers in preparation for spraying.
- **Spray application:** The application of any chemical by spraying greatly increases the potential for worker exposure. The electrostatically charged powder coating particles are sprayed onto earthed metal objects by means of a spray gun. The powder coatings are applied either through fully automated application lines, by manual spray or, in some cases, a combination of both automatic and manual touch-up. In the automated application lines the metal objects to be sprayed usually hang from metal hooks and pass automatically through a spray booth to the ovens. In these booths air flow is directed to the bottom of the booth. In a fully automated application line the powder coating is applied by automatic spray guns. Alternatively, workers stand outside the booths and only their hands holding the spray guns enter the booth through apertures. Other spray booth designs in common use include walk-in or open fronted booths in which the objects are manually sprayed. The air flow in these booths is usually directed horizontally by local ventilation from behind the worker and towards the object being sprayed. In these types of booths the objects are usually manually moved into the booth for spraying and then to the ovens for curing. The potential for worker exposure is low if spraying is fully automated and carried out in an adequately enclosed and ventilated spray booth. When spraying is conducted with the objects in a properly ventilated spray booth with small apertures and the operator standing outside, exposure is likely to be slightly greater. Dermal exposure can occur if no hand protection is used, as the operators bare hand must be in contact with the spray gun to ensure good earthing. Operators either cowl the hand using a cover sleeve or cut out the palm of an insulating glove. Exposure will potentially be the greatest when walk-in or open fronted booths are used.
- **Cleaning booths and reclaiming powder:** Significant exposure can result from the use of industrial vacuum cleaners to remove dust from booths and extraction units. Emptying the vacuum cleaners into the original powder containers prior to oven curing, the recommended procedure for disposal, also offers potential for exposure as does transfer of powder recovered to the hopper for reuse. Cleaning and changing the booth filters is a potential source of exposure. The use of compressed air to clean booths and for personal cleaning will result in greater atmospheric levels of dust, with greater exposure potential to TGIC.

- **General:** Air movement throughout the powder coating area may lead to exposure both in the spray area and in the factory as a whole.

(NICNAS 1994)

Exposure during manufacture of solder mask inks

The method of manufacture and use of solder mask ink tends to be highly automated, well contained and carried out under "clean room" conditions and using personal protective equipment.

- Transport and storage of raw material
  TGIC is packaged in 25 kg lots and sealed in a plastic bag inside a fibreboard box. Under normal transport and storage conditions, exposure is unlikely to occur unless the boxes are damaged and spillages occur.
- Transfer process:
  The highest potential level of exposure to TGIC will be when workers transfer TGIC to the mixing hopper. Duration of process is typically under 15 minutes.
- Formulation process
  After transfer to the mixer the substance passes through an automated pre-mix and dispersion milling process.
- After the dispersion milling stage the resulting liquid solder mask ink (containing ca. 25% TGIC) is then dispensed via an automated system into plastic containers.

Use of solder mask ink

- Transport and storage of solder mask ink
  Solder mask ink hardener component containing ca 25% TGIC is packaged and transported in plastic containers. Under normal transport and storage conditions, exposure is unlikely to occur unless the boxes are damaged and spillages occur
- Transfer process:
  Solder mask ink operators transfer the liquid ink into the solder mask ink application machines. Duration of process is typically under 15 minutes.
- Solder mask ink application:
  The two solder mask ink components are mixed (after mixing the TGIC concentration in solder mask ink is typically under 10%) and then can be applied by a range of methods as described below.
- The main application method is screen printing, where the solder mask ink is applied to the printed circuit board with a squeegee blade through a tensioned mesh.
  Another application method is by curtain coating where the solder mask is applied as the printed circuit board passes through a 'curtain' of low viscosity ink which falls through a narrow slot in a holding 'head'.
  A niche application method is electrostatic spraying where the solder mask ink is applied with a serrated turbine bell using compressed air that atomises the ink and deposits it on the printed circuit board. Here the solder mask ink is given a negative charge and the printed circuit board is earthed.

- Optional. Pre-cure followed by UV exposure:
  One of the major solder resist applications "Photoimageable solder resist" contains additional stages not involved in other application types. Here, after solder mask application the printed circuit board is pre-cured by heating at 80°C for 20-30 minutes so that a "tack-free" finish is achieved. The printed circuit board is then exposed to UV light through a negative film. The boards are then rinsed using an alkaline aqueous solution which removes photoresist areas which have not been exposed to UV light.

