National Industrial Chemicals Notification and Assessment Scheme

Priority Existing Chemical No. 1

Triglycidylisocyanurate (TGIC)

Full Public Report

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Preface

This assessment is made under the National Industrial Chemicals Notification and Assessment Scheme (NICNAS). This Scheme was established by the Commonwealth *Industrial Chemicals (Notification and Assessment) Act 1989* (the Act), which came into operation on 17 July 1990.

The principal aim of NICNAS is to help protect people and the environment from the harmful effects of industrial chemicals by finding out the risks to occupational health and safety, to public health and the environment.

NICNAS has two major parts: one focussing on the risks associated with new chemicals before importation or manufacture; and one focussing on existing industrial chemicals already in use in Australia. As there are many thousands of existing industrial chemicals in Australia, NICNAS has a mechanism of prioritising assessments by declaring certain existing chemicals to be Priority Existing Chemicals (PECs). This report provides the full public report of a PEC assessment. A summary report is also publicly available and has been published in the Commonwealth *Chemicals Gazette*.

NICNAS is administered by Worksafe Australia. Assessments under NICNAS are done in conjunction with the Commonwealth Environment Protection Agency and and the Department of Health, Housing, Community Services and Local Government.

This assessment report has been prepared by the Director, Chemicals Notification and Assessment in accordance with the Act. This report has not been subject to tripartite consultation or endorsement by the National Occupational Health and Safety Commission.

The Director, Chemicals Assessment has delayed publication of this report by ten months while the Administrative Appeals Tribunal (AAT) finalised an application for review of the Director's decision to refuse to vary this report. The AAT considered application number P93/339 and handed down the decision and the reasons for their decision on 18 March 1993. All decisions of the Director were affirmed by the AAT.

In accordance with section 40 of the Act, a person may apply to the Director for variation of this full public report using the approved form by 3 May 1994. A fee must be paid with the application.

On publication of the Summary Report in the *Chemicals Gazette* of 5 April 1994, the chemical will no longer be a Priority Existing Chemical in accord with Section 62 of the Act.

Copies of the full public report can be purchased from Commonwealth Government Bookshops.

For the purposes of subsection 78(1) of the Act, copies of full public reports may be inspected by the public at the Library, Worksafe Australia, 92-94 Parramatta Road, Camperdown, NSW 2050, between 10am and 12 noon and 2pm and 4pm each weekday except on public holidays.

A pamphlet giving further details of the PEC program and approved forms to apply for variation of this report are available from Worksafe Australia. Please contact the Chemicals Assessment Branch at:

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1. Introduction

The chemical known as triglycidylisocyanurate (TGIC), CAS Number 2451-62-9, was declared by the Minister for Industrial Relations as a Priority Existing Chemical (PEC) by notice in the *Chemical Gazette* of 5 November 1991.

TGIC is a triepoxy compound used as a cross-linking agent. The declaration was to apply in general with no limitation as to specified purpose or geographical area. The main use for TGIC in Australia is as an ingredient in powder coatings used in the metal finishing industry.

The declaration by the Minister was made on the basis that there were reasonable grounds for believing that handling, storage, use and disposal of the chemical could give rise to a risk of adverse health effects.

In summary these grounds were:

recent animal toxicity studies indicated a potential for TGIC to cause genetic damage. The studies raised concern that TGIC could be a human carcinogen and mutagen and could have adverse reproductive effects; and

- there were a significant number of workers exposed to TGIC.

- The objectives of the assessment were to:

- characterise the potential health hazards presented by TGIC, and in particular its genotoxicity; and

- to determine if these hazards could be satisfactorily controlled in the workplace.

In order to meet the assessment objectives, information was collected from a range of sources, including the information dossiers documenting toxicology, manufacturing and data relevant to occupational exposure obtained from applicants, a literature search and site visits.

Following declaration of TGIC as a PEC, importers and manufacturers were required to apply for assessment of the chemical. The applications received indicate that while there is significant importation of TGIC and TGIC powder coatings, there is no intention to manufacture TGIC in Australia. This report therefore focuses on the use of TGIC in the manufacture of powder coatings for metal finishing and in the application of powder coatings to metal objects.

2. Background

2.1 Uses of TGIC

TGIC has been used as a curing agent in weather-resistant powder coatings in Europe for about 20 years. For much of this time TGIC powder coatings have also been in use in Australia, either imported or manufactured by ICI Dulux Pty Ltd, Taubmans Pty Ltd or Paint Industries Pty Ltd. Powder coated objects are now ubiquitous in Australia, and include office and garden steel furniture, car parts, metal fencing, window and door frames, shelving, electrical equipment, and domestic appliances such as refrigerators, washing machines and ovens.

TGIC contains three epoxide groups which give alkylating and cross-linking properties to the chemical. TGIC, in its molten state reacts easily with various functional groups in the presence of catalysts or promoters. TGIC, like other similar epoxides, can react with amines, carboxylic acids, carboxylic acid anhydrides, phenols and alcohols. In the actual curing process, these reactions are more complex because of their side reactions.

Commercial (technical) grade TGIC is a mixture of two optical stereoisomers, alpha and beta. The alpha isomer was used as an experimental anti-tumour agent under the names of 'Teroxirone', 'alpha-TGT', and 'Henkels compound'. Clinical use of the alpha isomer was not pursued.

There are two main technical grades of TGIC used in the manufacture of powder coatings worldwide. These are 'Araldite PT 810' (also known as 'TK 10622') manufactured by Ciba-Geigy Pty Ltd, Switzerland, and 'TEPIC', manufactured by Nissan Chemical Industries Pty Ltd, Japan.

2.2 Health Issues

During the manufacture and use of TGIC over the last 20 years the only human health effect reported in the published literature is allergic dermatitis. There is a range of animal toxicological studies available in unpublished and published literature.

In 1991, inhalational studies in animals raised concerns that TGIC may be genotoxic at low dose levels, and may therefore act as either a reproductive toxicant, an inducer of heritable mutations and/or a carcinogen in humans. This report assesses the data and makes recommendations on the safe use of TGIC and products containing it.

3. Applicants

Ciba-Geigy Australia Ltd
235 Settlement Rd,
Thomastown, Victoria 3074

Dulux Powder Coatings
40 Sarton Rd,
Clayton, Victoria 3168

Evode Powder Coatings Pty Ltd
Unit 1/3,
Jindalee Pl,
Riverwood, NSW 2210

Itochu Australia Ltd
35th Floor,
530 Collins St,
Melbourne, Victoria 3000

Jotun Powder Coatings Pty Ltd
9 Cawley Rd,
Brooklyn, Victoria 3025

Sumitomo Australia Limited
Level 47, Nauru House,
80 Collins St,
Melbourne, Victoria 3000

Taubmans Pty Ltd
Birmingham Ave,
Villawood, NSW 2163

Western Coatings Pty Ltd
49B Kangaloon Rd,
Bowral, NSW 2576

4. Chemical identity

4.1 Chemical name and Chemical Abstracts Service (CAS) Registry number;

Triglycidylisocyanurate 2451-62-9

4.2 Other names

1,3,5-Triglycidyl isocyanurate

TGIC

1,3,5-Triazine-2,4,6(1H,3H,5H)-trione1,3,5-tris (oxiranylmethyl)-

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

Tris(2,3-epoxypropyl) isocyanurate

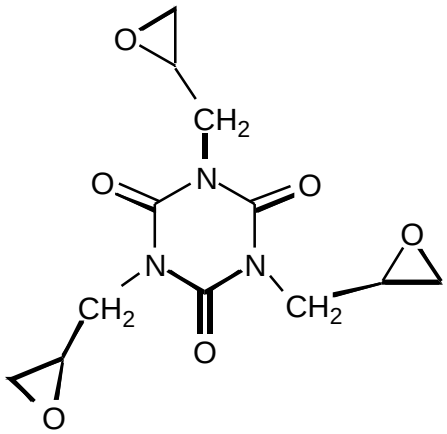
4.3 Trade names

Araldite PT 810
TEPIC
TK 10622

4.4 Molecular formula

$C_{12}H_{15}N_3O_6$

4.5 Structural formula



4.6 Molecular weight

297.3

4.7 Spectral data

For the IR spectrum provided, major identifying peaks were at 927, 1465 and 1685 cm^{-1}. The mass spectrum provided was consistent with the structure of TGIC.

5. Physical and chemical properties

TGIC is manufactured and supplied as the technical grades TEPIC and Araldite PT 810 (also known as TK 10622). The physical and chemical properties listed below are those of the technical grades.

5.1 Degree of purity

- TEPIC 90% TGIC (approximately)
- Araldite PT 810 > 97% TGIC

5.2 Appearance

At 20˚C and 101.3 kPa, TGIC technical grades are white, granular solids with no discernible odour.

5.3 Melting point

- TEPIC 90-125˚C
- Araldite PT 810 95˚C

5.4 Density

- TEPIC 1420 kg/m^3
- Araldite PT 810 1460 kg/m^3

5.5 Vapour pressure

- Araldite PT 810 7.2 mPa at 20˚C

5.6 Water solubility

- TEPIC 9 g/L at 25˚C

5.7 Partition coefficient

- TEPIC log $P_{o/w}$-0.8

5.8 Hydrolysis as a function of pH

TEPIC has a half-life of approximately 1.25 hr at 70˚C in aqueous solution. Araldite PT 810, at 37˚C, is not hydrolysed at pH 7 in 3 hr or at pH 2 in 1 hr and it has a half-life of approximately 40 minutes at pH 11.

5.9 Dissociation constant

Not applicable as TGIC contains no dissociable groups.

5.10 Flash point

- TEPIC > 170˚C

5.11 Combustion products

CO_2, CO and oxides of nitrogen.

5.12 Autoignition temperature

- TEPIC > 200˚C

5.13 Reactivity/stability

Molten TGIC reacts rapidly with the following functionalities: primary and secondary amines, carboxylic acids and anhydrides, thiols, phenols and alcohols (the latter at higher temperatures). It can also be polymerised by catalysts. Molten TGIC may undergo hazardous autopolymerisation.

5.14 Particle size distribution

Particle size distribution for a TGIC technical grade granules (TEPIC):

- 0.003% < 10 mm,
  0.12% < 150mm,
  99.6% > 400 mm.

Particle size distribution of two powder coatings:

a) 99.7% < 105 mm,
   6.2% < 9.56 mm,
   2.3% < 7 mm; and

b) 96% < 106 mm,
   4.0% < 9.4 mm,
   1.0% < 6.6 mm.

6. Methods of detection and analysis;

Methods of detection and analysis include infrared spectroscopy, mass spectroscopy, epoxy equivalent weight, gas chromatography and High Performance Liquid Chromatography (HPLC).

Methods for determination of TGIC in dust were submitted by Nissan Chemical Industries Pty Ltd and Ciba-Geigy Pty Ltd. The methods are similar and are included in Attachment 1 and Attachment 2.

7. Use

TGIC is used as a three-dimensional cross-linking or curing agent for polyester resins. TGIC is either imported as technical grade TGIC for the manufacture of polyester powder coatings in Australia or as an ingredient of polyester powder coatings which have been formulated overseas.

The powder coatings 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 metal objects are then placed in a stoving oven where at temperatures of approximately 200˚C the resin melts, flows and chemically cross-links to form a durable paint film. The powder coated articles are allowed to cool prior to inspection, packing and despatch.

TGIC is not manufactured in Australia.

The estimated amount of TGIC, imported as technical grade and as a component of powder coatings, is 100-1000 tonnes per year.

8. Manufacture of TGIC powder coatings

Technical grades of TGIC, known as TEPIC and Araldite PT 810, are imported into Australia as granules.

In the manufacture of powder coatings, TGIC is mixed with resin, pigments, fillers and additives at a level of between four and ten per cent by weight of the final product. Pigmented powder coatings usually contain between four and five per cent of TGIC. Clear powder coatings do not include pigments and contain between seven and ten per cent TGIC. The estimated ratio of pigmented powder coatings to clear powder coatings used in Australia is in the order of 100:1.

The raw materials, including TGIC in dry granulate form, are weighed into a mixing hopper. Batched raw materials are dry blended in a sealed mixer and then transferred to an extruder where initially the mixture is heated until melting occurs (>100˚C). This melt is mixed to ensure homogeneity and is then extruded onto a roller which spreads the extrudate out into a thin sheet. The sheet is carried on a conveyor belt where it cools and solidifies. The solid material is then automatically chipped, milled and sieved to remove coarse particles. The resulting fine powder is packed into polythene bags which are placed in cardboard boxes and finally despatched to customers. In the resultant powder coating, TGIC is partially cross-linked to the polyester resin.

9. Occupational exposure

Occupational exposure is expected to occur in two general settings:

- plants, where powder coatings are manufactured using technical grade TGIC; and
- factories and paint shops, where TGIC powder coatings are sprayed onto metal objects prior to curing in ovens.

9.1 Exposure during manufacture

There are only a few powder coating manufacturing plants in Australia. The number of workers involved in powder coating formulation in Australia is approximately 150.

The following is a general description of the likely worker exposure in a plant manufacturing TGIC powder coatings.

9.1.1 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.

9.1.2 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.

9.1.3 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 of disposable dust masks and personal protective clothing as required, such as when weighing, spraying or when cleaning equipment.

9.1.4 Research and development

Research and development is carried out on TGIC in the form of:

(a) the dry granulate;

(b) as part of the dry blend;

(c) as part of the melt mix; and

(d) as part of the final product, in a laboratory environment.

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.

9.1.5 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.

9.2 Exposure during use - spray application

There are over 500 powder coating establishments nationally. The number of spray painters using powder coatings containing TGIC is difficult to estimate, but is likely to be at least 3,000 workers. 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.

9.2.1 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.

9.2.2 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.

9.2.3 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.

9.2.4 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.

9.2.5 General

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

10. Evaluation of animal toxicological data

The toxicological studies reviewed used a number of technical grade TGIC and TGIC powder coatings. These include:

- Technical grade TGIC:
  - TEPIC,
  - TK 10622,
  - PL90-810,
  - LMB 364,
  - PL88 810,
  - Araldite PT 810, and
  - LMB 281; and
- Powder coatings:
  - PL90-810PC,
  - TK 10622/1 powder coating,
  - TK 10622/2 powder coating, and
  - U.60092.100 G.

10.1 Acute toxicity

10.1.1 Oral toxicity [2-6]

In each of the acute oral toxicity studies five male and five female animals per dose were used and the observation period was 14 days. The results of the studies are summarised in Table 1.

The variability in the LD_{50} values may be partially accounted for by the different vehicles used. On the basis of oral LD_{50} figures, TGIC was more acutely toxic to rats than hamsters.

From the results of these studies, the acute oral LD_{50} (rat) for TGIC is < 100 mg/kg (male) and 255 mg/kg (female).

Table 1
Acute oral toxicity of TGIC

Chemical	*Species*	*LD_{50} mg/kg*	*Dose mg/kg*	*Pathology*	*Ref*
TK 10622	Rat: Tif, RAI f (SPF)	< 100 (m) 255 (f) (0.5% CMC)	100-500	Oedematous and haemorrhagic lungs; liquid-filled thoracic cavity; spotted, haemorrhagic or involuted thymus; involuted testes; enlarged kidney; dilated stomach; dilated small intestine	2
TK 10622	Rat: Tif, RAI f (SPF)	302 (m) 305 (f) (A.O.)	100-1000	No compound-related gross organ changes	3
TEPIC	Rat: Sprague-Dawley CFY	447 (m) 948 (f) (A.O.)	100-1290	Haemorrhagic lungs; dark or pale liver;intestinal haemorrhage; pale kidneys; sloughing and haemorrhage of gastric epithelia	4
TK 10622	Hamster	1672 (m/f) (A.O.)	300-3000	No compound-related gross organ changes	5
TK 10622	Rat: Tif, RAI f (SPF)	431 (m/f) (2% CMC)	100-1290	No compound-related gross organ changes	6

m males
f females
CMC carboxymethylcellulose, vehicle
A.O. arachid oil, vehicle

10.1.2 Dermal toxicity[7-9]

In three acute dermal toxicity studies, technical grade TGIC was applied to intact shaven skin prior to the application of a semi-occlusive dressing. After 24 hours the skin was washed clean. The animals were observed for 14 days. The studies are summarised in Table 2.

From the observations, there were no deaths, no treatment-related adverse clinical signs and, at necropsy, no gross organ changes.

The acute dermal LD_{50} (rat) for TGIC was > 2000 mg/kg in all three studies.

Table 2
Acute dermal toxicity of TGIC

Chemical	*Species*	*Number of animals*	*Dose (mg/kg)*	*LD_{50} (mg/kg)*	*Ref*
TK 10622	Rat: Tif, RAI f (SPF)	5/dose group	200 (m) 2000 (m,f)	> 2000 (0.5% CMC)	7
TK 10622	Rat: Tif, RAI f (SPF)	3 m, 3 f per dose group	215-3170	> 3170 (2% CMC)	8
TEPIC	Rat: Sprague-Dawley CFY	5 m, 5 f limit test	2000	> 2000 (A.O.)	9

m males
f females
CMC carboxymethylcellulose, vehicle
A.O. arachid oil, vehicle

10.1.3 Inhalational toxicity[10-13]

A. Technical grade TGIC

Single, four-hour inhalational exposure studies using technical grade TGIC were conducted[10-12]. The studies are summarised in Table 3.

Two of the studies[10, 11] employed nose-only exposure to groups of 10 male and 10 female Tif, RAI f (SPF) rats, while the other study[12] employed whole body exposure to groups of five male CD-1 mice. In the study using whole body exposure[12] to PL90-810, TGIC encrustation of the eye, nose and mouth was observed and therefore ingestion of the chemical is likely to have occurred.

Data on particle size showed that the majority (60-100 per cent) of the particles in these technical grade TGIC samples were within the respirable range (that is, < 7 mm).

The acute inhalational LC_{50} (rat) for TGIC is 650 mg/m^3/4h (0.65 mg/L/4h) for females and > 650 mg/m^3/4h for males (no males died during the study)[10].

Table 3
Acute inhalational toxicity of TGIC

Chemical	*Species*	*Study type and dose*	*LC_{50} mg/m^3/4h*	*Pathology*	*Ref*
TK 10622	Rat: Tif, RAI f (SPF)	Nose-only, dust 0 mg/m^3 410 mg/m^3 650 mg/m^3	> 650 (m) 650 (f)	No substance-related gross organ changes in sacrificed animals; partial haemorrhage in lungs of dead animals	10
TK 10622	Rat: Tif, RAI f(SPF)	Nose-only, liquid aerosol 0 mg/m^3 309 mg/m^3	> 300 (m/f)	No substance-related gross changes	11
PL90-810	Mouse: CRL, CD-1 (ICR)BR	Whole body, dust 1050 mg/m^3 2390 mg/m^3 3880 mg/m^3	2000 (m)	Perinasal/periocular/perioral encrustation; lung discolouration	12
	m f	males females			

A further study[13] was conducted using only two male and two female rats, nose-only exposed for 30 minutes to TK 10622 at an atmospheric level of 3200 mg/m^3. This was the highest achievable concentration under the test conditions and 18.3 per cent of the particles had an aerodynamic diameter < 3 mm. The animals were observed for five days. Breathing frequency and tidal volume showed minor variations during the exposure period. No deaths occurred and the only clinical sign noted was a five per cent loss in body weight among females. At necropsy several dark red loci were observed on the lungs of one male and several grey-white foci on the lungs of one female.

B. Powder coating

An inhalational study using PL90-810PC powder coating[14] employed a single, four-hour, whole-body exposure to groups of five male Crl, CD-1 (ICR)BR mice. The mice were exposed to powder coating at atmospheric concentrations of 0, 2480, 5160 or 11,640 mg/m^3. The particle size distribution of the powder coating was 3.8-6.9 mm.

No substance-related gross organ changes were observed in the mice. The LC_{50} (mouse) of > 11,640 mg/m^3/4h for powder coating is higher in comparison with the studies using technical grade TGIC. The percentage of TGIC in the powder coating was not stated.

10.1.4 Skin irritation[15-19]

A. TK 10622[15-19]

Three male and three female New Zealand white rabbits were used in each of the three studies using TK 10622. In two studies the test article was 0.5 ml of TK 10622 as a 50 per cent solution in polypropylene glycol[15, 17]. In the other study 0.5 ml of TK 10622 in an unknown solvent was applied to the skin[16]. In all studies the semi-occlusive dressing was removed after 24 hours and observations continued for at least 72 hours.

Skin reactions were scored for erythema and oedema. Similar results, consisting of very slight erythema and oedema in the intact skin of some animals up to 72 hours post application, were obtained in all studies.

The results of these studies indicate that TK 10622 is not a skin irritant.

B. TEPIC[18, 19]

The procedure used in these two studies was similar to that used for TK 10622 except that 0.5g of TEPIC powder was moistened with distilled water prior to application on intact skin.

In one study[18], the semi-occlusive wrap was held in place for four hours instead of the usual 24 hours. Both studies gave similar results, which consisted of very slight erythema and no oedema observed at the treated skin sites in all animals. The results indicate that TEPIC is not a skin irritant.

The studies using TK 10622 and TEPIC indicate that TGIC is not a skin irritant.

10.1.5 Eye irritation[20-22]

The procedure used in the three eye irritation studies was the same. One 0.1 g sample of TK 10622 was placed in the conjunctival sac of the left eye of each of three male and three female New Zealand white rabbits. The untreated right eye served as control. In three of the six rabbits, the treated eye was flushed with saline. Eyes were assessed for irritation at 24, 48, 72 hours and four and seven days post-treatment.

In one of the studies20, TK 10622 was not an eye irritant. In the other two studies[21, 22] with TK 10622, severe eye reactions were noted. Moderate to severe corneal opacity, redness, chemosis and discharge were present in all treated, unwashed eyes up to seven days post-instillation. Rinsing of the eyes was found to have a palliative effect.

The results of these studies indicate that TGIC can be considered to present a risk of serious damage to eyes.

10.1.6Skin sensitisation[23, 24]

Groups of 10 male and 10 female guinea pigs were used to test the sensitisation potential of TK 1062223 or TEPIC24. In both studies the induction was carried out in two stages, followed by a challenge phase.

A. TK 10622[23]

The test procedure for the study with TK 10622 was as follows:

Induction
Stage I. Intradermal injections of adjuvant only in the neck area of each animal and 40 mg TK 10622 applied topically over injection sites and occluded for 24 hours.

Stage II. One week later 120 mg TK 10622 in vaseline was applied occlusively to the injection site for 48 hours.

Challenge
Two weeks after stage II induction, 20 mg TK 10622 was applied occlusively for 24 hours to the flank. A second challenge, similar to the first challenge, was performed after a further 10 days.

In this study, four of 20 treated animals and five of 20 treated animals showed a positive response at the first and second challenges with TK 10622, respectively. A positive response was seen as slight to moderate erythema and/or oedema. No adverse skin responses were noted at the vehicle control skin sites of the test group animals. The animals in the control group did not show a positive response when challenged with TK 10622.

B. TEPIC[24]

The test procedure for the study with TEPIC was as follows:

Induction
Stage I. Intradermal injections of 0.5 mg TEPIC in arachid oil and of 0.5 mg TEPIC in adjuvant, to the shoulder area of each animal.

Stage II. One week later 100-150 mg of TEPIC in arachid oil was applied topically to the injection site and held under an occlusive wrap for 48 hours.

Challenge
Two weeks after Stage II induction 50-100 mg TEPIC in arachid oil was applied occlusively for 24 hours to the right flank of each animal.

In this study 12 of 20 treated animals showed a positive response (seen as erythema) when challenged with TEPIC. No adverse skin responses were noted at the vehicle control skin sites of the test group animals. No adverse skin responses were noted when control groups were challenged with TEPIC.

On the basis of these animal studies, TGIC is considered to be a skin sensitiser.

10.2 Short-term repeated dose toxicity

10.2.1Oral[25]

Groups of 10 male CFE rats were administered 0, 54 or 216 mg/kg/day technical grade TGIC, LMB 364, in dimethylsulfoxide (DMSO) by gavage. In the same study, female CFE rats (10/dose) were administered LMB 364 dissolved in DMSO at dose levels of 0, 43 and 172 mg/kg. All rats were administered LMB 364 for seven consecutive days.

No abnormal clinical signs and symptoms were observed.

Male rats in the 54 mg/kg dose group showed a minor degree of cytoplasmic vacuolation of the epithelium of the renal distal convoluted tubules. One female in the 43 mg/kg dose group showed extensive necrosis and desquamation of the epithelium in the renal tubules. In both high dose groups renal tubular damage was observed, with necrosis of the epithelium of the loop of Henle and distal convoluted tubules evident.

Haemorrhagic and degenerative changes involving the gastric and duodenal mucosa were also observed in the high dose groups.

10.2.2Inhalation[26, 27]

A. Technical grade TGIC

Groups of twelve CD-1 male mice were subjected to nose-only exposure to atmospheres containing 0, 10, 40 or 140 mg TEPIC/m^3 for six hours/day for five days[26]. Two animals from each group were killed six hours after the final exposure and cytotoxicity was assessed. The surviving animals were observed over a 17 day recovery period. Clinical signs of toxicity were observed in the intermediate and high dose groups. These signs included hunched posture, pilo-erection, lethargy, ptosis, decreased respiratory rate and noisy or gasping respiration. There were increased body weight losses and high mortality in the high and intermediate dose groups. There was one death unrelated to treatment (the animal turned around and suffocated in the restraining tube) in the low dose group. The mortality and pathology results are summarised in Table 4.

The particle size data showed that between 79 and 88 per cent of the particles were less than 4 mm and therefore respirable.

Approximately 400 metaphase cells were scored per animal. Cytotoxicity in germ cells,

measured as spermatogonial mitoses/first and second meiotic metaphases was not increased in the treated groups. This indicates a lack of effect of TGIC on germ cell survival at high mortality levels.

In this study, no adverse effects were observed in rats exposed to 10 mg/m^3 of TGIC. However, adverse clinical signs, increased bodyweight losses and higher mortality occurred at inhalational levels of 40 and 140 mg TGIC/m^3.

Table 4
Five day, repeated dose, nose-only inhalational exposure to TGIC in male mice[26]

Dose (mg/m^3)	*Mortality*	*Pathology*
10	1/10	Single death was unrelated to treatment; slightly reddened lungs in one animal.
40	4/10	Dark or reddened lungs in some animals which died during the study.
140	9/10	Decedents showed dark or reddened lungs, pale liver, pale kidneys and congestion of the small intestine.

B. Powder coating

In another study[27], groups of ten male CD-1 mice were subjected to whole body exposure to atmospheres containing PL90-810PC powder coating at doses of 0, 300, 1000 or 1700 mg/m^3, for 6 hr/day, for five days. Animals were observed for 14 days after the last dose was administered. The percentage of TGIC in the powder coating was not stated. The average particle size was 3.0 to 3.5 mm.

In the high dose group, one animal died and two animals had swollen periocular tissue and blepharospasm. Mean body weights of the treated groups were not different to the control group. Body weight gain was lower in both the high and intermediate dose groups. At necropsy no substance-related gross lesions were observed in surviving animals. However, severe post-mortem changes in all organs were evident in the high-dose mouse which died during the study. In this study there were no adverse effects observed in mice exposed to 1000 mg/m^3 of PL90-810PC powder coating.

10.3 Genotoxicity

10.3.1 *Salmonella typhimurium* reverse mutation assay[28-31]

Two reverse mutation assays (Ames tests), a total of three individual experiments, tested the mutagenic potency of TK 10622 in *Salmonella typhimurium*[28, 29]. The solvent used was DMSO. The strains used were TA1535, TA1538, TA1537, TA98 and TA100 in both studies. In one of the studies[29] *E. coli* WP2*uvrA* was included in addition to the standard tester strains.

TK 10622 did not induce back mutation to prototrophy in TA1537 or *E. coli* WP2*uvrA*, with and without metabolic activation (S9). In both studies, although TK 10622 was mutagenic in TA1535 and TA1538, a more pronounced effect was observed in the pKM101 derivatives, TA100 and TA98 respectively. The average mutagenic potencies were 0.22 induced mutants/mg in TA98 and 0.33 induced mutants/mg in TA100, without metabolic activation. The mean number of spontaneous mutants per plate was 21 for TA98 and 107 for TA100, both within the limits acceptable for spontaneous levels of back mutants. The maximum mean number of induced mutants was 410 at 2500 mg/plate for TA98 and 637 at 2500 mg/plate for TA100. Similar results were obtained in the presence of S9. TGIC was positive in these Ames tests but the data suggests that it is a weak mutagen given that potencies for mutagens vary from about 10-2 to 104 mutants/mg[32].

There were two other reports on mutagenic potency in *Salmonella typhimurium*. One study using a pigmented powder paint containing 4.5 per cent TGIC[30], and the other using an unpigmented powder paint containing ten per cent TGIC[31]. In each case, doses up to 20,000 mg of test article in DMSO were used in strains TA1535, TA1537, TA1538, TA98 and TA100. Induced mutants were not observed in either study.

In all of the above Ames tests, appropriate negative and positive controls were included and the spontaneous levels of back mutants in all experiments were within acceptable limits.

Results of the Ames tests indicate that TGIC is a weak direct-acting mutagen.

10.3.2 Mouse lymphoma cells mutagenicity test[33]

The ability of TK 10622 to induce forward mutation to 5-bromodeoxyuridine resistance was measured in mouse lymphoma L5178/TK$^{+/-}$ cells. The test substance was dissolved in DMSO. The study was performed with and without metabolic activation. The results are summarised in Table 5.

Without metabolic activation, the positive control 0.75 ml/ml of ethylmethanesulphonate increased the mutation frequency to 32.9 times that of the negative control and 2.8 mg/ml of TK 10622 increased the mutation frequency to 9.4 times that of the solvent control.

The effect of metabolic activation by rat liver S9 was to decrease the induced mutation frequency to control levels up to 3.0 mg/ml of TK 10622. At 6.0 mg/ml TK 10622 increased the mutation frequency to 7.5 times that of the solvent control. The presence of S9 also decreased the cytotoxic effect of TK 10622, reflected by an increase in the relative cloning efficiency. This happened in association with a decrease in mutation frequency.

TK 10622 was mutagenic in this mouse lymphoma cells forward mutation assay, both in the presence and absence of metabolic activation.

Table 5
The induction of forward mutation by TGIC
in mouse lymphoma cells - *in vitro*

Conditions		*+/- S9*	*Mutants/106 surviving cells*
Solvent Control - DMSO		-S9	18.0
Negative Control - untreated		-S9	15.2
Positive Control - EMS 0.75 ml/ml		-S9	500.0
TK 10622	0.175 mg/ml	-S9	9.34
	0.35 mg/ml	-S9	20.2
	0.7 mg/ml	-S9	15.2
	1.4 mg/ml	-S9	42.6
	2.8 mg/ml	-S9	169.4
Solvent Control		+S9	25.6
Negative Control - untreated		+S9	12.9
Positive Control - DMN			
	0.75 ml/ml	+S9	129.2
TK 10622	0.375 mg/ml	+S9	21.6
	0.75 mg/ml	+S9	19.4
	1.5 mg/ml	+S9	14.1
	3.0 mg/ml	+S9	29.2
	6.0 mg/ml	+S9	192.9

DMS	dimethylsulphoxide
EMS	ethylmethane sulphonate
DMN	dimethylnitrosamine

10.3.3 Unscheduled DNA synthesis in rat hepatocytes[34]

TK 10622 was tested for DNA-damaging effects in rat hepatocytes *in vitro* as measured by induction of unscheduled DNA synthesis (UDS).

Treatment of cells with chemicals can cause DNA-damage. Subsequent DNA repair can be measured by incorporation of ^{3}H-thymidine which may be determined by counting the silver grains on the autoradiograph. In this assay, rat hepatocytes were incubated with concentrations of 1.0, 2.5, 5, 10 and 20 mg TK 10622/ml for 18 hours.

The results shown in Table 6 demonstrate a clear dose response after TGIC treatment at concentrations from 5-20 mg/ml, and it is concluded that TGIC was genotoxic to rat hepatocytes.

Table 6
Unscheduled DNA synthesis in isolated rat hepatocytes incubated with TGIC

Treatment		*Net grains/nucleus ± SD*
Negative Control	medium	-0.26 ± 2.04
	DMSO	-0.98 ± 2.81
Positive Control	DMN 25 mM	6.46 ± 4.97
	50 mM	7.50 ± 5.31
TK 10622 (mg/ml)	0.2	-0.44 ± 3.36
	1.0	1.56 ± 4.43
	2.5	0.99 ± 3.16
	5.0	2.18 ± 2.74
	10.0	7.13 ± 5.04
	20.0	8.81 ± 9.0

DMSO dimethylsulphoxide
DMN dimethylnitrosamine

10.3.4 Cell transformation[35, 36]

In each of two studies, mouse embryo fibroblasts (BALB/3T3) were tested for the induction of colony formation by TK 10622. Under normal conditions, these cells grow in flasks as a monolayer. Induction of colony formation has been shown to correlate with the ability of a chemical to induce malignant transformation. Taking both studies together, 10 doses between 8.8 and 5000 ng TK 10622/ml were used. Incubation of TGIC with mouse embryo fibroblasts was not associated with an increase in colony formation at any of the dose levels tested and did not significantly increase the number of colonies. Positive controls used in both assays showed a significant increase in the number of colonies formed. TGIC tested negative in these cell transformation assays.

10.3.5 Chromosomal aberrations in human lymphocytes[37]

TK 10622 was tested for its ability to induce structural chromosomal aberrations in human lymphocytes isolated from freshly collected blood. Cells were seeded into flasks 46 hours prior to treatment and then grown for 43.5 hours. Two and a half hours prior to harvesting, the cultures were treated with 0.4 mg/ml Colcemide.

One hundred metaphases were examined in the negative control cultures and in those cultures treated with TK 10622 at doses between 62.5 and 10,000 ng/ml. No structural chromosomal aberrations were observed in cells exposed to concentrations of TK 10622 of up to 2,500 ng/ml. One aberration was observed at 5,000 ng/ml and one at 10,000 ng/ml. TK 10622 was negative for mutagenic effects in this assay. Significant numbers of chromosomal aberrations were observed in the positive controls.

10.3.6 Unscheduled DNA synthesis in human fibroblasts[38]

TK 10622, in the concentration range of 2.7 to 400 mg/ml, was tested for its ability to induce unscheduled DNA synthesis in human fibroblasts (cell line: CRL 1521) *in vitro*. The methodology was similar to that used for the measurement of unscheduled DNA synthesis in rat hepatocytes (section 10.3.3). The mean number of nuclear grain counts varied from 0.18 to 0.26 for the cultures treated with TK 10622 compared to 0.29 for the negative control and 15.08 for the positive control 4-nitroquinoline-N-oxide. The results of this study indicate that TGIC did not induce unscheduled DNA synthesis in human fibroblasts *in vitro*.

10.3.7 *In vivo* nucleus anomaly test[39]

TK 10622 in arachid oil was administered by gavage to groups of three male and three female randomly outbred Chinese hamsters at dose levels of 0, 140, 280 or 560 mg/kg/day for two days. The animals were sacrificed 24 hours after the second dose and femoral bone marrow samples were taken. One thousand bone marrow cells were scored per animal.