- Curing:
  After solder mask ink is applied to the printed circuit board the boards are transferred via a generally automated process to an oven where the boards are heated at 150°C typically for 50-60 minutes to complete the curing process
- Removal from oven:
  Once the printed circuit boards are removed from the oven the solder mask ink containing TGIC has been fully cured and no unreacted TGIC remains.

(Industry, personal communication)

2.1.1 Workplace concentrations and exposure measurements

No recent measured data was provided in Chemical Safety Report on TGIC (a combination of isomers).

Measured data from open sources (from before 2001)
Data describing actual exposure levels at workplaces are limited. No monitoring data are available for the manufacture of TGIC and data for the manufacture and use of TGIC containing products are restricted to powder coatings. These data have shown marked differences in the air levels of TGIC between and within workplaces (Table 13). (Nordic Council of Ministers 2001)

Table 5: Workplace concentrations of TGIC in powder coating industries.

Industry	Process/work operation	Exposure level (TWA) (mg/m3)
manufacture of powder coatings	make up extruder mill laboratory	0.032-0.19 0.023-0.27 0.085-1.34 0.047
manufacture of powder coatings	warehouse mixing extruder mill bulk laboratory	0.002-0.007 0.00001 0.003-0.013 0.006 0.004 0.004-0.030
manufacture of powder coatings	weighing raw materials filling raw materials mixing pulverisation packing cleaning work: mixer cleaning work: pulveriser cleaning work: cyclone	0.005* 0.004* trace* 0.002* 0.009* 0.006* trace* 0.009*

	cleaning work: sieve cleaning work: packing hopper	0.035* 0.005*
manufacture of powder coatings	Weighing and milling	0.01-0.44
use of powder coatings	spray painting	<0.001-6.5
use of powder coatings	e.g. spraying cleaning, colour changes	0.001-1.5 mean: 0.24 mean**: 0.95

*determination of TEPIC
**short-term exposure

In an Australian powder coating manufacturing plant the levels of atmospheric TGIC in July/August 1991 varied between 0.023 and 1.34 mg/m^3 (time-weighted average, TWA). The data showed that dust levels for different operators performing the same job varied considerably. Later work practices were improved and dust levels were considerable lowered. In October 1991, the levels of TGIC (TWA) were between 0.00001 and 0.03 mg/m^3. In a Japanese powder coating manufacturing plant TGIC levels up to 0.035 mg/m^3 (TWA) and dust levels up to 1.12 mg/m^3 were measured in 1991. In 5 plants manufacturing TGICcontaining powder coatings in the United Kingdom (UK) in 1994, TGIC levels ranged from 0.01 to 0.44 mg/m$_3$ with a mean of 0.1 mg/m$_3$ (8-hour TWAs). Corresponding total inhalable particulate levels were 1.1-64 mg/m^3 (8-hour TWAs). The highest exposures were found during weighing (TGIC mean: 0.27 mg/m^3) and milling (TGIC mean: 0.08 mg/m^3). High exposures were, however, found for all the tasks monitored (weighing, mixing, extrusion, milling, packing, cleaning). The high exposures were generally due to poor working practices.

In a survey of 8 spray painting workplaces in Australia in 1991 the TGIC content in dust from 7 workplaces was up to 6.5 mg/m^3 (TWA; personal air monitoring). Total dust levels were up to 132 mg/m^3. The results of a survey of 16 similar workplaces in the UK in 1994 showed TGIC levels between 0.001 and 1.5 mg/m^3 (8-hour TWAs; mean: 0.24 mg/m^3). Corresponding total inhalable particulate levels were 0.2-131 mg/m^3 (8-hour TWAs). Exposures were high during all the tasks measured (spraying, loading, cleaning). Furthermore, high full-shift exposures to TGIC were measured for both manual spray operators and sprayers at automated booths. High short-term exposures were measured during cleaning and colour changes. The high exposure levels of TGIC in the investigated workplaces in the UK were generally attributed to poor working practices.
(Nordic Council of Ministers 2001)

These exposure values have been determined when appropriate exposure controls and appropriate PPE (Personal Protection Equipment) have not yet been implemented. The values reported may not reflect workplace exposure today.

For the recent modeled and historical measured workers exposure data from the Registration Dossier see confidential Annex 2.