The mean percentage of nuclear anomalies was 0.2 for the vehicle control (arachid oil) and 6.9 for the positive control, cyclophosphamide at a dose level of 128 mg/kg.

The mean percentage of nuclear anomalies for the TK 10622 low dose group was 0.3, not significantly different from the negative control. But those of the intermediate and high dose groups were 0.6 and 1.6 respectively, significantly different from the negative control.

The increases in nuclear anomalies were mainly due to increases in single Howell-Jolly

bodies, although small non-dose-dependent increases in micronucleated erythroblasts, erythrocytes and leucopoietic cells were seen.

The results indicate that TGIC is clastogenic, that is, it can cause chromosome breakage.

10.3.8 *In vivo* sister chromatid exchange study[40,41]

Two studies were conducted to determine the ability of TK 10622 to induce sister chromatid exchanges (SCEs) in the bone marrow cells of Chinese hamsters. In each study TGIC was suspended in arachid oil and administered by gavage.

Two hours prior to TK 10622 treatment, a 45 mg tablet of 5-bromodeoxyuridine was implanted subcutaneously in the neck of the experimental animals. In both studies the hamsters were killed 24 hours after dosing. Two hours prior to killing, an intraperitoneal injection of 10 mg/kg Colcemide was administered. Twenty-five cells per animal were scored for SCEs.

In one study[40], groups of four males and four females were treated with TK 10622 at dose levels of 0, 35, 70 and 140 mg/kg. In this study no increases in the number of SCEs were observed.

In the second study[41], groups of two males and two females were treated with TK 10622 at doses of 0, 140, 280 and 560 mg/kg and a positive effect was observed. These results are shown in Table 7 and were statistically analysed using the t-test. These results indicate that TGIC induced a dose-related increase of SCEs in bone marrow cells of Chinese hamsters when administered by gavage. The positive control, 7,12-dimethyl benz(a)anthracene (DMBA), yielded a significant increase in SCEs per cell.

Table 7
SCE* induction in bone marrow cells of Chinese hamsters administered TGIC[41]

Treatment		*SCEs per cell*
Vehicle Control (Arachid oil)		5.07 ± 2.63
Positive Control (DMBA, 100 mg/kg)		10.66# ± 5.04
TK 10622 (mg/kg):	140	8.26# ± 4.36
	280	8.30# ± 8.25
	560	9.85# ± 10.9

* Sister Chromatid Exchanges
\# $p < 0.01$
DMBA 7,12-dimethylbenz(a)anthracene

10.3.9 Chromosomal aberrations in mouse germ cells - *in vivo*[42-50]

A number of studies have been conducted to determine the genetic effects of TGIC, either technical grade or formulated, on mouse germ cells as measured by induction of chromosomal aberrations. The routes of administration used were gavage, whole body exposure to dust and nose-only exposure to dust.

A. Gavage[42-47]

The results of experiments involving oral administration of TGIC are summarised in Table 8 and Table 9. In each of the studies male mice were dosed orally on five consecutive days. In one study[42] the mice were killed on the day following the final treatment and statistical analysis was not carried out on the data. In the other four studies the mice were killed six hours after the final dose and statistical analyses were carried out.

The studies using technical grade TGIC[42, 43, 44] indicate that TGIC is able to induce chromosomal aberrations in mouse spermatogonia when administered orally. The lowest dose at which cytotoxicity was observed was 57.5 mg/kg.

In the studies with TGIC powder coatings[45, 46], chromosomal aberrations were significantly induced at only one dose level in one study[45].

Table 8
Induction of chromosomal aberrations in mouse spermatogonia following oral administration of TGIC
(data not statistically analysed)

Chemical	*Strain*	*Number of animals*	*Dose (mg/kg)*	*Number of aberrations*	*Number of Metaphases*	*Ref*
TK 10622	Tif MAGf (SPF)	12	0	1	700	42
		15	42.7	4	800	
		15	128.0	7	300*	

* Cytotoxicity observed.

Table 9
Induction of chromosomal aberrations in mouse spermatogonia following oral administration of TGIC and TGIC powder coatings (data statistically analysed)

Chemical	*Strain*	*Dose (mg/kg)*	*% Aber-rations*	*Number of metaphases*	*Ref*
PL88 810	ICR	0	0.6	1000	43
		30	0.5	1000	
		125	2.5*	1000	
		350	3.0*	1000#	
TK 10622	B6D-2F1	0	0.8	500	44
		28.75	3.1+	481	
		57.5	2.1+	478#	
		115	5.1+	413#	
TK 10622/1	BCD-2F1	0	0.2	500	45
Powder Coating	29.6	0.2	500		
(8.92% TGIC)		88.9	0.8	500	
		266.7	0.7	500	
		800	1.6*	500	
TK 10622/2	B6D-2F1	0	0.4	500	46
Powder Coating	185.2	0.2	500		
(4.8% TGIC)		555.6	1.2	500	
		1667	0.0	500	
		5000	1.4	500	

* $p < 0.05$
\+ $p < 0.01$
\+ $p < 0.001$
\# Cytotoxicity observed.
\+ Several chromatid exchanges, which are extremely rare in untreated animals, were observed.

Another study[47] tested the effect of oral administration of TK 10622 on the induction of chromosomal aberrations in primary and secondary mouse spermatocytes. In this case TK 10622 in arachid oil was administered to groups of 15 male Tif:MAGF(SPF) mice at dose levels of 0, 32 or 96 mg/kg. Twelve male mice served as the negative control. Administration by gavage occurred on days 0, 2, 3, 5 and 9. Animals were killed 3 days after the final dose. The results of this study were negative.

B. Whole body exposure[48, 49]

Two inhalational studies were conducted, by Bushy Run Research Centre, using male CD-1 mice exposed to TGIC atmospheres for 6 hr/day for five days. One study[48] used technical grade TGIC, PL90-810, and the other study[49] used a ten per cent powder coating formulation. The incidences of chromosomal aberrations in the spermatogonial cells were measured following exposure.

Technical grade TGIC

In the study with technical grade TGIC[48], groups of 10 mice were exposed to PL90-810 at concentrations of 0, 2.5, 10 and 50 mg/m^3. The positive control, cyclophosphamide, was administered intraperitoneally at a dose of 50 mg/kg and the animals were killed 30 hours later. The particle size range of PL90-810 was 2.5 to 3.5 mm. Large amounts of dust were deposited on the chamber walls, animal fur and animal cages during the study.

No deaths occurred and no adverse clinical signs were observed in the TGIC-treated animals. Body weight losses occurred in all groups. Animals were killed six hours after the end of the last exposure. The results of the study, when only animals with greater than 50 scorable cells are considered, are summarised in Table 10. The study suggests TGIC was cytotoxic to spermatogonial cells at doses of 10 and 50 mg/m^3. However, the cytotoxic ratios were not calculated. There was a decrease in the mitotic indices as TGIC concentration increased. The report stated that statistical analysis could not include the 10 and 50 mg/m^3 groups due to the small number of animals in these groups with sufficient numbers of scorable cells. At the low dose of 2.5 mg/m^3 the percentage of cells with chromosomal aberrations was not significantly different from the negative control.

Data presented in this study indicated that large quantities of dust were deposited on the chamber wall, cage and animal fur. Therefore, ingestion as a result of grooming probably occurred and the dose taken in by the animal cannot be exactly determined.

There were some other inconsistencies with this study. There was a very low number of scorable cells at the higher dose groups and the cytotoxic ratio was not measured. The mean number of cells with chromosomal aberrations in the control group was 4.5 per cent, much higher than the expected value.

The results of this study were therefore inconclusive. The potential for TGIC to produce chromosomal damage in spermatogonial cells could not be determined. The study suggests that TGIC was toxic to mouse spermatogonial cells at atmospheric concentrations of 10 mg/m^3 and 50 mg/m^3. However, cytotoxicity was not clearly established and the low number of cells could have been a result of poor technical skill.

Table 10
Induction of chromosomal aberrations in mouse spermatogonia following whole body exposure to TGIC

Treatment group	Total number of cells scored	% Aberrant cells in animals with > 50 scorable cells	Number of animals with > 50 scorable cells
PL90-810			
0.0 mg/m^3	664	4.7	9
2.5 mg/m3	797	5.1	9
10.0 mg/m^3	390	2.1*	5
50.0 mg/m^3	253	8.3*	3
Cyclophosphamide i.p.			
50.0 mg/kg	553	12.7‡	7

* Statistical significance not evaluated.
‡ 0.05 | p > 0.01
i.p. intraperitoneal

Ten per cent TGIC powder coating

In a second study[49], groups of 10 CD-1 male mice were whole body exposed to atmospheres containing 0, 100, 1000 or 1700 mg/m^3 PL90-810PC powder coating. The powder coating contained ten per cent TGIC. The animals were killed six hours after the last exposure period. The positive control, cyclophosphamide, was administered intraperitoneally at a dose of 50 mg/kg and the animals were killed 30 hours later.

Table 11 shows the results obtained when only animals with greater than 50 scorable cells were considered. The test material significantly increased the number of chromosomal aberrations in spermatogonial cells of the animals exposed to 1700 mg/m^3 powder coating. An anomaly in the study was a reduction in the number of animals with ≥ 50 scorable cells at the low dose compared to the mid dose. This could have been a result of cytotoxicity or poor experimental skill. Large quantities of dust were deposited on the chamber wall, cage and animal fur. Grooming was likely to have occurred and the dose taken in by the animal cannot be accurately determined.

Table 11
Induction of chromosomal aberrations in mouse spermatogonia cells following whole body exposure to ten per cent TGIC powder coating

Treatment group	*Total number of cells scored*	*% Aberrant cells in animals with ≥ 50 scorable cells*	*Number of animals with ≥ 50 scorable cells*
10% TGIC powder coating			
0.0 mg/m^3	704	0.3	9
100.0 mg/m^3	314	0.3	4
1000.0 mg/m^3	621	1.6	8
1700.0 mg/m^3	204	2.5*	3
Cyclophosphamide i.p.			
50.0 mg/kg	713	6.9‡	9

* $0.01 \geq p > 0.001$
‡ $p \geq 0.001$
i.p. intraperitoneal

C. Nose-only exposure[50,51]

TEPIC and ten per cent TEPIC powder coating[50]

A nose-only, five day inhalational study was conducted by Safepharm Laboratories, in which CD-1 mice were exposed to TEPIC or ten per cent TEPIC powder coating for 6 hr/day. Oral administration of TEPIC was included in this study for comparison. The authors stated that the methodology complied with OECD *Guideline Number 483*[52] 'Mammalian germ-cell cytogenetic assay', except that the animals were killed six hours after the final exposure to the test material, instead of 24 hours.

The results are summarised in Table 12. The cytotoxic ratio is the number of spermatogonial metaphases divided by the number of first and second meiotic metaphases. The lower the ratio the greater the toxicity of the test material to spermatogonial cells.

In groups 1 to 5, ten mice per group were treated for five consecutive days and killed 6 hours after the final exposure. In groups 6 and 7, positive controls, five mice per group were treated once only and were then killed 24 hours after treatment.

The particle size distributions for the dusts used in the inhalational studies were 95% < 4 μm in group 2, 80% < 4 μm in group 3, and 69% < 4 μm in group 4.

Table 12
Induction of chromosomal aberrations in mouse spermatogonia

Treatment Group	*Dose*	*Number of cells scored*	*Exposure*	*Cytotoxic ratio*	*Aberration /100 cells (without gaps)*
1. Control	0.0 mg/m^3	882	inhalation	5.04	0.6
2. TEPIC	7.8 mg/m^3	747	inhalation	3.95	0.9
3. TEPIC, 10% powder	95.3 mg/m^3	759	inhalation	3.41	1.4
4. TEPIC, 10% powder	255.3 mg/m^3	821	inhalation	3.70	1.2
5. TEPIC	115.0 mg/kg	293	oral	0.76‡	3.1*
6. Cyclophosphamide	50.0 mg/kg	386	oral	3.36	0.3
7. Mitomycin C	3.0 mg/kg	297	i.p.	1.35*	40.7‡

* p< 0.01
‡ p< 0.001
inhalation nose-only inhalation
i.p. intraperitoneal

There were no deaths during the study. The only adverse clinical signs noted were confined to one animal exposed to 255.3 mg/m^3 of ten per cent TEPIC powder coating on day four and all animals treated orally with 115 mg/kg/day on day five. These animals displayed hunched posture and pilo-erection. Bodyweight gain was unaffected in all groups.

Administration of TEPIC and ten per cent TEPIC in powder coating by the inhalational route slightly increased cytotoxicity. As the vehicle control group had a cytotoxic ratio slightly greater than historical controls, the ratios for TEPIC and ten per cent TEPIC powder exposure groups were considered to be normal. TEPIC and ten per cent TEPIC powder administered by inhalation did not significantly increase chromosomal damage in spermatogonial cells at the doses tested.

Oral administration of TEPIC, 115 mg/kg bodyweight, significantly increased both cytotoxicity and total chromosomal aberrations in spermatogonial cells.

The cyclophosphamide positive control did not increase chromosomal damage. The authors concluded that "the cell cycle kinetics of spermatogonial cells are such that the effects of this chemical (cyclophosphamide) cannot be detected at a 24 hour kill-time". There was no significant reduction in the cytotoxic ratio in the cyclophosphamide group. However, intraperitoneal injection of Mitomycin C significantly increased total aberrations and significantly reduced the cytotoxic ratio.

OECD *Guideline Number 483*52 states that when one dose of the test compound is used, it should be the maximum tolerated dose or that producing some indication of cytotoxicity. Only one dose of TEPIC was used in this study and cytotoxicity and clinical effects were not evident. These effects were also not observed at the doses of ten per cent TEPIC

powder selected in this study. The guidelines also state that to establish a dose-response relationship, at least three doses are required. Using ten per cent TEPIC powder did not assist in establishing a dose response for TEPIC.

In a similar repeated dose, nose-only, inhalational study[26], TEPIC at concentrations of 10, 40 and 140 mg/m^3 was not cytotoxic toward spermatogonial cells, but clinical signs of toxicity were seen at 40 mg/m^3. In the above chromosomal aberration study50, the dose should have been increased until there were some indication of cytotoxicity or clinical signs of toxicity.

In this nose-only inhalation study, exposure of mice to 7.8 mg/m^3 of TGIC for five days did not induce chromosomal aberrations in spermatogonial cells. However, at this level of exposure cytotoxicity or adverse clinical effects were not observed. This study did not indicate at what level, if any, TGIC causes chromosomal aberrations in mouse spermatogonial cells following inhalational exposure. The study did indicate that no adverse effects were observed at a dose level 7.8 mg/m^3 of TGIC.

4.6 per cent TGIC powder coating[51]

In an inhalational study by Hazelton Microtest Laboratory[51], groups of six B6D2F1 male mice were exposed for 6 hr/day to powder coating U.60092.100 G, a white pigmented powder containing 4.6 per cent TGIC. The mice were exposed to atmospheres containing 250, 500, 1000 or 2000 mg/m^3 of powder coating. The animals were killled six hours after the end of the final exposure. The positive control, Mitomycin C, was administered intraperitoneally at a dose level of 0.3 mg/kg and the animals were killed 24 hours later.

The results are summarised in Table 13. The cytotoxic ratio was slightly lower for the 1000 and 2000 mg/m^3 dose groups. A statistically significant increase in the number of spermatogonial cells with chromosomal aberrations was observed in animals exposed to the highest concentration - 2000 mg/m^3. The increase was mainly due to chromosme damage in a single animal. Among the aberrations observed in the 1000 and 2000 mg/m^3 dose groups there were three chromatid exchanges. The positive control group showed a significant increase in the number of cells with chromsomal aberrations.

The body weights of the animals exposed to powder coating remained the same or decreased slightly during the period of exposure. No other compound-related sign of toxicity were observed.

The mean mass median aerodynamic diameter of the particles in the atmosphere for the treated groups was 6.53 to 11.54 μm.

Table 13
Induction of chromosomal aberrations in mouse spermatogonia

Treatment	*Number of cells scored*	*Cytotoxic ratio*	*Cells with aberrations (without gaps)*
Control	600	3.2	0
4.6% TGIC powder coating			
250.0 mg/m^3	500	2.8	3
500.0 mg/m^3	500	3.9	2
1000.0 mg/m^3	500	2.4	3
2000.0 mg/m^3	600	2.3	6*
Mitomycin C i.p.			
0.3 mg/kg	500		26‡

* $p < 0.05$
‡ $p < 0.001$
i.p. intraperitoneal

10.3.10 Dominant Lethal Tests[53-55A]

Four dominant lethal studies were available for assessment - three studies with technical grade TGIC and one study with powder coating.

In the first study[53], TK 10622 in arachid oil was administered by single gavage at doses of 0, 160 and 480 mg/kg to groups of 20 male Tif MAGf(SPF) mice. These mice were mated over three periods of six days to 40 female mice per dose group. The female mice were replaced at the end of each period. Females were killed on day 14 of gestation and the numbers of live and dead foetuses and foetal resorptions were noted.

Females mated to males given 480 mg/kg of TK 10622 during the first period showed a significant increase in the number of embryonic deaths, compared with the negative control. No increase was seen in the females mated in the second and third periods at the same dose, nor in the females in the other treated groups.

In the second study[54], PL88-810 suspended in peanut oil was administered by single gavage at doses of 0, 138, 275 or 550 mg/kg to 20 male ICR mice per dose group. These mice were then mated over three periods of five days to 40 female mice per dose group. The female mice were replaced at the end of each period. No significant difference was observed in the number of embryonic deaths in test groups compared to the negative control. In this study, TGIC did not induce dominant lethal mutations in male mice.

In the third study[55], ten per cent TGIC in the powder coating PL90-810PC was administered by whole body inhalational exposure to dust at doses of 0, 100, 1000, or 1700 mg/m^3 for six hours per day for five consecutive days to 30 male CD-1 mice per group. Following treatment each male was mated to two virgin females for eight weekly periods with the females being replaced at the end of each period. Positive and negative control groups were included and increased embryonic deaths were noted in the positive control group. No increase in embryonic deaths was observed and

therefore TGIC powder coating did not induce heritable dominant lethal mutations under the conditions of the experiment.

In a fourth study[55A], a technical grade of TGIC (PL90-810) of unspecified purity and isomer composition was administered by whole body inhalation to dust at concentrations of 0.25 mg/m^3, 10 mg/m^3 and 50 mg/m^3 for six hours per day for five consecutive days to 30 CD-1 male mice per group. Following treatment, each male was mated to two virgin females of the same strain for eight weekly periods with the females being replaced at the end of each period. This was the only dominant lethal study for which the mating period covered all stages of the spermatogenic cycle.

In this study, TGIC did not induce dominant lethal mutations. In the third mating week there was a slight increase in the number of non-viable implants and early resorptions, but this was not statistically significant.

The study showed reduced fertility in males at 50 mg/m^3 with:

- reduced number of males impregnating females in the first three and six mating weeks; and
- a ten per cent reduction in testes weight in the 50 mg/m^3 group, but it was not statistically significant.

At 10 mg/m^3 there was also a reduction in the males impregnating females in the third mating week. The reductions in fertility were consistent with an effect on mature sperm, maturing spermatids and Type B spermatogonia at the 50 mg/m^3 levels. Fertility effects seen at 10 mg/m^3 were associated with Type B spermatogonia.

As there was only one positive dose point in one of four studies with TGIC, the evidence that TGIC induces dominant lethal mutations in mice is equivocal.

10.3.11 Alkylation of DNA[1, 56, 57]

In vitro[1]

In vitro TGIC induced alkylation of p-nitrobenzyl-pyridine, a model DNA substrate, has been tested at 37°C as a function of pH 1. The alkylation rate was maximal at pH 7 to pH 9 and the reaction rate proceeded linearly for up to three hours. The alkylation rate was greatly reduced by preincubating the TGIC for one hour at pH 0 and pH 1. This study shows that TGIC can alkylate a model DNA substrate and that TGIC is hydrolysed at low pH.

In vivo

An *in vivo* study[56] was conducted to determine alkylation of mouse liver, stomach and testis DNA by TGIC. Alkylation of DNA was measured as the Covalent Binding Index (CBI). The CBI is equivalent to μmol chemical bound per mol nucleotides/mmol chemical applied per kilogram of body weight. Radiolabelled TGIC, in either aqueous solution or in oil, was administered by gavage to at least two male Tif:MAGf(SPF) mice per group at doses of 5, 17 and 200 mg/kg. DNA was isolated at three, eight or 24 hours from the liver, stomach and testes and measured for radioactivity levels.

Dose-dependent increases in TGIC-DNA adduct formation were observed. The study

demonstrated that radioactivity in isolated DNA was due to covalent binding of TGIC to DNA. The CBIs for liver, stomach and testes DNA after administration of 200 mg/kg of TGIC are shown in Table 14.

This study also demonstrated, by measuring the levels of radioactivity in the blood, liver and testes, that the absorption of TGIC in oil is lower compared to the absorption from an aqueous vehicle. CBI values were lower after administration of TGIC in oil compared to TGIC in an aqueous vehicle, due to lower absorption.

Table 14
Covalent Binding Indices (CBI) for TGIC binding to DNA, at a dose level of 200 mg TGIC/kg bodyweight

Hours after administration	*CBI - Stomach*	*CBI - Liver*	*CBI - Testis*
3	8.9	2.0	0.3
8	6.1	1.6	0.2
24	3.2	1.2	0.2

CBI Covalent Binding Index, see text for explanation

By comparison, the CBI for liver DNA for the potent liver carcinogen aflatoxin B1 is about 20,000. For the moderate carcinogen 2-acetylaminofluorene the CBI is about 20056.

This study demonstrates that TGIC is capable of covalently binding to stomach, liver and testis DNA in mice following oral administration.

A recent *in vivo* study[57] was conducted in rats to assess the effect of induction of microsomal and cytosolic epoxide hydrolase activity on the hydrolysis of Araldite PT 810 and on the binding of Araldite PT 810 to liver DNA.

Initially, to induce epoxide hydrolase (EH) and glutatione S-transferase (GST) activities, groups of two to four male Tif:RAIf(SPF) rats were pretreated for five days with trans-stilbene oxide (TSO) at dose levels of 400 or 100 mg/kg body weight. TSO was administered intraperitoneally in sesame oil. Control animals received the vehicle only. The animals were then intraperitoneally or orally administered 20 mg [14C]Araldite PT 810/kg body weight on day six. Twenty-four hours later the animals were killed and the livers excised.

The activities of microsomal and cytosolic EH and GST were measured in subcellular liver fractions with Araldite PT 810 as the substrate. Cytosolic GST activity was also determined with the standard substrate chlorodinitrobenzene (CDNB). The results are summarised in Table 15. The results indicate that Araldite PT 810 in rat liver is hydrolysed by microsomal EH but not substantially by either cytosolic EH or GST. The hydrolysis rate for Araldite PT 810 increased following the induction of microsomal EH activity with TSO. Similar hydrolysis rates were also noted for styrene oxide following induction of microsomal EH.

DNA-binding activity of Araldite PT 810, calculated as CBI, and microsomal EH activity were measured in the livers of untreated rats and rats treated with TSO at dose levels of 100 or 400 mg/kg body weight. The results are summarised in Table 16 and are the mean of 4 animals ± 1 SD. The induction of microsomal EH activity in rat liver by TSO resulted in a concentration-dependent decrease in DNA binding by Araldite PT 810.

Human microsomal EH activity with Araldite PT 810 substrate was measured in livers from two healthy kidney donors. For comparison, the activities were measured with styrene oxide substrate in these and two other human livers. The microsomes were thawed and refrozen at least once before use. The microsomal EH activity with Araldite PT 810 was 17.1 and 30.3 nmol/min/mg. Similar activities were noted with styrene oxide as the substrate.

Table 15
Enzyme activities with Araldite PT 810 substrate in subcellular liver fractions of rats treated with TSO

	Enzyme activity (nmol/min/mg protein)		
Enzyme	*Control*	*TSO 100 mg/kg*	*TSO 400 mg/kg*
With PT 810			
Microsomal EH	6.4 ± 1.9	20.6 ± 0.6	31.8 ± 4.8
Cytosolic EH	< 0.05+	*	*
Cytosolic GST	0.46 ± 0.04	0.4 ± 0.02	0.4 ± 0.1
With CDNB			
Cytosolic GST	360 ± 100	670 ± 100	1280 ± 430

* not determined
\+ limit of detection
EH epoxide hydrolase
GST glutathione S-transferase
TSO trans-stilbene oxide

Table 16
Araldite PT 810 binding to DNA and microsomal epoxide hydrolase activity in rat livers

	Control rats	*TSO treated rats - 100 mg/kg*	*TSO treated rats - 400 mg/kg*
Microsomal EH activity (nmol/min/mg protein)	4.8 ± 0.4	11.8 ± 2.2	31.2 ± 9.6
CBI	4.5 ± 0.9	3.6 ± 0.5	2.4 ± 0.9

EH epoxide hydrolase
CBI covalent binding index
TSO trans-stilbene oxide

The results of this study indicated that increased microsomal EH activity was associated with increased hydrolysis of TGIC and a corresponding decrease in TGIC-DNA adduct formation in the rat liver. The study demonstrated that TGIC does bind to DNA *in vivo* in rats. However, the CBI values were relatively low suggesting that only a small proportion of administered TGIC binds to DNA in the rat liver.

10.3.12 Mouse spot test[58]

This test system permits the detection of mutational events in the melanoblasts of embryos exposed in utero to a chemical. The mutational events resulting from the expression of recessive genes involved in coat colour determination are observed as spots in the fur of young mice.

TK 10622 was administered in a single intraperitoneal injection to pregnant mice (C57 Bl/6) on the 10th day after conception. There were 96 females in each of the treatment groups and a total of 1518 animals were examined for spots.

At doses of 13.5, 27.0 and 54.0 mg/kg, the percentages of offspring with spots were 0.72, 1.07 and 0.28 per cent respectively, compared with 0.54 per cent for the negative control. The positive control of ethylmethanesulphonate at 100 mg/kg yielded 1.41 per cent of offspring with spots.

There was no evidence for *in vivo* mutagenicity of TGIC in the mammalian spot test.

10.4 Skin tumour promotion study[59]

The tumour initiating agent, dimethylbenzanthracene (DMBA), was applied dermally to the shaved backs of four groups of 24 male and 24 female CF-1 mice. Three weeks later these mice were painted with either 2.5 per cent LMB 281 (TGIC), 2.5 per cent beta-Propiolactone (BPL), solvent (acetone only) or received no secondary treatment. The mice were painted twice weekly for 26 weeks. After 27 weeks the mice were killed and the skin from the treated areas was examined microscopically.

Only mice who received the tumour promoting agent BPL developed skin tumours. Of those mice exposed to TGIC, one female showed severe acanthosis and two males showed ulceration.

This study provides very little relevant data on the carcinogenic potential of TGIC. In this study, 2.5 per cent TGIC did not promote skin tumour formation in mice initiated with DMBA.

10.5 Alpha-TGIC

Technical grade TGIC is a mixture of two optical stereoisomers, alpha and beta TGIC, which can be separated by fractional crystallisation. Alpha-TGIC was shown to cause regression of solid and ascitic tumours in mice. The alpha stereoisomer was used in the early 1980s as an experimental anti-tumour agent in human clinical trials.

No data were provided on the isomeric proportions of technical grade TGIC. The physico-chemical properties of the two isomers are quite different. For example, there

is approximately 20-fold difference in water solubility (alpha-TGIC = 10.01 g/L, beta-TGIC = 0.53 g/L at 20˚C). In light of these differences data submitted on the toxicity of the alpha isomer were not considered in this report.

10.6 Overall assessment of toxicological data

Acute animal toxicity studies showed that for TGIC the oral LD_{50} for male rats is < 100 mg/kg and for female rats the LD_{50} is 255 mg/kg [2-6]. In the acute oral studies, the LD_{50} values were variable but this may be due, in part, to the different vehicles used for the test substance. The dermal LD_{50} for rats is > 2000 mg/kg [7-9]. The acute inhalational LC_{50} of TGIC in female rats is 650 mg/m^3 and in male rats is > 650 mg/m^3 [10-14]. No deaths occurred in the male rats exposed to the dose level of 650 mg/m^3.

The results of short term repeated dose studies with TGIC suggest that, other than at the site of administration, the major effects were lung, gastric/duodenal and renal damage[25-27].

TGIC presents a risk of serious eye damage in rabbits[20-22], is not a skin irritant in rabbits[15-19] and is positive as a skin sensitiser in guinea pigs[23, 24].

TGIC was shown to be positive in a number of *in vitro* and *in vivo* genotoxicity tests.

In the *in vitro* studies, TGIC did not induce chromosomal aberrations or unscheduled DNA synthesis (UDS) in human lymphocytes[37] or fibroblasts[38] respectively, but was able to induce UDS in isolated rat hepatocytes[34]. TGIC induced mutations in *Salmonella typhimurium*[28-31] and mouse lymphoma cells33 but was unable to induce cell transformation in mouse embryo fibroblasts[35, 36]. In the Ames tests[28-31] TGIC was not a potent mutagen.

Other studies published in the literature demonstrated positive *in vitro* tests for induction of SCEs and chromosomal aberrations using Chinese hamster ovary cells and Chinese hamster lung cells[60, 61]. In one report[61], a reduction in the response to treatment was noted when metabolic activation was present. A similar effect was noted in the mouse lymphoma mutagenicity test[33].

The results of *in vivo* studies indicate that TGIC is genotoxic. A number of studies using oral administration of TGIC have been conducted. In the Chinese hamster, induction of nuclear anomalies[39] and sister chromatid exchanges[40, 41] were demonstrated, indicating that TGIC has genotoxic effects on somatic cells *in vivo*. Similar effects on germ cells were also demonstrated by the induction of chromosomal aberrations in mouse spermatogonia together with marked cytotoxicity[42-47] following oral administration of TGIC. Another chromosomal aberration study, using lower doses of TGIC, was negative in mouse spermatocytes[47]. A positive dominant lethal effect was observed at only one dose point in one of four experiments[53-55A] and the results should be considered equivocal, with one study[55A] showing reproductive toxicity (reduced fertility).

In a whole body inhalational study[48], the clastogenic potential of TGIC could not be determined because of the shortcomings of the study. In this chromosomal aberration study, there appeared to be a high level of cytotoxicity caused by TGIC in the mouse spermatogonial cells at doses of 10 and 50 mg/m^3. However, it is possible that the low number of cells was due to technical error. In a similar, repeated dose toxicity study

using nose-only exposure to TGIC, cytotoxicity was not observed at dose levels of up to 140 mg/m^3 [26].

In a more recent report[50] both nose-only inhalational and oral administration of TGIC were studied. Only one dose of TGIC was administered by inhalation, 7.8 mg/m^3, and there were no signs of cytotoxicity, adverse clinical effects or induction of chromosomal aberrations. Oral administration of 115 mg/kg TGIC did induce chromosomal aberrations and cytotoxicity. The clastogenic potential of TGIC, as a result of inhalational exposure, could not be determined because a dose response relationship was not studied and neither cytotoxicity nor adverse clinical effects were observed.

The results of a mouse spot test, following intraperitoneal administration of TGIC, were negative[58].

The molecular structure of TGIC indicates a potential for alkylating DNA. This was confirmed in a study where DNA-binding of ^{14}C-TGIC was measured in stomach, liver and testis DNA following oral administration in mice56. Three hours after administration the ratio of TGIC-DNA adducts in stomach, liver and testis DNA was about 30:6.5:1.

In a recent study[57], TGIC was shown to bind to DNA in rat livers *in vivo* following oral and intraperitoneal administration. Induction of liver microsmal epoxide hydrolase activity was associated with increased hydrolysis of TGIC and a corresponding decrease in TGIC-DNA adduct formation. The microsomal epoxide hydrolase activity was measured in only two human livers and found to be greater than the activity in non-induced rat livers.

In both these *in vivo* studies, the CBI values for TGIC in rat liver were relatively low, suggesting that only a small proportion of the administered dose binds to DNA.

No studies for carcinogenicity or reproductive effects of TGIC were available for assessment.

Table 17
Summary of toxicological data

Toxicological endpoint	*Result*	*Section*
Acute toxicity		
Oral (rat)	LD_{50} < 100 mg/kg (m) LD_{50} = 255 mg/kg (f)	10.1.1
Dermal (rat)	LD_{50} > 2000 mg/kg	10.1.2
Inhalational (rat)	LD_{50}= 650 mg/m^3/4h (f) LD_{50} > 650 mg/m^3/4h (m)	10.1.3
Irritation		
Skin (rabbit)	Non-irritant	10.1.4
Eye (rabbit)	Serious eye effects	10.1.5
Sensitisation		
Skin (guinea pig)	Positive	10.1.6
Short term repeated dose		
Oral (rat)	Renal tubular, gastric and duodenal damage	10.2.1
Inhalational (mouse)	Lung damage	10.2.3
Genotoxicity		
A. *in vitro*		
Ames test	Positive	10.3.1
Mouse lymphoma	Positive	10.3.2
UDS, rat hepatocytes	Positive	10.3.3
Cell transformation	Negative	10.3.4
Chromosomal aberration, human lymphocytes	Negative	10.3.5
UDS, human fibroblasts	Negative	10.3.6
B. *in vivo*		
Oral Route		
Nuclear anomaly, Chinese hamster	Positive	10.3.7
SCE, Chinese hamster, bone marrow	Positive	10.3.8
Chromosomal aberration, mouse spermatogonia	Positive	10.3.9
Chromosomal aberration, mouse spermatocytes	Negative	10.3.9
Dominant lethal	Equivocal	10.3.10
Alkylation of DNA:		
· mice	Stomach>Liver>Testis	10.3.11
· rats	Liver	10.3.11
Inhalational Route		
Chromosomal aberrations, mouse spermatogonia	Inconclusive	10.3.9
Intraperitoneal Route		
Mouse spot test	Negative	10.3.12

m	males
f	females
UDS	unscheduled DNA synthesis
SCE	sister chromatid exchange

11. Human health effects

Available data on the effects of TGIC exposure in humans are limited to:

- three published case reports,
- some health effects data from ICI Dulux Australia and
- results of a survey of spray painting workplaces using TGIC powder coatings conducted by the WorkCover Authority of New South Wales (WorkCover Authority).

Allergic dermatitis is the only human health effect due to exposure to TGIC which has been reported in the literature[62-64].

Case reports

The first published report[62] is a case study of a spray painter exposed to powder paint containing five per cent (by weight) TGIC. Severe allergic dermatitis of the ear, forehead, perioral skin and cheeks of the worker developed within two weeks of him starting a new procedure for cleaning spray booths. A series of patch tests were carried out on the subject, using one per cent dilutions of the paints, 0.5 per cent technical grade TGIC and one per cent polyester resin (the other major paint component). Positive responses were observed with all the paints tested, regardless of colour, and with TGIC. The response to polyester resin was negative. Patch testing with TGIC on three volunteer controls without dermatitis were negative.