2.1.2 Regulations and guidelines for occupational exposure

TGIC is a CMR due to its mutagenic potential in rodents. Based on this classification and labelling an Occupational Exposure Limit has been established by the Regulatory Authorities, and in addition, Regulations concerning release to the environment have been issued by the European Authorities. Based on these Regulations the Occupational Exposure Limit is 0.05 mg/m3 air at the workplace.
(Registration Dossier 2010)

The following occupational exposure limits for TGIC for various countries are given in Nordic Council of Ministers (2001).

The Netherlands	0.1 mg/m^3.
United Kingdom	0.1 mg/m^3.
USA (ACGIH)	0.05 mg/m^3.

For current data on the risk reduction measures see confidential Annex 2.

2.1.3 Consumer exposure

According to NICNAS the TGIC in powder coated metal articles available to the public is fully cross-linked with the polyester resins, that is, it is completely reacted into an inert form, and therefore poses no health risk (NICNAS 1994).

Even with these two statements, without measurements (leaching data) it is not possible to say that consumer exposure is negligible, although this seems likely.

For further information from the Registration Dossier see confidential Annex 2.

2.1.4 Man exposed via the environment

TGIC is hydrolyzed in the environment to the respective triols. The hydrolysis half-life of TGIC was 5 days at pH7 and 22°C. In addition, if TGIC is taken up by fish and plants, it is also hydrolyzed by epoxide hydrolases.
Total daily dose for oral exposure of humans via the environment was calculated (EUSES) to be 0.002 – 0.022 mg/person/(Registration Dossier 2010).

3 INFORMATION ON ALTERNATIVES

3.1 CURRENT KNOWLEDGE ON ALTERNATIVES

The powder coating market has been growing substantially ever since its inception, and from 1980 until 2005, the total global production has increased from less than 100,000 tons to over one million tons. There are three classifications powder coatings, based on use – functional (high chemical resistance), exterior (high UV and weathering resistance), and interior (general performance).

The principal chemistries of exterior powder coatings are TGIC (triglycidyl isocyanurate), HAA (hydroxylalkylamide), glycidylesters, and so-called polyurethanes using isocyanate cross-linkers.

TGIC coatings are principally used for the exterior market, meaning that their greatest requirement is weathering resistance. This application includes, e.g. coatings for various vehicle pieces, architectural paints for aluminum window frames and facade metal elements, garden furniture and fences, as well as agricultural machinery. The coating for these applications may experience some contact with solvent and gasoline, plus long term exposure to the sun. (Smart Formulating Journal 02).

Following the labeling of TGIC with T; R46, the substance has been banned in several countries or has been voluntarily substituted by Industry by various alternative cross-linkers. Beta-hydroxyl alkylamide and glycidylesters are the mostly used alternative cross linkers to TGIC. However, none of them is a one to one drop-in alternative product.

- Glycidylesters are based on a very similar chemistry like that of TGIC and provide formulated paints with a nearly identical technical profile as when TGIC is used.
- Beta-hydroxyl alkyl amide products cover a major part of the technical requirement profiles and are cost effective.

Using alternatively both technologies, almost all TGIC formulations have been replaced on the European market after 1990.

(Industry, personal communication)

Substitution of TGIC hardener in powder finish by beta-hydroxy alkylamide. (CAS Reg. No. 68368-33-2, **IUPAC Name:** 4-tert-butyl-N,N-bis(2hydroxyethyl)benzamide was proposed by the Danish EPA. (Nielsen C. W., 1999)

Commercial glycidylester products are mixture of bis (2,3-epoxypropyl) terephthalate (CAS Reg. N°. 7195-44-0 /EC-N°. 230-565-0) and tris(oxiranylmethyl)benzene-1,2,4-tricarboxylate (CAS Reg N°. 7237-83-4 / EC-N°. 230-638-7).