The second case report[63] is of a man working in the TGIC production department of a chemical factory. The man complained of having had symptoms of contact dermatitis on his face and hands since being transferred to the TGIC production department. The man tested positive to 0.1 to two per cent concentrations of TGIC in a series of patch tests. His IgE level was within the normal range. Patch tests to TGIC in 10 control subjects were negative.

The other report[64] stated that a worker in a powder coating factory suffered from itchy eczema on the face, neck, behind the ears and forearms. His eczema developed after he had been assigned to cleaning TGIC equipment. The worker was patch tested with several different coloured powder coating and the results were negative. Further patch testing with TGIC and fove per cent TGIC were strongly positive and with saturated polyester resin (an ingredient of powder coatings) was weakly positive. Patch tests with TGIC and the saturated polyester resin in five control subjects were negative.

ICI Dulux, Australia

As part of this assessment, ICI Dulux provided a summary of the health status of employees at a plant manufacturing powder coating in Australia. In 1991, two employees had allergic dermatitis and two employees had intrinsic asthma which was being aggravated by TGIC. The two employees with allergic dermatitis were found to be positive when patch tested with TGIC. Shortly after, in response to new information on purported reproductive effects of TGIC in animals[48, 49], twenty-eight employees underwent medical examinations. Respiratory effects were present or reported in five

employees and irritant effects in eight employees. Irritant effects included nasal, eye and throat irritation, skin rash and nose bleeds. The report states that stricter controls were implemented which resuled in the elimination of occupational health effects among employees.

WorkCover Authority of New South Wales survey

In 1992-1993, WorkCover Authority conducted an inspection of workplaces in Sydney using TGIC powder coatings. Spray painters were asked about the health effects they had suffered as a result of using TGIC powder coatings. At each workplace the first aid and compensation records were also examined by WorkCover Authority inspectors. The survey indicated that 11 of the 232 spray painters experienced adverse health effects, mostly skin rashes, as a result of using TGIC powdered coatings.

12. Public health assessment

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.

It is possible that public exposure could result from an accident during transport of either TGIC or TGIC powder coatings. In the case of TGIC spills, the risk of exposure from TGIC is minimal as it is imported in a pelletised or granular form which reduces dust production.

13. Environmental assessment

13.1 Environmental exposure

13.1.1 Release

During formulation

The three Australian formulators of TGIC powder coatings are ICI Dulux, Paint Industries Pty Ltd and Taubmans Pty Ltd.

The ICI Dulux plant is served by bag filters. Residues of TGIC discharged into exhaust air are estimated at 71 g (1.7 kg product) daily. Extracted dust is packed in heavy-walled polythene bags, together with dust from vacuum cleaning and solids extracted from the aqueous waste stream, for consignment to landfill, at an estimated daily rate of 21 kg TGIC (500 kg product).

Equipment is washed with water which passes to a settling tank prior to filtration and discharge to sewer. The notifier estimates that 42 g TGIC passes to sewer during an average day of operations, with settled and filtered solids sent to landfill. The waste material is mainly melt-mixed product in which the TGIC is, to a certain extent, immobilised.

Assuming continuous production, the above estimates correspond to annual TGIC discharges from the ICI Dulux plant of 26 kg to the atmosphere, 15 kg to sewer and 7.5 tonnes to landfill.

Paint Industries Pty Ltd has indicated that similar pollution control devices are used, but that solid wastes are stored on site in 200-litre sealed drums, rather than sent to landfill. Approximately 400 tonnes of powder coatings (containing 16 tonnes TGIC) were manufactured during 1991.

Taubmans Pty Ltd did not provide any estimates of releases to sewer or the atmosphere, but indicated that adequate precautions (settling tank and baghouse, respectively) were in place to minimise such release. After settling, liquid wastes are subjected to a caustic process, which would decompose any dissolved TGIC. A total of 300 kilograms of solid waste (containing 6 kg TGIC) is disposed of daily, presumably to landfill. Assuming continuous plant operation, this corresponds to slightly over two tonnes per annum.

During use

Environmental exposure to TGIC resulting from normal use in spray painting workplaces is expected to be low as electrostatic application is an efficient application method. Powder which does not reach the target article (estimated at two per cent) will be removed using dust extractors or cured in the original containers before sending to landfill.

13.1.2 Fate

A high proportion of the TGIC in powder coatings will become immobilised through cross-linking in an insoluble polyester matrix. As TGIC is an epoxide, any residues which escape such capture and enter the open environment are expected to be rapidly degraded, either through microbial action or abiotic hydrolysis.

TGIC did not satisfy the criteria for ready biodegradability of the modified Sturm test, in which 9 and 48 per cent, respectively, of the theoretical amounts of carbon dioxide were evolved from solutions of 10 and 20 ppm exposed for 28 days to bacteria from a sewage treatment plant[65]. While these results indicate incomplete mineralisation, they are likely to reflect complete primary degradation, with slow opening of the triazine ring restricting the rate of mineralisation as has been noted for triazine herbicides[66].

In a modified Zahn-Wellens test[67], measuring CO_2 evolution rather than loss of dissolved organic carbon, TGIC was inherently biodegradable at 11.3 mg/L but not at 21.1 mg/L (44 per cent and one per cent, respectively, after 28 days). The solubility of TGIC in this test was said to be poor, necessitating use of an emulsifier to achieve the stated test concentration, and the results should therefore be treated with caution. TGIC is not expected to accumulate in soil or sediment because of high mobility and limited persistence. High mobility may be predicted by analogy with the triazine herbicide hexazinone, a known leacher. The oxirane substituents are not expected to significantly retard the mobility as methyloxirane has low soil organic matter adsorption coefficients, generally between 3 and 3069.

Persistence in the aquatic environment is expected to be limited by analogy with methyloxirane[68] which has a half life in fresh surface waters of 6.6 days at pH 5 and 11.6 days at pH 7 to pH 9. Hydrolysis proceeds more rapidly in the marine envrionment because of more rapid ring opening by chloride ions. The reactivity of TGIC precludes any possibility of bioaccumulation.

13.2 Environmental effects

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), as did the NOEC[69]. The 24 h EC_{50} in a static *Daphnia magna* immobilisation test was above 100 mg/L, with a NOEC of 58 mg/L[70]. These results indicate that TGIC is, at most, slightly toxic to aquatic fauna under conditions of acute exposure. Chronic effects would not be expected because of limited aquatic persistence.

While algal tests were not submitted, adverse effects are not expected because of very low environmental exposure and limited persistence of TGIC. TGIC shows some structural similarities to the triazine herbicide hexazinone, which is highly toxic to algae[71]. While this allows prediction of certain environmental characteristics, such as soil mobility, it is probably not ecotoxicologically significant as hexazinone and other triazine herbicides characteristically carry amino substituents.

13.3 Environmental hazard

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.

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 this release to a concentration of 30 ppb, assuming that mixing is uniform and no removal takes place. This clearly provides an adequate safety margin for aquatic fauna, even when other waste streams containing TGIC are added, since the NOEC for daphnids was some 2000 times this level. The predicted environmental hazard is low.

14. Assessment of occupational health and safety effects;

14.1 Health effects

The health effects of a chemical are dependent on many factors, including:

toxicity of the chemical;

particle size;

bioavailability;

metabolism; and

duration and level of exposure level.

14.1.1 Toxicity

The only human health effect reported in the literature is allergic dermatitis in workers exposed to TGIC or TGIC powder coatings. Patch tests with TGIC of these workers were positive. A summary of the health effects in workers in an Australian plant formulating TGIC powder coatings was provided by ICI Dulux. Health effects included nasal, eye and throat irritation, skin rash and nose bleeds. A WorkCover Authority survey of 232 spray painters using TGIC powder coatings indicated that 11 had adverse health effects, mostly skin rashes. No other health effects have been reported.

Acute toxicity studies in animals have shown that TGIC is toxic by the oral and inhalational routes but has low acute dermal toxicity. TGIC causes serious eye effects, is a skin sensitiser and is not a skin irritant. The major effects in short term repeated dose studies were at the site of application and renal, lung and gastric/duodenal damage.

The evidence for induction of dominant lethal mutations by TGIC is equivocal. TGIC did induce chromsomal aberrations in mouse spermatogonia following oral administration. TGIC was also positive in *in vivo* nucleus anomaly and SCE assays and in a number of *in vitro* genotoxicity studies. On the basis of these studies and as TGIC has been shown to covalently bind to DNA *in vivo*, TGIC should be classified as a Category 2 mutagen.

There have been no studies conducted to determine the carcinogenic potential of TGIC. Scientific data indicates that short-term tests for genotoxicity are helpful in predicting carcinogenic potential of chemicals. As TGIC was positive in a number of short term *in vitro* and *in vivo* genotoxicity studies and has been shown to covalently bind to DNA *in vivo*, TGIC has the potential to be carcinogenic and further testing is recommended.

Studies of the reproductive effects of TGIC have not been conducted. Genotoxicity studies[48, 49] indicated that inhalation of TGIC resulted in cytotoxicity and chromosomal aberrations in the spermatogonial cells of mice. This raised concerns that there may be a risk of reproductive effects from exposure to TGIC.

While measurement of the cytotoxic and genotoxic effects of TGIC on germ cells may indirectly indicate possible reproductive effects, these studies do not directly measure effects on reproduction or development. The reproductive effects due to TGIC exposure cannot be determined from the genotoxicity data. In order to assess the reproductive effects of a chemical, appropriate reproduction toxicity studies should be performed.

14.1.2 Particle size

The ability of particles to be inhaled depends on a number of factors, and in particular particle size or aerodynamic diameter. Inspirable particles are those that are inhaled, and thereby enter the respiratory tract. In a particulate sample, 50 per cent of particles with an aerodynamic diameter of < 100 mm are likely to be inhaled. The ability of a particle to be inhaled decreases rapidly as a function of increasing aerodynamic diameter. The inspirable fraction may further be divided into 'respirable' and 'non-respirable' fractions. The respirable fraction is composed of the very fine particles, < 7 mm, which are able to reach the lower bronchioles and alveolar regions of the lungs. The non-respirable fraction is deposited in the upper respiratory tract, including the nose, pharynx and larynx.

In the animal inhalational studies with TGIC and TGIC powders, the majority of particles were within the respirable range. This is not the case for TGIC and TGIC powder coatings commercially available in Australia.

Technical grade TGIC is available as granules and the particle size data indicate that the granules are unlikely to be inhaled. Only very small amounts of technical grade TGIC are respirable. For example, 99.6 per cent of TEPIC is larger than 400 mm. Only 0.003 per cent of TEPIC is < 10 mm and therefore potentially respirable.

TGIC powder coatings have very low levels of particles in the respirable range. For example, data provided for a powder coating indicate that 2.3 per cent of the particles were in the respirable range. The particles in this same powder coating were all < 130 mm and therefore have the potential to be inhaled. Removal of fines from powder coatings appears to be a standard procedure in the manufacture of powder coatings.

Therefore, the hazards of commercially available TGIC and TGIC powder coatings are expected to be lower than the materials tested in the toxicity studies, due to their larger particle size.

14.1.3 Bioavailability

The extent of bioavailability of TGIC in powder coatings is essential in determining the risk to humans of using powder coatings. In powder coatings, TGIC is partially cross-linked to the polyester resin and is expected to be biologically unavailable when so bound. Ciba-Geigy Pty Ltd has stated that they have preliminary results which indicate that the amount of unbound TGIC in formulated powder coatings is 10 to 15 per cent of the nominal TGIC content. Nissan provided limited data indicating that the amount of

unbound TGIC in two five per cent TGIC pigmented powders was 39.5 per cent and 54.5 per cent.

The data indicate that the amount of unbound TGIC varies between different powder coatings. It is therefore advisable to assume that all TGIC in powder coatings is bioavailable when considering powder coatings as a group.

14.1.4 Metabolism

There are a number of biochemical processes that transform chemicals into metabolites. Metabolism, such as by hydrolysis, usually results in detoxification of the chemical.

Some mitigation of the mutagenic effects of TGIC seen *in vitro* may be expected through enzymatic hydrolysis. This hydrolysis is likely to be catalysed by microsomal epoxide hydrolase and involve the hydrolysis of the epoxy groups. Hydrolysis of TGIC was observed in the blood of mice55A and the inclusion of a metabolic activation system (rat liver S9) in some genotoxicity tests led to an abolition of the effects, although in other tests (such as the Ames test) no such effect was found.

There is some evidence that epoxide hydrolase activity in some human tissues may be higher than in rodent tissues[72-75]. This is supported in that TGIC induction of chromosomal aberrations could not be demonstrated in human lymphocytes and induction of unscheduled DNA synthesis could not be demonstrated in human fibroblasts. In a recently conducted study, induction of epoxide hydrolase activity in rat livers was associated with increased hydrolysis of TGIC and a corresponding decrease in binding of TGIC to DNA. However, this study only examined oral and intraperitoneal administration and did not consider dermal and inhalational exposure.

There are data which show that there is considerable variation in epoxide hydrolase activity between tissues and also significant (approximately 100-fold) interindividual variation of epoxide hydrolase activity in humans[76]. The available data does not demonstrate that epoxide hydrolase is protective against the adverse effects of TGIC in humans.

To assess the protective effect of hydrolysis in humans biological monitoring of the formation of TGIC-induced adducts in the protein or DNA of exposed individuals could be researched.

14.2 Survey of the use of TGIC powder coatings - Sydney, Australia

WorkCover Authority, that state's occupational health and safety authority, surveyed powder coating workplaces in the Sydney metropolitan area between September 1992 and February 1993. Of the 133 workplaces using powder coatings, 101 were using TGIC products, 57 were using TGIC products only, 44 were using both TGIC and substitute products and 32 were using TGIC substitutes only.

The survey found that there were 232 spray painters using TGIC powder coatings. In most cases the employer knew of the potential hazards of TGIC but few of the operators did. The average daily operator exposure was 4.2 hours.

Assessment of the workplace, including work practices, availability and wearing techniques of personal protective equipment and the collection efficiency of the spray booths was undertaken at each workplace. The results are summarised in Table 18. The work practices and collection efficiency of the spray booths in the majority of workplaces appeared satisfactory on visual inspection. In a few workplaces, spray painters were observed spraying directly across each other in a manner liable to cause contamination. WorkCover Authority inspectors observed a few operators covered in excessive amounts of powder.

The spray painters were questioned regarding any health effects they had suffered due to TGIC handling. First aid and compensation records were examined at each workplace. Of the 232 spray painters, 11 had suffered health problems, mostly skin rashes, as a result of using TGIC powder coatings.

The survey indicated that many powder coaters had changed to TGIC substitue powders in response to recent information received on the potential health hazards of the chemical. However, a number of workplaces have since changed back to using TGIC powder coatings as they found that the substitutes did not provide the same quality in the final finish. This suggests that the number of workers using TGIC powder coatings may increase in the future.

Table 18
Inspection of workplaces using TGIC powder coatings by the WorkCover Authority of New South Wales

Operator/plant work practices	Satisfactory	85
	Fair	4
	Unsatisfactory	12
Supply of personal protective equipment	Correct	53
	Partial	34
	Incorrect	14
Collection efficiency of spray booth	Satisfactory	91
	Unsatisfactory	10

14.3 Workplace air monitoring data

14.3.1 Powder coating manufacturing plants

ICI Dulux plant, Australia

An indication of exposure levels in manufacturing plants was provided by dust monitoring data collected in two periods in an Australian ICI Dulux plant. The data for July/August 1991 are presented in Table 19 and for October 1991 in Table 20. At the time of monitoring the recommended industry-based occupational exposure limit for total dust was 0.5 mg/m^3 and for TGIC was 0.025 mg/m^3.

In July/August 1991, the levels of atmospheric TGIC varied between 0.023 and 1.34 mg/m^3 and only one measurement was below 0.025 mg/m^3. Levels of total dust were well above the industry limit of 0.5 mg/m^3.

The data for July/August 1991 demonstrate that measured dust levels for different operators performing the same job varied by up to five-fold, suggesting that work practices significantly affected the level of exposure. Workers in all the tested areas wore RACAL powered air helmets. These helmets have a filter with a rated protection factor of 100, effectively reducing the workers' exposure to atmospheric dust by approximately 100-fold. The level of exposure to TGIC for workers was therefore well below 0.025 mg/m^3.

In response to these air monitoring results, ICI Dulux implemented some changes. The major change was improved work practices, which were supported with increased education and training for workers. Subsequently, the atmospheric levels of TGIC and total dust were monitored during October 1991. The levels were found to be lower than July/August and most of the measurements were below 0.025 mg/m^3 for TGIC and 0.5 mg/m^3 for total dust.

Table 19
Atmospheric levels of TGIC and dust in ICI Dulux powder coating manufacturing plant - July/August 1991

Area tested		*Dust (mg/m^3)*	*TGIC (mg/m^3)*
Make up	Operator 1	1.74	0.032
	Operator 2	3.09	0.19
	Operator 3	-	0.081
Extruder	Operator 1	4.8	0.27
	Operator 2	-	0.023
Mill	Operator 1	24.9	1.34
	Operator 2	5.3	0.32
	Operator 3	-	0.085
QC Laboratory		0.91	0.047

Table 20
Atmospheric levels of TGIC and dust in
ICI Dulux powder coating manufacturing plant - October 1991

Area tested		*Dust (mg/m^3)*	*TGIC (mg/m^3)*
Warehouse	Operator	0.774	0.007
	Static sampler	0.266	0.002
	Static sampler	0.041	0.002
Mixing	Static sampler	0.0001	0.00001
Extruder	Static sampler	0.386	0.003
	Static sampler	0.813	0.013
Mill	Static sampler	0.340	0.006
	Static sampler	0.523	0.006
Bulk	Static sampler	0.351	0.004
QC Laboratory	Operator	0.309	0.008
	Operator	0.717	0.026
	Operator	1.132	0.030
	Static sampler	0.312	0.004

Nissan plant, Japan

Limited atmospheric monitoring data for 1991 were provided for the Sodegaura plant of Nissan Chemical Industries Ltd, Japan, and is summarised in Table 21. Low volume air samplers were used and dust and TEPIC concentrations were measured. The sampling method for dust and determination of TEPIC were performed by the then standard method of Nissan. Acetonitrile was used as the extraction solvent and the amount of TEPIC was determined by HPLC.

In nine of the ten operations (workplace activities), the levels of dust and TGIC were below the recommended current industry exposure limits stated above. Only one operation, cleaning the sieves used for powder coatings, registered higher levels of 1.12 mg/m^3 for dust and 0.035 mg/m^3 for TGIC. No information was supplied on the control measures or work practices in place in the factory.

Table 21
Atmospheric levels of TGIC and dust in Nissan powder coating manufacturing plant, 1991

Operation	*Sampling place*	*Dust mg/m^3*	*TEPIC mg/m^3*
Normal operation	Weighing raw materials	0.17	0.005
	Filling raw materials	0.13	0.004
	Mixing	0.01	Trace*
	Pulverisation	0.07	0.002
	Packing	0.28	0.009
Cleaning work	Mixer	0.20	0.006
	Pulveriser	Trace*	Trace*
	Cyclone	0.28	0.009
	Sieve	1.12	0.035
	Packing Hopper	0.16	0.005

* Limits of detection not stated

14.3.2 Spray painting workplaces

The Department of Occupational Health, Safety and Welfare of Western Australia (DOHSWA) in 1991 undertook personal air monitoring in eight factories using TGIC powder coatings. Several samples were taken in some factories. Inspirable total dust levels and TGIC content of most of these samples were measured in all factories. Respirable dust levels were also measured in some factories. The personal monitoring data are summarised in Table 22. At the time of sampling, the exposure limit recommended by industry for total dust was 0.5 mg/m^3 and for TGIC was 0.025 mg/m^3.

All workplace atmospheric total dust levels exceeded 0.5 mg/m^3, the recommended industry exposure limit. Only those factories using window type booths (workplaces 2 and 6) were able to maintain their dust levels near this limit. Three workplaces exceeded the limit by more than 28-fold. In these workplaces there were also significant amounts of respirable dust present.

The TGIC content in the inspirable dust was measured in samples from seven workplaces. In four workplaces the TGIC level exceeded 0.025 mg/m^3, the recommended industry exposure limit. Respiratory protection was used by all these workplaces, however not all the time and of variable standards. Some respirable dust levels were also measured. The respirable to total dust levels varied greatly, from two to 75 per cent. This indicates that a substantial amount of total dust is respirable in some workplaces.

In the workplaces with the highest levels of atmospheric TGIC and dust levels, the workers wore the lowest degree of respiratory protection, Class 'M' disposable masks. These disposable masks effectively reduce exposure by ten-fold. Disposable masks do not provide full facial skin protection. The workers in these workplaces were also the most reluctant to wear adequate full skin protection.

In the workplaces with the lower levels of atmospheric TGIC and dust levels, the workers wore airline hoods or powered air-purified respirators. These respiratory devices provide approximately 100-fold reduction in exposure.

Generally, during the spray process the best protection was provided by the automated, enclosed spray booth, followed by the window booth, with the walk-in booths giving potentially the highest exposures. One of four workplaces with walk-in booths (workplace number 4) achieved TGIC levels below 0.025 mg/m^3. This establishment used efficient equipment and had an efficient spray applicator. This demonstrates that low levels of atmospheric TGIC are achievable in walk-in booths.

The air monitoring data demonstrated that there was considerable variability between workplaces regarding control of TGIC and total dust levels.

DOHSWA also completed workplace assessments and provided comments on four of the workplaces where air monitoring was carried out (numbers 1, 4, 6 and 7) and also on two workplaces where air monitoring was not done. The data are summarised in Table 23. The data show that there were considerable variability in the degree of enclosure of the application process, the engineering controls and work practices in place, and workers awareness of the health issues concerning TGIC. Some workplaces had very stringent controls and efficient spray methods. In contrast, workers in other workplaces were seen to handle powder coatings without any protection and powder visibly covered some workers clothing and exposed body areas.

Table 22
Atmospheric levels of TGIC and dust in spray painting workplaces - DOHSWA, 1991

Workplace	*Inspirable dust (mg/m^3)*	*TGIC content ($mg/^m3$)*	*Respirable dust (mg/m^3)*	*Respiratory protection*
1.	132*	-	-	Disposable mask 'M'
2.	0.8	< 0.001	-	Full face respirator
	0.7	0.003	-	
3.	40	1.6	15.7	Disposable mask 'M'
	131.6	6.5	-	
4.	4.86	0.01	1.9	Airline hood
5.	14.4	0.33	9.8	Disposable mask 'L' - periodic
6.	1.4	0.019	-	Disposable mask 'M'
	3.1	0.024	-	
	1.1	0.007	0.08	Powered air purifying respirator
	1.6	0.018	0.04	
7.	2.6	0.019	1.6	Airline hood
	7.7	0.097	5.8	
8.	3.3	0.055	0.94	Homemade airline hood

* Half hour period of personal monitoring of spray painter working in touch-up booth

Table 23
Workplace Assessments by DOHSWA, 1991

Workplace	*Comments*	*Awareness**
1	Continuous on-line process modified by an additional wet scrubber exhausted within the factory, causing deposit of fine dust over factory floor; automatic conveyor and spraying; powder observed on face of 'touch up' spray painter.	No
4	Walk-in booth; efficient equipment and efficient spray applicator; over-spray contained within spray booth.	Yes
6	Continuous on-line process; sprayed by applicators with cowled hand and personal protective clothing; no over-spray or deposits of powder visible in workplace; occupational hygiene standards very high.	Yes
7	On-line booth; occupational hygiene standards very high.	Yes
9	'Tunnel' type and walk-in spray booths; ventilation adequate; personal protective equipment except gloves; significant contamination of overalls and hands with powder; one applicator had powder on side of face as he left for home; significant over-spray in booths.	Yes
10	Large walk-in spray booth; applicator observed standing between extraction ventilation and the object being sprayed; poor occupational hygiene standard; reluctance to wear personal protective equipment especially respirator; overalls did not have hoods and applicator had powder on side of face.	Yes

* At each workplace the workers were asked whether they were aware of TGIC health **issues**.

14.4 Exposure standard

Exposure standards in Australia are set by the National Occupational Health and Safety Commission (NOHSC).

There is general agreement that a national exposure standard for atmospheric levels of TGIC in the occupational environment is needed. Exposure standards are usually established on either human or animal data. The majority of current exposure standards established on animal data are based on chronic data, and in particular chronic inhalational data. The general method for setting an exposure standard based on animal data is to take the 'No Observable Effect Level' (NOEL) from a chronic study and apply a safety factor of 100.

Recently, there has been a great deal of worldwide debate within the powder coating industry on what should be an appropriate exposure limit for TGIC. A number of occupational exposure limits for atmospheric levels of TGIC and TGIC powder coatings have been recommended by various industry groups. The majority of these limits have been based on the available toxicity data, such as the Bushy Run[48] and Safepharm[50] repeated dose, inhalational, chromosomal aberrations studies.

Based on the results of the Bushy Run whole body, inhalational exposure study[48], a number of companies have recommended an occupational exposure limit of 0.025 mg/m^3 for TGIC and 0.5 mg/m^3 for powder coatings containing five per cent TGIC. However, a number of experts were concerned about basing an exposure standard on a whole body exposure study in which it was very likely that an amount of TGIC had been ingested. There was also concern over the number of shortcomings in the study.

More recently, occupational exposure limits have been recommended by Nissan Chemical Industries Ltd, Japan, based on the Safepharm nose-only inhalational study[50]. The Safepharm test was designed to duplicate the Bushy Run study[48], using almost the same conditions, same sample types and same animal species, with the exception of the method of exposure and dose levels. The Bushy Run study was whole body exposure and the Safepharm study was nose-only exposure. In the Safepharm study the lowest levels at which no adverse effects were observed were 8 mg/m^3 for TGIC and 255 mg/m^3 for ten per cent TGIC powder coating. Based on these values Nissan has recommended occupational exposure limits of 0.08 mg/m^3 for atmospheric levels of TGIC and 5 mg/m^3 for atmospheric levels of powder coatings which contain five per cent TGIC.

Other recommended occupational exposure limits recommended by industry groups for TGIC powder coatings include 1 mg/m^3 and 2 mg/m^3.

The declaration of a national exposure standard for atmospheric levels of TGIC in the workplace is not within the scope of this assessment. However, to provide guidance for manufacturers and end users of powder coatings, this assessment has recommended an interim occupational exposure limit for TGIC.

There is no human health data available on which to establish such an occupational exposure limit. The toxicological animal data for TGIC are limited to acute studies and the results of some of these studies are questionable. In particular, no chronic toxicological data are available. The most sensitive measured endpoint for TGIC effects in animals is genotoxicity. Therefore, in the absence of other relevant information, the most appropriate studies for setting an interim exposure limit for TGIC are the five-day, repeated dose inhalational studies examining TGIC induction of chromosomal aberrations in mouse spermatagonia[48, 50].

These chromsomal aberrations studies[48,50] are acute studies and have further shortcomings. This assessment concluded that the results of the Bushy Run study[48] were inconclusive due to a number of deficiencies in the methodology, the cytotoxic ratio was not calculated and there were a high number of chromsomal aberrations in the control group. In the Safepharm study[50], the clastogenic potential of TGIC could not be assessed because a dose response relationship was not determined. However, for the purposes of setting an interim occupational exposure limit from the results of the Safepharm study, the lowest level at which no effect was observed, 8 mg/m^3, is used together with a safety factor of 100.

Therefore, it is recommended that an interim exposure limit for atmospheric levels of TGIC in the occupational environment of 0.08 mg/m^3 (time-weighted average concentration over an eight-hour working day) be used by industry. This interim exposure limit is provisional until chronic data is available or until declaration of a national exposure standard.

It was also recognised that users of TGIC powder coatings require guidance in determining what is adequate control. An exposure limit for powder coatings is not appropriate because the per centage of TGIC in powder coatings, the amount of cross-linking and the other ingredients and their concentrations may all vary. Measurement of atmospheric levels of TGIC by end users may not be practical. The measurement of total dust could provide a more practical although possibly less accurate method of determining atmospheric levels of TGIC.

When monitoring total dust levels in the workplace it must be assumed that all TGIC in powder coatings is bioavailable as the amount of bound TGIC in powder coatings varies and the bioavailability of the bound TGIC has not been established. For example, when using five per cent TGIC powder coatings a total dust level of 1.6 mg/m^3 should not be exceeded to ensure that the recommended occupational exposure limit for TGIC is not exceeded. It is recognised that this is a conservative approach as there is likely to be reduced bioavailabilty of TGIC in powder coatings.

Short term studies, such as the Safepharm and Bushy Run studies, should be regarded as severely limited with regard to setting occupational exposure standards. In the case of TGIC, the problem of using short-term, genotoxicity studies as a basis for an exposure limit is also exacerbated by the shortcomings of the available studies themselves. Chronic toxicity data are necessary in order to confidently set an exposure standard to protect human health.

Exposure standards are only set for airborne concentrations of single pure substances. It is recommended that NOHSC give consideration to an exposure standard for atmospheric levels of TGIC in the occupational environment.

14.5 Occupational exposure

The most likely route of worker exposure to TGIC and TGIC powder coating are inhalational and dermal. Hence, the greater the dust formation the greater the potential for worker exposure.

During the manufacture of TGIC of powder coatings the activities likely to cause high levels of worker exposure are:

- weighing out of TGIC;
- filling hoppers;
- mixing;
- transfer of powder mixes in open vessels;
- extrusion;
- milling;
- bagging;
- cleaning-up spills; and
- cleaning equipment.

During the use of TGIC powder coatings the most likely activities to cause high levels of worker exposure are:

- filling hoppers;
- spraying;
- cleaning-up spills;
- cleaning equipment; and
- cleaning spray booths.

Dust formation during these activities should be avoided or minimised by engineering controls and safe work practices. Personal protective equipment should be worn by workers if there is the potential for greater exposure, such as during manual spraying.

14.6 Assessment of control measures

To control worker exposure to TGIC, both manufacturers and users of powder coating have implemented a number of control measures.

14.6.1 Manufacture of powder coating

At the time of writing, there are three manufacturers of TGIC powder coatings in Australia, and these companies have implemented similar measures to control worker exposure to TGIC. The control measures include isolation, engineering controls, safe work practices and personal protective equipment.

- Engineering controls
- Automation of the process.
- Enclosure of mixers.
- Local exhaust ventilation provided in areas where TGIC dust may be generated, such as weigh booths, mixing, extrusion and milling areas and laboratory spray booths.

Safe work practices

- Regular equipment and plant cleaning, by a combination of vacuuming and wet scrubbing.
- Clean up of spills by vacuuming or removal by gentle shovelling, not sweeping.
- Good personal hygiene practices.

Personal protective equipment

Personal protective equipment includes overalls, gloves and a filtered air hood with safety glasses or powered air respirator with integral visors and is worn during:

- weighing processes;
- open transfer processes;
- some laboratory activities; and
- if necessary, during:
  - "extrusion",
  - "milling", and
  - "bagging processes".

Gloves and disposable dust masks are worn during clean-up of spills and maintenance work.

Assessment

Air monitoring data can be used to assess the effectiveness of these measures taken to control occupational exposure. Industry has been using exposure limits recommended by manufacturers as references for assessing control of exposure.

Air monitoring data for an Australian and a Japanese powder coating manufacturing plant are summarised in Section 14.3.1. The monitoring data can be assessed against the interim exposure limit of 0.08 mg/m^3 for TGIC recommended in this report. Although the control measures in place at the time of monitoring were not stated, these plants would have had control measures in place similar to those listed above.

In the ICI Dulux plant, the levels of atmospheric TGIC exceeded 0.08 mg/m^3 in four of nine measurements in July/August 1991 (Table 19). This data indicate that in order to meet the recommended control limit, respiratory protection for workers was necessary. The workers in the tested areas were required to wear powered air respirators with a protection factor of 100. Therefore, the workers were adequately protected at the time of monitoring. The air monitoring data also suggest that the nature of the work practices was directly related to atmospheric levels of TGIC and total dust. Atmospheric levels of TGIC were below 0.08 mg/m^3 for one operator in each area tested, indicating that levels could be controlled.

In response to the July/August 1991 air monitoring results, ICI Dulux introduced some changes in the plant. The principal change was improved work practices. The level of atmospheric TGIC did not exceed 0.08 mg/m^3 during subsequent air monitoring of the plant in October 1991 (Table 20). The data indicate that efforts to improve work practices can assist in reducing the atmospheric levels of TGIC below the recommended interim exposure limit and thereby reduce the need to wear respiratory protective equipment.

Data from the Nissan plant (Table 21) indicate that atmospheric levels of TGIC were maintained well below 0.08 mg/m^3.

Air monitoring data show that levels of atmospheric TGIC and total dust in powder coating manufacturing plants can be controlled below the recommended occupational exposure limit of 0.08 mg/m^3 for TGIC. The results also indicate that maintaining the total dust levels below 1.6 mg/m^3 did ensure that the limit of 0.08 mg/m^3 for TGIC was not exceeded.

14.6.2 Application of powder coating

There are over 500 spray paint workplaces applying powder coatings onto metal objects in Australia. The control measures taken by applicators of TGIC powder coatings vary greatly. The control measures includes enclosure, such as in spray booths, ventilation, safe work practices and personal protective equipment. All or some of these measures are implemented in various degrees and quality in spray paint workplaces.

Engineering controls

Spray booth design includes:

- automation of the spray process;
- enclosure of spray booths;
- local exhaust ventilation;
- appropriate size spray booths for the articles being sprayed;
- openings as few and as small as practicable;
- average air velocity through each booth opening greater than 0.4 m/sec; and
- where two or more manual spray guns are operated the openings are staggered.

Safe work practices

- Restricted access to spray booth.
- Vacuuming or removal by gentle shovelling of TGIC spills Ω no sweeping.
- Good personal hygiene practices.

Personal protective equipment

Personal protective equipment includes overalls, safety glasses, gloves and a filtered air hood or powered air respirator with integral visors and are worn during:

- filling hoppers;
- manual spraying inside spray booth; and
- clean-up of spray booth.

Gloves and disposable dust masks are worn during clean-up of spills and maintenance work.

Assessment

The degree to which powder coating applicators implement and adhere to the above control measures varies considerably between workplaces. For example, workplaces differ on the degree of automation of the spray process, the type of booth, type and efficiency of ventilation, and on the respirator and protective clothing type and frequency of wear.

The variation of control measures implemented in spray painting workplaces is exemplified in the limited data available on air monitoring of powder coating factories (Table 22). There were marked differences in the levels of atmospheric TGIC levels and total dust between and within workplaces. TGIC levels in dust samples taken from three of the seven factories measured were above 0.08 mg/m^3. In particular, in one workplace the atmospheric levels of TGIC were 20-fold greater than 0.08 mg/m^3.

Workplace assessment indicated that automated, enclosed spray booths provided the best protection and walk-in booths generally provided the least protection. However, in one workplace using a walk-in booth atmospheric levels of TGIC were maintained below 0.08 g/m^3. The data demonstrate that plant design, control measures and work practices affect the atmospheric levels of TGIC and total dust.