A broad range of raw materials is available for thermosetting powders. TGIC is one of the mostly used cross-linker OH-polyesters reacting with isocyanates either blocked or sometimes unblocked. TGIC is banned in many countries and replaced by β-hydroxy-alkylamides (HAA).
(Ullmann's Encyclopedia of Industrial Chemistry, 2011)

In weather-resistant powder coatings, hydroxyalkylamide (HAA) curing agents are becoming more popular as an alternative to triglycidyl isocycanurate (TGIC) products, although this trend varies

greatly from one region to another. In recent years, enormous progress has been made with the use of this crosslinking system to influence reactivity, optimize gas oven stability, and improve degassing properties.
A key demand made on all powder coating systems is simple and reproducible gloss reduction. About 30 percent of all durable outdoor powder coatings need to be matt, especially for applications such as automotive accessories, facades and housings for electronic components.
A new cost-efficient matting principle for the important hydroxyalkylamide powder coating segment has been developed. Samples should be available in 2010.
(Smart Formulating Journal 02)

Coating powders for exterior use are mainly based on the saturated polyester (SP)–TGIC system. The following alternatives have been found:

- SP–PUR system, i.e., the combination of hydroxy-functional polyester resins with caprolactam-blocked isocyanate adducts (primarily based on isophorone diisocyanate).
- Acrylic resins are of importance mainly in the United States (AC–PUR) and in Japan. The AC–PUR system is used for automotive components and in domestic appliances. The PUR systems based on uretdione (a dimerization product of isocyanates) do not release reaction products and may be mentioned as a specialty.

(Ullmann's Encyclopedia of Industrial Chemistry, 2011)

There are different grades of solder mask ink depending upon the electronic application. For some low performance applications TGIC free solder mask inks are available and suitable. However for high performance electronics to the best of our current knowledge, there are currently no viable alternatives to use of TGIC in solder mask ink.

(Industry, personal communication)

3.2 Conclusions on alternatives:

As discussed in the above paragraph, there are already several alternatives known and used for TGIC in coating powders. Further R&D activities are ongoing in direction of further search for new alternatives.
There is also information that TGIC is already banned in many countries and replaced by β-hydroxy-alkylamides (HAA). (Grenda 2000)

According to the Industry, in recent years more than 90% of the TGIC powder coating formulations have successfully been replaced in Europe using beta-hydroxyl alkyl amide or glycidylester alternative cross linkers. A few TGIC based powder coatings are however still being used. It is considered that for some applications the current alternative cross linkers do not completely satisfy the most demanding technical profiles or that the switch to an alternative technology may be shifted or hindered because the volume in use at some powder users is too small to justify for economic reason any development work, parameter adjustment.
(Industry, personal communication)

Replacement of TGIC with alternatives in solder mask inks is possible for low performance elecronics, but not possible for high performance electronics.
(Industry, personal communication)

4 RISK-RELATED INFORMATION

4.1 Minimal Risk Levels

RISK-RELATED INFORMATION

As TGIC is not produced in EU, exposure and risk due to this step are not relevant for REACH.
Due to TGIC being cross-linked and no longer present as epoxide in coating, there is no consumer exposure.

For workers exposure the following life-cycle steps are relevant:

- Powder coating formulation
- Formulation of powder coating
- Transfer and Packaging of Powder Coatings
- Transfer of PC preparation into small containers and milling
- Production / Formulation of Solder mask inks.
- Transfer of SR For Solder Resist Applications
- Industrial Application of Solder Resist Inks
- Professional Application of Solder Resist Inks
- Maintenance and clean-up for all above mentioned processes

Older measured workers exposure concentrations indicate, that the proposed Occupational Exposure limits (0.05 mg/m^3 - 0.1 mg/m^3) are exceeded for all processes; the highest workers exposure was noted for application of powder coating. Modelled exposure values from the Registration Dossier shows much lower concentrations than the older (1993 – 1994) monitored workers exposure. Recent measurements of the workers exposure are not available.

From solder mask ink applications the processes employed in the EU tend to be conducted under highly automated systems with LEV and under “Clean room” conditions. The primary potential occasions for worker exposure are during the brief process of transfer to equipment where workers take appropriate measures to reduce exposure including use of PPE and LEV is in operation. Application processes themselves take place under automated closed processes with LEV in operation.

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ANNEX 1: RELEVANT HUMAN HEALTH ENDPOINTS

1 TOXICOKINETICS (ABSORPTION, METABOLISM, DISTRIBUTION AND ELIMINATION)

No information of β-TGIC toxicokinetics is available. Data for α-TGIC is used as an indication.