14.7 Code of practice

NOHSC is proposing to declare a national code of practice for spray painting. At present the draft code of practice is still under review and development and in particular considers the hazards of spray painting with the organic solvents.

Arising out of the assessment process, a recommendation has been made to the National Commission that electrostatic spray painting with TGIC powder coatings be considered in the code of practice for spray painting.

15. Conclusion

From the assessment of the hazards of TGIC it is concluded that the chemical is a hazardous substance. TGIC is toxic by oral and inhalational routes, a skin sensitiser, genotoxic and capable of causing serious eye damage.

Given that the available toxicological data are limited and some of the results are questionable and that there are a number of critical data gaps, further studies are recommended in order to confidently predict the potential human health effects of TGIC.

To provide guidance for manufacturers and applicators of TGIC powder coatings, this report has recommended an interim occupational exposure limit of 0.08 mg/m^3 for TGIC. This limit is provided as guidance until chronic data are available or until setting of a national exposure standard.

Adequate control measures must be implemented in powder coating manufacturing plants and in spray painting workplaces to ensure worker exposure is maintained at the lowest practicable level. In any case, the level of exposure should not be greater than the recommended interim occupational exposure limit.

Air monitoring data for powder coating manufacturing plants in Australia and Japan have shown that levels of atmospheric TGIC and total dust can be maintained below the recommended occupational exposure limit. Manufacturing plants as a rule have stringent control measures which include automation and enclosure of the process, ventilation, safe work practices and the wearing of respiratory protective equipment. The data suggest that where the recommended limit was exceeded at the ICI Dulux, adequate control was later achieved primarily by improvements in work practices.

In the case of spray painting workplaces, adequate control can also be achieved but there is greater scope for worker exposure. Air monitoring data and workplace assessments have shown that there is a much greater variability in the control of worker exposure during application of powder coatings. Workplaces were able to control atmospheric levels of TGIC below the recommended limit using control measures such as enclosure, automation, ventilation and safe work practices. However, it was evident that some workplaces did not have the necessary controls to adequately protect workers unless they wore full protective equipment.

From the assessment of the known hazards of TGIC, overseas experience and air monitoring data, we have concluded that TGIC is unlikely to cause adverse human health effects if the appropriate control measures and atmospheric monitoring strategy are implemented. However, the lack of chronic data makes it difficult to predict the long term health effects in workers exposed to TGIC.

TGIC is unlikely to present a risk to the public or the environment and there are no specific recommendations for controls in these areas.

16. Recommendations

16.1 Classification and labelling

TGIC is classified as toxic by the oral and inhalational routes, capable of causing serious eye damage, a skin sensitiser, and a Category 2 mutagen, in accordance with the health effects criteria detailed in the National Commission's *Guidance Note for Determining and Classifying a Hazardous Substance*[77]. Based on the classification of its health effects and in accordance with the guidance note, TGIC is considered to be a hazardous substance.

The complete requirements for the labelling of hazardous substances are detailed in the *Guidance Note for the Labelling of Workplace Substances*[78]. The following risk phrases and appropriate safety phrases have been determined by application of the criteria given in the labelling guidance note and will ensure that the labelling requirements of the National Commission's *National Model Regulations to Control Workplace Hazardous Substances*[79] have been met.

Risk phrases

R23/25 Toxic by inhalation and if swallowed.

R41 Risk of serious damage to eyes.

R43 May cause sensitisation by skin contact.

R46 May cause heritable genetic damage.

Appropriate safety phrases include:

S22 Do not breathe dust.

S24/25 Avoid contact with skin and eyes.

S26 In case of contact with eyes, rinse immediately with plenty of water and contact a doctor or Poisons Information Centre.

S28 After contact with skin, wash immediately with plenty of...*[material to be specified by the manufacturer]*.

S36 Wear suitable protective clothing.

S37 Wear suitable gloves.

S38 In case of insufficient ventilation wear suitable respiratory equipment.

S39 Wear eye/face protection.

S44 If you feel unwell contact a doctor or Poisons Information Centre (show the label where possible).

Where TGIC is an ingredient in a mixture/preparation, as in powder coatings, the following concentration limits apply:

Table 24
Concentration limits and classifications for TGIC as an ingredient in mixtures/preparations

Concentration limit	*Classification*
25% ≤ C	Toxic; R23/25, R41, R43, R46
10% ≤ C < 25%	Harmful; R20/22, R41, R43, R46
5% ≤ C < 10%	Harmful; R20/22, R36, R43, R46
3% ≤ C < 5%	Harmful; R20/22, R43, R46
1% ≤ C < 3%	Harmful; R43, R46
0.1% ≤ C < 1%	Harmful; R46
C < 0.1%	Not a hazardous substance

C concentration of TGIC in powder coatings

The above data represent classifications for preparations containing TGIC at concentrations between the ranges shown. However, should there be other hazardous ingredients present in the preparation the overall classification for the preparation needs to be determined. In this case users should refer to the National Commission's *Guidance Note for Determining and Classifying a Hazardous Substance*[77] for further guidance.

As TGIC is a hazardous substance, employers and suppliers should be aware of their obligations to provide information, such as an MSDS, about the hazards of TGIC. Employers have a further obligation to assess and control the risks to health. Details of these obligations, consistent with employers general duty of care, are provided in the *National Model Regulations to Control Workplace Hazardous Substances*[79].

As all Australian states and territories have made a commitment to enact uniform regulations consistent with this national model regulation in 1993, employers should read the recommendations of this report in conjunction with the obligations set out in these regulations.

16.2 Exposure standard

It is recommended that the National Commission set an exposure standard for atmospheric levels of TGIC in the occupational environment.

In the interim, an occupational exposure limit for TGIC of 0.08 mg/m^3 (time-weighted average concentrations over an eight-hour working day) should be used by industry. This limit is provided as guidance only and the lack of proper scientific data for the setting of this limit is recognised.

16.3 Further toxicity testing

As a result of this assessment, it was recognised that there were a number of critical data gaps in the animal toxicity data for TGIC and that the results of some genotoxicity studies were questionable.

TGIC was positive in a number of short term *in vivo* and *in vitro* genotoxicity studies and has been shown to covalently bind to DNA. This raises the question of potential carcinogenic effects of TGIC. Estimation of carcinogenic potential can only be made from a cancer bioassay. It is recommended that a cancer bioassay with TGIC be conducted.

In addition, the lack of chronic toxicity data creates difficulties both in predicting potential human health effects and in satisfactorily establishing an occupational exposure standard. It is recommended that the toxic effects following prolonged and repeated exposure to TGIC be investigated. It would therefore be prudent that a combined chronic inhalational toxicity/carcinogenicity study be conducted to determine both the chronic toxicity effects and carcinogenic potential of TGIC in a mammalian species.

The reproductive effects of TGIC were brought into question when the results of chromosomal aberration studies[48, 49] indicated cytotoxicity of spermatogonia at low dose levels. This assessment concluded that the results of chromsomal aberration studies following inhalational exposure were inconclusive. However, TGIC did induce chromosomal aberrations and cytotoxicity following oral administration and showed reduced fertility following inhalation. This data suggests that TGIC may be a reproductive toxicant.

In order to determine the reproductive and developmental effects of TGIC, relevant animal studies, such as a multigeneration reproduction study, are advisable.

16.4 Atmospheric monitoring

Atmospheric monitoring in both powder coating manufacturing plants and spray painting establishments should be carried out routinely. The frequency of monitoring should ensure that the interim occupational exposure limit of 0.08 mg/m^3 for TGIC is not being exceeded and that the health of workers is therefore being protected. Atmospheric monitoring provides a quantitative estimate of worker exposure, identifies areas where high levels of atmospheric TGIC occur and provides a basis for measuring the effectiveness of control improvements.

As manufacturers of powder coatings handle 'pure' (technical grade) TGIC, routine air monitoring of total dust and TGIC should be carried out. Air monitoring in these plants should be carried out where exposure is likely to occur, such as where the filling of hoppers, milling, extrusion and bagging takes place.

Routine air monitoring of spray painting workshops should be carried out to ensure that the interim limit of 0.08 mg/m^3 for TGIC is not being exceeded. The most accurate method is to measure atmospheric levels of TGIC, but it is recognised that this method may not be practical. Routine monitoring for total dust may be more practical. However, when measuring total dust it must be assumed that all TGIC in the powder coatings is bioavailable. For example, in workplaces using five per cent TGIC powder

coating, the total dust level should not exceed 1.6 mg/m^3. Monitoring should be carried out where worker exposure to TGIC in spray painting workshops is likely to occur, such as during filling hoppers, spraying and clean-up operations.

Methods used for air monitoring and determination of TGIC content have been received from Nissan Chemical Industries Ltd, Japan, and Ciba-Geigy Pty Ltd, Switzerland, and are provided at Attachment 1 and Attachment 2. The validity and suitability of these monitoring techniques have not been assessed in this report.

For advice and assistance in monitoring contact, state and territory occupational health and safety authorities.

16.5 Control of occupational exposure

Consistent with good occupational hygiene principles, all worker exposure should be minimised and spray painters and manufacturers of powder coatings should aim for the lowest practicable levels of atmospheric TGIC and TGIC powder coating. In any case, the levels should not exceed the interim exposure limit of 0.08 mg/m^3 for TGIC.

Experience has shown that this level can be achieved and maintained in powder coating manufacturing plants where there are hazard control measures, safe work practices and, where necessary, personal protective equipment is worn.

Data indicate that although the recommended exposure limit can be achieved in spray paint workshops, it was often exceeded where control measures, work practices and personal protective equipment vary and often are inadequate.

The setting of an occupational exposure limit does not preclude efforts to further reduce exposure. To minimise worker exposure to TGIC, the control measures listed below should be followed. The control measures should be seen as a hierarchy, that is, implemented in the sequence in which they are presented.

16.5.1 Application of powder coating

Substitution

TGIC is used in powder coatings as a curing agent, primarily because it gives ultraviolet stability to the paint film. TGIC-free powder coatings are available which meet the specifications of the end users. Review of the hazards and efficacy of these TGIC-free powder coatings was outside the scope of this assessment.

Substitution with TGIC-free powder coatings should be considered. However, substitution should only be with less hazardous substances and the health hazards of any potential substitute should be known to employers and employees.

Isolation

The spray painting process should be separate from other workplace activities, such as by distance or in another building.

Engineering controls

The most effective engineering controls for reducing worker exposure are enclosure, local exhaust ventilation and automation of the spray process. In particular, this assessment recommends that:

- spray painting of TGIC powder coatings should be performed in a booth;

- spray painting booths and equipment should be in accordance with Australian Standard AS3754 -1990 - *Safe Application of Powder Coatings by Electrostatic Spraying*. In particular, the design of the booth should be such that airborne powder does not escape from the booth into the workplace. For all installations, local exhaust ventilation should be provided and the average air velocity through each booth opening should be not less than 0.4 m/sec;

- local exhaust ventilation should be used when spraying, during filling of hoppers, when reclaiming powder and during clean-up;

- automatic spray guns, feed lines and feed equipment should be used;

- spray gun air pressure should be minimised to prevent overspray as this could result in unnecessary powder build-up within the spray booth;

- the power supply and powder coating feedlines should be interlocked with the air extraction system so that if a fault develops in the ventilation system, the powder coating and power supplies are cut off;

- the spread of dust within the powder coating building should be minimised. Circumstances leading to draughts and air turbulence should be evaluated and controls implemented;

- operations of opening powder coating packages, loading of hoppers and reclaiming powder should be contained to prevent or minimise the generation of dusts;

- the layout of the workstation and the size of the hopper opening should be such that generation of dust is minimised in filling the hopper; and

- other methods in the use of hoppers should be considered, namely:

    - large hoppers should be used to avoid frequent refilling of smaller units, and

    - preference should be given to the use of powder coatings supplied in drums which allow mechanical transfer of the powder to hoppers.

Safe work practices

Safe work practices are necessary to supplement the engineering control measures in order to minimise worker exposure.

Safe work practices should include:

work practices designed to avoid the generation of dust;

restricting access to spray painting areas;

designing a safe workplace so that the spray painter is never between the object to be sprayed and the airflow of contaminated air;

situating the articles to be sprayed sufficiently within the booth to avoid ricochet;

implementating good personal hygiene practices, for example, powder coating dust should not be allowed to collect on the face, exposed body areas should be thoroughly washed and overalls should be regularly cleaned;

- storing powder coating and waste powder in a designated area and access restricted;
- cleaning booths and surrounding areas on a regular basis;
- promptly cleaning-up spills of powder coatings to reduce the spread of TGIC;
- not using compressed-air or dry sweeping during clean-up operations;
- using a spark-proof squeegee when a wet clean-up is required;
- emptying vacuum cleaners in the booth and under exhaust ventilation;
- taking care to avoid the generation of dust during disposal of waste powder.
- waste powder being baked in the original box for disposal to landfill as a solid;
- vacuuming primary decontamination of work clothing;
- checking regularly the cleaning and maintenance of plant equipment, including ventilation and spray equipment and filters; and
- proper induction training and general training of workers about the potential hazards of spraying with TGIC powder coatings and in the safe work practices necessary to minimise exposure.

Electrostatic spray painting brings with it electrical hazards and additional requirements for safe work practices are required. For example, all equipment, including spray guns and booth, should be earthed. All hooks used to suspend objects to be sprayed should be cleaned prior to re-use in order to maintain effective metal contact. Earthing of equipment, objects being coated and personnel ensures maximum coating efficiency, reduces free dust and prevents build-up of static charges capable of causing ignition.

Personal protective equipment

Control of worker exposure should be achieved as far as is practicable by means other than the use of personal protective equipment. However, when other control measures, such as engineering controls and safe work practices, do not adequately protect the worker, then personal protective equipment should be worn.

Personal protective equipment should include full protective clothing including overalls, gloves, head and eye protection and respiratory protection, selected and used in compliance with relevant Australian Standards. In particular:

- a full-face air-supplied particulate respirator should be worn, which complies with AS 1716 - 1991 - *Respiratory Protective Devices*, and used in accordance with AS 1715 - 1991 - *Selection, Use and Maintenance of Respiratory Protective Devices*;

- the respiratory protective equipment should provide head covering to avoid dust build-up around the edges of the face masks. A ventilated full-head covering may also be more comfortable in a hot environment;

- during manual spraying, the gun-hand must not be insulated from the gun. Either the gun hand should be cowled by a cover sleeve or the palm of an insulating glove may be cut out. Operators standing outside a booth and spraying inside a booth through an aperture should wear this type of protective equipment; and

- anti-static and conductive footwear should be provided.

Workers who may come into direct contact with TGIC powder coatings include persons:

- filling hoppers;

- manually spraying powder coatings, including 'touch-up' spraying;

- reclaiming powder;

- emptying or cleaning industrial vacuum cleaners;

- cleaning spray booths, filters and other equipment; and

- cleaning-up major spills of powder coating.

16.5.2 Manufacture of powder coating

Where applicable, the controls measures outlined above for spray painting should be implemented in the powder coating manufacturing plant. These measures include isolation of the formulation process, enclosure, automation, local exhaust ventilation and the wearing of personal protective equipment when necessary. Any open or manual process or leakage will increase worker exposure.

Local exhaust ventilation should be provided when filling the hoppers, adding to the mixer, during mixing, extrusion and bagging, and at open transfer points.

Personal protective equipment should be used when other control measures do not provide adequate protection. In the powder coating manufacturing plants, personal protective equipment worn by workers should be the same as that recommended for spray application (Section 16.5.1).

The most likely activities where workers may be exposed are:

- filling hoppers;
- mixing, extrusion, pulverizing, sieving and bagging processes;
- reclaiming TGIC and TGIC powder coatings;
- emptying or cleaning industrial vacuum cleaners;
- cleaning-up major spills of TGIC and TGIC powder coating;
- working in the quality control laboratory, such as during test spraying; and
- cleaning spray booths in a quality control laboratory.

17. Requirements for secondary notification;

Under the Act, secondary notification of Triglycidylisocyanurate shall be required if any of the circumstances stipulated under Subsection 64(2) of the Act arise.

18. References

1. Ciba-Geigy Ltd 1989, *Investigation of the Alkylation Activity of PT 810 (TK 10622) and its Hydrolysis Products (No. PS33-10891)*. Ciba-Geigy Ltd, Basel, Switzerland.

2. Ciba-Geigy Ltd 1990, *Acute Oral Toxicity in the Rat (No. 894516) of TK 10622 (Araldite PT 810)* Ciba-Geigy Ltd, Basel, Switzerland.

3. Ciba-Geigy Ltd 1982, *Acute Oral Toxicity in the Rat (No. 820694) with TK 10622*, Ciba-Geigy Ltd, Basel, Switzerland.

4. Safepharm Laboratories Ltd 1988, *TEPIC-G: Acute Oral Toxicity Test in the Rat (No. 14/10)*. Safepharm Laboratories Ltd, Derby, United Kingdom.

5. Ciba-Geigy Ltd 1982, *Acute Oral Toxicity of TK 10622 in the Chinese Hamster (No. 820695)*, Ciba-Geigy Ltd, Basel, Switzerland.

6. Ciba-Geigy Ltd 1975, *Acute Oral Toxicity in the Rat of TK 10622 (No. SISS 4735)*. Ciba-Geigy Ltd, Basel, Switzerland.

7. Ciba-Geigy Ltd 1990, *Acute Dermal Toxicity in the Rat (No. 894517) with TK 10622 (Araldlte PT 810)*,Ciba-Geigy Ltd, Basel, Switzerland.

8. Ciba-Geigy Ltd 1975, *Acute Dermal Toxicity of TK 10622 in the Rat*, Ciba-Geigy Ltd, Basel, Switzerland.

9. Safepharm Laboratories Ltd 1988, *TEPIC-G: Acute Dermal Toxicity (Limit Test) in the Rat (No. 14/11)*, Derby, United Kingdom.