Several biochemical and clinical studies indicate that α -TGIC is rapidly absorbed by the oral and inhalation route (mutagenicity studies), but that dermal absorption is slow and less efficient. Nevertheless, dermal absorption takes place as indicated by the moderate skin sensitization potential in experimental animals and by the numerous case reports on Human skin sensitization.
Once absorbed, TGIC is rapidly metabolized by epoxide hydrolases, in most of the organs and tissues of vertebrates, most efficiently in humans.
No bioaccumulation has been observed in humans during clinical trials, and recovery was fast after the end of treatment. In experimental animals treated for 90 days or 2 years no bioaccumulation was observed either.
TGIC is distributed via blood in the entire body causing effects in blood cells, liver, lymph system as well as in peripheral tissues. Metabolites are mainly the hydroxylates (either di-, tetra-or hexa-hydroxylated TGIC). No parent compound has been found in urine of humans.
In conclusion, TGIC is absorbed rapidly, distributed and metabolized in short time(hydrolysis half-life in humans < 2 minutes) and excreted within 24 hours. No bioaccumulation has been observed in experimental animals or in humans.

Non-guideline target-oriented studies have been conducted to investigate the influence of epoxide hydrolase and other enzymes on the hydrolysis and detoxification of TGIC, on the DNA-binding potential of TGIC, and in clinical trials to elucidate the potential anti-tumour activity of TGIC in humans. Epoxide hydrolase is the key enzyme to hydrolyse TGIC in many organs of the animal and human body. It forms the respective triols which are glucuronidated and excreted. Degradation / hydrolysis of TGIC also occurs in the stomach due to low pH of 1-3. The alkylation potential is rapidly eliminated by acid treatment of TGIC, thus, the mutagenic potential is dependent on the intact TGIC-molecule (hydrolysis products are inactive). Human clinical studies (Phase-1) have shown that the anti-tumour activity found in mice was lacking in Humans. This is due to the very short half-life of TGIC in the humans (t/2 < 2minutes).

Together with other repeated dose studies, the following toxico-kinetic picture of TGIC can be drawn:

- TGIC is rapidly absorbed from the lung, and the gastro-intestinal tract, but slowly and to a small extent from skin.
- In the stomach it is hydrolyzed by acid and in the organism by epoxide hydrolases.
- The serum half-life of the substance is <2 minutes; is metabolized to a large extent to a triol cyanurate, which is rapidly excreted.
- After oral exposure, the maximum blood levels are reached after 2-4 hours with a rapid decline afterwards.
- Due to the short serum half-life, no organ defects are found after acute exposure (oral, dermal, inhalation).
- Only after repeated exposure, hematological effects and effects on the lymph nodes, spleen and thymus are found. The same is true for effects in spermatogonial cells which appear

only after repeated exposure. Based on its half-life in the organisms and based on the logPow (-0.8) no bioaccumulation is expected.

(Registration Dossier 2010)

Mechanism of toxicity: No information is available concerning the mechanism of toxicity of TGIC. Considering that TGIC contains three reactive epoxide groups it is plausible that it reacts with macromolecules causing different adverse effects, e.g. inducing mutations by binding directly to DNA and sensitization by binding to proteins. Dose dependent increases in TGIC-DNA adduct formation were reported in a non peer reviewed study. (Nordic Council of Ministers 2001)

2 MUTAGENICITY

This is an overview of data for TGIC (a combination of α and ß TGIC; technical grade TGIC contains 90% α -and 10% ß-isomer). As there is no data for pure ß-TGIC, information on TGIC isomer combination is given. Both mixture TGIC and ß-TGIC are classified as Mutagen Category 1B (mutagen category 2).

2.1 Non-human information

2.1.1 In vitro data

The results of experimental studies are summarised in the following table:

Table 6: Overview of experimental in vitro genotoxicity studies

Method	Results	Remarks	Reference
bacterial reverse mutation assay (e.g. Ames test) (gene mutation) S. typhimurium TA 1535, TA 1537, TA 98 and TA 100 (met. act.: with and without) S. typhimurium TA 1538 (met. act.: with and without) Doses: 1.22 – 10000 microgram/plate OECD Guideline 471 (Bacterial Reverse Mutation Assay)	Test results: positive for S. typhimurium TA 1535; met. act.: with and without; cytotoxicity: yes positive for S. typhimurium TA 98; met. act.: with and without; cytotoxicity: yes positive for S. typhimurium TA 100; met. act.: with and without; cytotoxicity: yes ambiguous for S. typhimurium TA 1538; met. act.: with and without; cytotoxicity: yes	2 (reliable with restrictions) key study experimental result	A.J.W. Hoorn (1987)
mammalian cell gene mutation assay (gene mutation) mouse lymphoma L5178Y cells (met. act.: with and without) Doses: Seven TGIC-concentrations were tested (15.63 1000 g/ml) in the first and second (0.47 - 30 g/ml) test. TGIC without S9 (0.175, 0.35, 0.7, 1.4, and 2.8 g/ml) TGIC with S9 (0.375, 0.75, 1.5, 3.0, and 6.0 g/ml) method according to Clive, D. et	Evaluation of results: positive (with and without metabolic activation) Test results: positive for mouse lymphoma L5178Y cells(strain/cell type: 2) TGIC was dissolved in DMSO, and diluted into the culture medium. 3) In a preliminary toxicity test the concentration of TGIC causing a 85% reduction of the viability of cells was determined in	2 (reliable with restrictions) key study experimental result	P. Beilstein & D. Müller. (1983)

Method	Results	Remarks	Reference
al Validation and characterization of the L5178Y/TK+/- mouse lymphoma mutagen assay system. Mutation Res. 59, 61-108 (1979)	suspension growth after 4-hour treatment and 72 hour susp); met. act.: with and without; cytotoxicity: yes		
bacterial reverse mutation assay (e.g. Ames test) (gene mutation) S. typhimurium TA 1535, TA 1537, TA 98 and TA 100 (met. act.: with and without) Doses: 312.5 - 5000 micrograms/plate JAPAN: Guidelines for Screening Mutagenicity Testing Of Chemicals	Test results: positive for S. typhimurium TA 1535; met. act.: with and without; cytotoxicity: no, but tested up to precipitating concentrations positive for S. typhimurium TA 100; met. act.: with and without; cytotoxicity: yes positive for E. coli WP2 uvr A; met. act.: with and without; cytotoxicity: yes negative for S. typhimurium TA 1535, TA 1537, TA 98 and TA 100; met. act.: with and without; cytotoxicity: yes positive for S. typhimurium TA 98; met. act.: with and without; cytotoxicity: yes	2 (reliable with restrictions) supporting study experimental result	PC Jenkinson (1988a)
bacterial reverse mutation assay (e.g. Ames test) (gene mutation) S. typhimurium TA 1535, TA 1537, TA 98 and TA 100 (met. act.: with and without) E. coli WP2 uvr A (met. act.: with and without) Doses: 312.5 - 5000 micrograms/plate JAPAN: Guidelines for Screening Mutagenicity Testing Of Chemicals	Test results: negative for S. typhimurium TA 1537; met. act.: with and without; cytotoxicity: yes positive for S. typhimurium TA 1535; met. act.: with and without; cytotoxicity: yes positive for S. typhimurium TA 98; met. act.: with and without; cytotoxicity: yes positive for S. typhimurium TA 100; met. act.: with and without; cytotoxicity: yes positive for E. coli WP2 uvr A; met. act.: with and without; cytotoxicity: yes	2 (reliable with restrictions) supporting study experimental result	PC Jenkinson (1988b)
in vitro mammalian chromosome aberration test (chromosome aberration) lymphocytes: Human (met. act.: with and without) Doses: 0.0625, 0.125, 0.25, 0.5, 1.0 g/ml without S9-activation 0.625, 1.25, 2.5, 5.0, 10.0 g/ml with S9-activation Method according to Obe, G. , Beek, B., Vaidya, VG. (1975). The Human Leucocyte test system. III. Premature chromosone condensation from chemically and X-ray induced micronuclei. Mutation Research 27, 89-101	Evaluation of results: positive Test results: positive (upper two dose levels) for lymphocytes: Human; met. act.: with and without; cytotoxicity: yes	2 (reliable with restrictions) key study experimental result	F. Strasser & P. Arni (1985)

Method	Results	Remarks	Reference
DNA damage and repair assay, unscheduled DNA synthesis in mammalian cells in vitro (DNA damage and/or repair) primary culture, other: Human fibroblasts (CRL 1521, passage no. 11, 18) (met. act.: without) Doses: Toxicity test: 7.81 1800 g/ml DNA-damage test: 250, 100, 30, 9, and 2.7 g/ml. performed according to the published method of San, R.H.C. and Stich, H.F. DNA repair synthesis of cultured human cells as rapid bioassay for chemical carcinogens. Int. J. Cancer 16, 284-291 (1975)	Evaluation of results: negative Test results: negative for mammalian cell line, other: Human fibroblasts (CRL 1521, passage no. 11, 18)(strain/cell type: Human fibroblasts (CRL 1521, passage no. 11, 18)); met. act.: without; cytotoxicity: yes	2 (reliable with restrictions) supporting study experimental result	Th. Hertner and E.
DNA damage and repair assay, unscheduled DNA synthesis in mammalian cells in vitro (DNA damage and/or repair) primary culture, other: rat hepatocytes (met. act.: without) Doses: 28.1 1750 g/ml for cytotoxicity testing 0.2, 1, 2.5, 5, 10 and 20 g/ml for the main test OECD Guideline 482 (Genetic Toxicology: DNA Damage and Repair, Unscheduled DNA Synthesis in Mammalian Cells In Vitro)	Evaluation of results: positive Test results: positive for hepatocytes: rat(strain/cell type: primary rat hepatocytes); met. act.: without; cytotoxicity: yes	2 (reliable with restrictions) supporting study experimental result	Th. Hertner and E. Puri (1988)
mammalian cell gene mutation assay (Transformation test) BALB/3T3 mouse embryo fibroblasts, clone A31-1-1 (T. Kakanuga NCI NIH, Bethesda, USA). (met. act.: without) Doses: 3.75 ng/ml 1000 g/ml (toxicity rest) 8.75 140 ng/ml (transformation test). Transformation assay in BALB/3T3 mouse embryo Fibroblasts. Transformation requires gene mutations to abolish contact inhibition between fibroblast cells.	Evaluation of results: negative Test results: negative for BALB/3T3 mouse embryo fibroblasts(strain/cell type: BALB/3T3 mouse embryo fibroblasts); met. act.: without; cytotoxicity: yes	2 (reliable with restrictions) supporting study experimental result	P. Beilstein & D. Müller (1983)

(Registration Dossier 2010)

2.1.2 In vivo data

The results of experimental studies are summarised in the following table:

Table 7: Overview of experimental in vivo genotoxicity studies

Method	Results	Remarks	Reference
mammalian germ cell cytogenetic assay (chromosome aberration) mouse (strain B6D2F1) male oral: gavage 0, 28.75, 57.5, and 115 mg/kg (analytical conc.) OECD Guideline 483 (Mammalian Spermatogonial Chromosome Aberration Test)	Evaluation of results: positive Test results: Genotoxicity: positive (increase in major chromosomal aberrations) (male); toxicity: yes (change of cytotoxic ratio)	1 (reliable without restriction) key study experimental result	R. Marchall (1991)
micronucleus assay (chromosome aberration) hamster, Chinese (, raised in Ciba-Geigy premises as outbred strain) male/female oral: gavage 0, 140, 280, and 560 mg/kg (nominal conc.) The methods applied in this study are referenced as follows: Boller, K. & Schmid, W. Humangenetik 11, 35-54 (1970); Matter, B. & Schmid, W. , Mutation Research 12, 417-425 (1971); Müller, D. et al., Verh. Dtsch. Ges. Path. 56, 381-384 (1972).	Evaluation of results: positive Test results: Genotoxicity: positive (male/female); toxicity: no effects	2 (reliable with restrictions) key study experimental result	G. Hool & P. Arni (1983a)
chromosome aberration assay (chromosome aberration) mouse (strain B6D2F1 (hybrid of C57B1/6 x DBA/2)) male oral: gavage 0 (control), 28.75 mg/kg (low dose), 57.5 mg/kg (intermediate dose), and 115 mg/kg (high dose), (analytical conc.) OECD Guideline 483 (Mammalian Spermatogonial Chromosome Aberration Test)	Evaluation of results: positive Test results: Genotoxicity: positive (male); toxicity: no effects (no clinical signs recorded, no bw changes)	1 (reliable without restriction) key study experimental result	R. Marshall. (1991)
chromosome aberration assay (chromosome aberration) mouse (male Crl:CD-1(ICR)BR mice) male inhalation: dust 0, 1.79, 10.3, and 49.6 mg/m3 air (analytical conc.) EPA OTS 798.5380 (In Vivo Mammalian Cytogenetic Tests: Spermatogonial Chromosomal Aberrations)	Evaluation of results: positive Test results: Genotoxicity: positive (at 10.3, and 49.6 mg/m3 air) (male); toxicity: yes (loss of weight during exposure period)	2 (reliable with restrictions) weight of evidence experimental result	J.J. Vergnes & E.R. Morabit. (1992a)
sister chromatid exchange assay (chromosome aberration) hamster, Chinese male/female oral: gavage 0. 140, 280, and 560 mg/kg (nominal conc.) no guideline cited ,but performed	Evaluation of results: positive Test results: Genotoxicity: positive (male/female); toxicity: no effects	2 (reliable with restrictions) supporting study experimental result	G. Hool & P. Arni (1983b)

Method	Results	Remarks	Reference
according to Allen, J.W. et al, Cell Genetics 18, 231-237, 1977, and Marquardt, H. & U. Bayer, Mutation Research 56, 169-176, 1978, Chinese hamster bone marrow cells in-vivo were evaluated with respect to sisterchromatid exchange (SCE).			
mammalian germ cell cytogenetic assay (chromosome aberration) mouse (CD-1) male inhalation: dust 1.79, 10.3, and 49.6 mg/m3 air (mean gravimetric measurements) EPA OPPTS 870.5380 (In Vivo Mammalian Cytogenetic Tests: Spermatogonial Chromosomal Aberrations)	Evaluation of results: ambiguous Test results: Genotoxicity: negative (male); toxicity: yes (decreased mitotic index, insufficient analysable metaphases)	2 (reliable with restrictions) supporting study experimental result	J.J. Vergnes & E.R. Morabit. (1992b)
micronucleus assay (Nucleus anomaly Test) hamster, Chinese male/female oral: gavage 0, 140, 290 and 560 mg/kg bw (nominal conc.) no guideline cited, but the method used is Matter, B. and Schmid, W. Mutation Research 12, 417-425 (1971). Study on interphase nuclei in bone-marrow cells of chinese hamster after oral exposure (gavage) of a single dose.	Evaluation of results: positive Test results: Genotoxicity: positive (single Jolly bodies increased) (male/female); toxicity: no effects	2 (reliable with restrictions) supporting study experimental result	G. Hool & P. Arni (1983d)

(Registration Dossier 2010)

2.2 Human data

There are no Human mutagenicity data available.

2.3 Summary and discussion of mutagenicity

Discussion

TGIC has been shown to cause gene mutations in-vitro in bacterial systems as well as in mammalian cell cultures systems.
It also caused chromosomal aberrations, micronuclei, and sister chromatid exchanges in mammalian cell systems.
In-vivo, TGIC caused in a variety of rodent assays chromosomal aberrations, in both somatic as well as in germinal tissues.
The reason for the lack of gene mutations in-vivo is not known, but it could have many reasons: Either the systems used were not sensitive enough for gene mutations, or the major mutagenic activity of TGIC is to cause chromosomal aberrations, e. g. DNA breaks and not base modifications or base substitutions.

However, the observed effects are significant and make TGIC a category 2 mutagen (according to 67/548/EEC classification) or mutagen 1B (according to CLP classification).

The following information is taken into account for any hazard / risk assessment:
TGIC is genotoxic in-vitro and in-vivo.
It causes chromosomal effects in male germinal tissues such as testis and seminiferous tubules.
Primary and secondary spermatocytes are affected.

Justification for classification
Based on the in-vitro mutagenic effects and based on the in-vivo clastogenic effects in somatic as well as in germ cells the classification and labelling as category 2 mutagen and R46 or mutagen 1B and H340 (according to CLP classification) is justified.

(Registration Dossier 2010)

Remark: This is an overview of data for TGIC (a combination of α and ß TGIC isomers; technical grade TGIC contains 90% α -and 10% ß-isomer). As there is no data for pure ß-TGIC, information on TGIC isomer combination is given. Both the combination of TGIC isomers and ß-TGIC are classified as Mutagen Category 1B (mutagen category 2).

ANNEX 2: CONFIDENTIAL DATA

The information contained in this Annex has been removed in this public version.

1 CONFIDENTIAL DATA ON SUBSTANCE COMPOSITION

2 CONFIDENTIAL DATA ON PRODUCTION AND USE VOLUMES

3 CONFIDENTIAL DATA ON USE AND INDUSTRIAL PROCESSES OF TGIC (A COMBINATION OF ISOMERS)

4 RECENT MODELED AND HISTORICAL MEASURED WORKERS EXPOSURE DATA FROM THE CONFIDENTIAL CSR

5 CONFIDENTIAL DATA ON CONSUMER EXPOSURE

6 RISK REDUCTION MEASURES THAT ARE ALREADY IN PLACE ACCORDING TO REGISTRATION DOSSIER