10. Ciba-Geigy Ltd 1979, *Acute Aerosol Inhalation Toxicity in the Rat of TK 10622/3 (No. 790339)*, Ciba-Geigy Ltd, Basel, Switzerland.

11. Ciba-Geigy Ltd 1979, *Acute Aerosol Inhalation Toxicity in the Rat of TK 10622 (No. 790336)*, Ciba-Geigy Ltd, Basel, Switzerland.

12. Bushy Run Research Center 1991, *PL90-810: Acute Dust Inhalation Toxicity Test in Mice*, BRRC, Export, Pennsylvania, USA.

13. RCC Research and Consulting Company 1990, *Pre-test study with TK 10622 Ω Particle Size Measurements and Evaluation of Sensory Irritating Effects*, Project 894035, Ciba-Geigy Ltd, Basel, Switzerland.

14. Bushy Run Research Center 1991, *PL90-810PC: Acute Dust Inhalation Toxicity Test in Mice*, BRRC, Export, Pennsylvania, USA.

15. Ciba-Geigy Ltd 1979, *Skin Irritation in the Rabbit After Single Application of TK 10622/3 (No. 790340)*, Ciba-Geigy Ltd, Basel, Switzerland.

16. Ciba-Geigy Ltd 1982, *Acute Skin Irritation in the Rabbit with TK 10622 (No. 820697)*, Ciba-Geigy Ltd, Basel, Switzerland.

17. Ciba-Geigy Ltd 1979, *Skin Irritation in the Rabbit After Single Application of TK 10622 (No. 790337)*, Ciba-Geigy Ltd, Basel, Switzerland.

18. Safepharm Laboratories Ltd 1988, *TEPIC-G: Acute Dermal Irritation Test in the Rabbit (No. 14/12)*, Safepharm Laboratories Ltd, Derby, United Kingdom.

19. Safepharm Laboratories Ltd 1988, *TEPIC-G: Acute Dermal Irritation Test in the Rabbit (24-Hour Exposure) (No. 14/13)*, Safepharm Laboratories Ltd, Derby, United Kingdom.

20. Ciba-Geigy Ltd 1979, *Eye Irritation in the Rabbit After Single Application of TK 10622 (No. 790338)*, Ciba-Geigy Ltd, Basel, Switzerland.

21. Ciba-Geigy Ltd 1979, *Eye Irritation in the Rabbit After Single Application of TK 10622/3 (No. 790341)*, Ciba-Geigy Ltd, Basel, Switzerland.

22. Ciba-Geigy Ltd 1982, *Acute Eye Irritation Study in the Rabbit with TK 10622 (No. 820696)*, Ciba-Geigy Ltd, Basel, Switzerland.

23. Ciba-Geigy Ltd 1988, *Skin Sensitization Test in the Guinea Pig, Modified Maximization Test (No.884210)*, Ciba-Geigy Ltd, Basel, Switzerland.

24. Safepharm Laboratories Ltd 1988, *TEPIC-G: Magnusson and Kligman Maximisation Study in the Guinea Pig (No. 14/14)*. Safepharm Laboratories Ltd, Derby, United Kingdom.

25. Shell Research Ltd 1971, *Toxicity Studies on the Diglycidyl Esters of Tetrahydrophthalic and Hexahydrophthalic Acids and of Trigiycidylisocyanurate: Repeated Dosing Experiments with Rats (TLGR.0019.71)*. Shell Research Ltd, London, United Kingdom.

26. Safepharm Laboratories Ltd 1991, *TEPIC SP: Five-Day Repeat Exposure Inhalation Toxicity Study in the Male Mouse (No. 14/68)*. Safepharm Laboratories Ltd, Derby, United Kingdom.

27. Bushy Run Research Center 1991, *PL90-810PC: Five Day Dust Inhalation Study in Mice*, Report No. 54-557, BRRC, Export, Pennsylvania, USA.

28. Hazleton 1987, *Mutagenicity Test on Araldite PT 810 in the Ames Salmonella/Microsome Reverse Mutation Assay (No. E-9782-0-401)*, Hazleton, The Netherlands.

29. Ciba-Geigy Ltd 1982, *Salmonella and Escherichia/Liver Microsome Test with TK 10622*, Ciba-Geigy Ltd, Basel, Switzerland.

30. Hazleton 1987, *Mutagenicity Test on Pigmented Powder Paint in the Salmonella/Microsome Reverse Mutation Assay (No. E-9781-0-401)*, Hazleton, The Netherlands.

31. Hazleton 1988, *Mutagenicity Test on Unpigmented Powder Paint in the Salmonella/Microsome Reverse Mutation Assay (No. E-9843-0-401)*, Hazleton, The Netherlands.

32. McCann, J., Gold, L.S., Horn, L., McGill, R., Graedel, T.E. & Kaldor, J. 1988, 'Statistical Analysis of Salmonella Test Data and Comparison to Results of Animal Cancer Tests', *Mutation Research*, vol. 205, pp. 183-195.

33. Ciba-Geigy Ltd 1983, *L5178Y/TK+/- Mouse Lymphoma Mutagenicity Test with TK 10622 (No. 830797)*, Ciba-Geigy Ltd, Basel, Switzerland.

34. Ciba-Geigy Ltd 1988, *Autoradiographic DNA Repair Test on Rat Hepatocytes with TK 10622 (No. 874266)*, Ciba-Geigy Ltd, Basel, Switzerland.

35. Ciba-Geigy Ltd 1983, *BALB/3T3 Cell Transformation Assay with TK 10622 (No. 820934)*, Ciba-Geigy Ltd, Basel, Switzerland.

36. Ciba-Geigy Ltd 1986, *Transformation/Liver Microsome Test with TK 10622 (No. 850072)*, Ciba-Geigy Ltd, Basel, Switzerland.

37. Ciba-Geigy Ltd 1985, *Chromosome Studies on Human Lymphocytes in vitro with TK 10622 (No. 850071)*, Ciba-Geigy Ltd, Basel, Switzerland.

38. Ciba-Geigy Ltd 1988, *Autoradiographic DNA Repair Test on Human Fibroblasts with TK 10622 (No. 874267)*, Ciba-Geigy Ltd. Basel, Switzerland.

39. Ciba-Geigy Ltd 1983, *Nucleus Anomaly Test in Somatic Interphase Nuclei of Chinese Hamster with TK 10622 (No. 820931)*, Ciba-Geigy Ltd, Basel, Switzerland.

40. Ciba-Geigy Ltd 1984, *Sister Chromatid Exchange Studies on Somatic Cells of Chinese Hamster (No. 830989)*, Ciba-Geigy Ltd, Basel, Switzerland,.

41. Ciba-Geigy Ltd 1983, *Sister Chromatid Exchange Studies on Somatic Cells of the Chinese Hamster (No. 820932)*, Ciba-Geigy Ltd, Basel, Switzerland.

42. Ciba-Geigy Ltd 1986, *Chromosome Studies on Male Germinal Epithelium of Mouse, Spermatogonia (No. 850067)*, Ciba-Geigy Ltd, Basel, Switzerland.

43. Hazleton Laboratories America Inc 1989, *Mutagenicity Test on PL88-810 in the Mouse Spermatogonial Cell Cytogenetic Assay (No. 10386-0-474)*. Hazleton Laboratories America Inc, USA.

44. Hazleton Microtest 1991, *Study to evaluate the Chromosome damaging Potential of TK 10622 (PT810 [TGIC, 97%]) by its effects on the Spermatogonial Cells of Treated Mice*, Hazleton Microtest, Heslington, York, United Kingdom.

45. Hazleton Microtest 1991, *Study to evaluate the Chromosome damaging Potential of TK 10622/1, a Polyester Formulation Containing 91 per cent Polyester (E2514, UCB) and 8.92 per cent TGIC by its Effects on the Spermatogonial Cells of Treated Mice*. Hazleton Microtest, Heslington, York, United Kingdom.

46. Hazleton Microtest 1991, *Study to evaluate the Chromosome damaging Potential of TK 10622/2, a Polyester Formulation Containing 60.2 per cent Polyester (P 2400, DSM Resins), 4.8 per cent TGIC and 35 per cent TiO2 (CL 2310, Kronos) by its Effects on the Spermatogonial Cells of Treated Mice*. Hazleton Microtest, Heslington, York, United Kingdom.

47. Ciba-Geigy Ltd 1986, *Chromosome Studies on Male Epithelium of Mouse, Spermatocytes (No. 850068) with TK 10622*, Ciba-Geigy Ltd, Basel, Switzerland.

48. Bushy Run Research Center 1992, *PL90-810: Chromosomal Aberrations Assay in Mouse Spermatogonial Cells*, Project no. 54-520, BRRC, Export, Pennsylvania, USA.

49. Bushy Run Research Center 1991, *PL90-810PC: Chromosomal Aberrations Assay in Mouse Spermatogonial Cells (No. 54-562).*, BRRC, Export, Pennsylvania, USA.

50. Safepharm Laboratories Ltd 1992, *TGIC Technical and TGIC ten per cent Powder: Chromosome Analysis in Mouse Spermatogonial Cells, Comparative Inhalation Study (No. 14/75)* (Draft), Safepharm Laboratories Ltd, Derby, United Kingdom.

51. Hazelton Microtest, 1993, *Study to Evaluate the Chromosome Damaging Potential of U.60092.100 G by its Effect on the Spermatogonial Cells of Treated Mice (No. CGP 7/SGC).* Hazelton Microtest, Harrogate, England.

52. Organisation for Economic Cooperation and Development 1986, 'Genetic Toxicology: Mammalian Germ-Cell Cytogenetic Assay', *OECD Guideline for Testing of Chemicals*, no. 483.

53. Ciba-Geigy Ltd 1986, *Dominant Lethal Test, Mouse, Three Weeks (No 850069)*, Ciba-Geigy Ltd, Basel, Switzerland

54. Hazleton Laboratories America Inc 1989, *Mutagenicity Test on PL88-810 in the Dominant Lethal Assay (No. 10386-0-471).* Hazleton Laboratories America Inc, USA.

55. Bushy Run Research Center 1991, *Dominant Lethal Assay of Inhaled PL90-810PC Dust in CD-1 Mice (No. 54-540)*, BRRC, Export, Pennsylvania, USA.

55A. Bushy Run Research Center 1992, *Dominant Lethal Assay of Inhaled Ph 90-810 Dust in CD-1 Mice (No. 54-515),* BRRC, Export, Pennsylvania, USA.

56. Ciba-Geigy Ltd 1990, *Potential for DNA Binding of Araldite PT 810 (No. PS32-01903).* Ciba-Geigy Ltd, Basel, Switzerland.

57. Ciba-Geigy, Ltd 1993, *Hazard Assessment with Araldite PT 810: Inactivation by Subcellular Liver Fractions and Binding to Liver DNA,* Project no. 924004, Ciba-Geigy Ltd, Basel, Switzerland.

58. Ciba-Geigy Ltd 1986, *Mammalian Spot Test, Mouse, 8 weeks (No. 850070) with TK 10622*, Ciba-Geigy Ltd, Basel, Switzerland.

59. Shell Research Ltd 1971, *The Potential Skin Tumour Promoting Properties in the Mouse of the Diglycidyl Esters of Tetrahydrophthalic acid and Hexahydrophthalic Acid and of Triglycidylisocyanurate (No. TLGR.0006.71).* Shell Research Ltd, London, United Kingdom.

60. Loveday, K.S., Anderson, B.E., Resnick, M.A. & Zeiger, E. 1990, 'Chromosome Aberration and Sister Chromatid Exchange Tests in Chinese Hamster Ovary Cells *In vitro*. V: Results with 46 Chemicals'. *Environmental and Molecular Mutagenesis*, vol. 16, pp. 272-303.

61. Sofuni, T., Matsuoka, A., Sawada, M., Ishidate Jr., M., Zeiger, E. & M.D. Shelby 1990, 'A Comparison of Chromosome Aberration Induction by 25 Compounds Tested by Two Chinese Hamster Cell (CHL and CHO) Systems in Culture'. *Mutat. Research*, vol. 241, pp. 175-213.

62. Mathias, C.G. 1988, 'Allergic Contact Dermatitis from Triglycidyl isocyanurate in Polyester Paint Pigments', *Contact Dermatitis*, no. 19(1), pp. 67-68.

63. Nishioka, K., Ogasawara, M. & Asagami, C. 1988, 'Occupational Contact Allergy to Triglycidyl isocyanurate (TGIC, Tepic)', *Contact Dermatitis*, no. 19(5), pp. 379-380.

64. Dooms-Goossens, A., Bedert, R., Vandaele, M. & Degreef, H. 1989, 'Airborne Contact Dermatitis due to Triglycidylisocyanurate', *Contact Dermatitis*, no. 21(3), pp. 202-203.

65. Ciba-Geigy Ltd 1988, *Report on the Test for Ready Biodegradability of TK 10622 in the Modified Sturm Test (No. 884053).* Ciba-Geigy Ltd, Basel, Switzerland.

66. Scheunert, I. 1992, 'Transformation and Degradation of Pesticides in Soil', *Terrestrial Behaviour of Pesticides*, ed W. Ebing, p. 64, Springer Verlag, Germany.

67. Ciba-Geigy Ltd 1993, *Report on the Test for Inherent Biodegradability in a Combined Zahn-Wellens / Carbon dioxide Evolution Test of Araldit PT 810*. , Basel, Switzerland.

68. Howard, P. 1989, 'Large Production and Priority Pollutants', *Handbook of Fate and Exposure Data for Organic Chemicals*. vol. I, Lewis Publishers, Michigan, USA.

69. Ciba-Geigy Ltd 1988, *Report on the Test for Acute Toxicity of TK 10622 to Zebra Fish (Brachydanio rerio)*. Ciba-Geigy Ltd, Basel, Switzerland.

70. Ciba-Geigy Ltd 1988, *Report on the Test for Acute Toxicity of TK 10622 to Daphnia magna*, Ciba-Geigy Ltd, Basel, Switzerland. March.

71. Fowler, M. C. 1977, *Weed Research*, vol. 17, pp. 191-195.

72. Seidegard, J. et al. 1986, *European Journal of Biochemistry*, no. 159, pp. 415-423.

73. Schmidt, U. & Loeser, E. 1985, 'Species Differences in the Formation of Butadiene monoxide from 1,3-Butadiene', *Arch. Toxicol*. no. 57, pp. 222-225.

74. Glatt, H.R. & Oesch, F. 1987, 'Species Differences in Enzymes Controlling Reactive Epoxides', *Arch. Toxicol*. suppl. 10, pp. 111-124.

75. Pacifici, G.M., Franchi, M., Bencini, C., Repetti, F., Di Lasio, N & Muraro, G.B 1988, 'Tissue distribution of drug-metabolizing enzyme in humans'. *Xenobiotica*, vol. 18, no. 7, pp. 849-856.

76. Mertes, I., Fleischmann, R., Glatt, H.R. & Oesch, F 1985, 'Interindividual variations in the activities of cytosolic and microsomal epoxide hydrolase in human liver', *Carcinogenesis*, vol. 6, no. 2, pp. 219-223.

77. National Occupational Health and Safety Commission 1993,*Approved Criteria for Classifying a Hazardous Substance*, Australian Government Publishing Service, Canberra.

78. National Occupational Health and Safety Commission 1993, *National Code of Practice for the Labelling of Workplace Substances*, Australian Government Publishing Service, Canberra.

79. National Occupational Health and Safety Commission 1993, *National Model Regulations to Control Workplace Hazardous Substances*, Australian Government Publishing Service, Canberra.

Sampling Method of Dust and Determination of TGIC (Nissan Method) 6/2/92

1. Dust Sampling

Equipment	:	Low Volume Air Sampler
Filter	:	Membrane type (ADVANTEC (TOYO) GB 100R 55mm)
Suction Flow Rate	:	20-30 L/min
Suction Time	:	15 min (for STEL), 1-2 hr (for TWA)

2. Condition of TGIC Extraction

Remove the collected filter from the holder and immerse it in 10 ml of acetonitrile. Vibrate it by supersonic vibrator for 5 mins, and filter the solution into an evaporating bottle. After repeating the process twice, condense and dry the solution for 1 hour at 40° C and 20-40 torr. The dissolved solution is analysed by HPLC.

3. Calibration

The accurate 20 mg of TGIC in a measuring flask is dissolved with 100ml of acetonitrile [Solution A]
10ml of Solution A is diluted to 100ml [Solution B]
25ml of Solution B is diluted to 100ml [Solution C]
20 ml of Solution C is diluted to 100ml [Solution D]

TGIC quantity in 1ml of four reference solutions is 200, 20, 5, 1 μg.

1ml of each reference solution is dried up in the evaporating bottle, dissolved thoroughly with 1ml of acetonitrile and 1 ml of water added.
20μl of each solution is injected to the HPLC with a micro-syringe under the following conditions and the calibration curve plotted.

Column	:	Zorbax RX-C18 4.5mm x 250mm
Column Temperature	:	40°C
Wavelength	:	UV 215nm
Mobile Phase	:	acetonitrile/water 1/4
Flow Rate	:	1.0 ml/min
Sensitivity	:	0.08 aufs

4. Measuring TGIC

20μg of the sample solution (2 above) is injected in to the HPLC under the same conditions as 3 above and the quantity of TGIC determined using the calibration curve. The TGIC concentration in the dust is calculated as follows:

$$\text{TGIC Concentration (mg/m}^3\text{)} = \frac{\text{TGIC [}\mu\text{g]}}{\text{(Suction flow rate [L/min] x Suction time[min])}}$$

Ciba Forschungsdienste
Zentrale Analytik
Environmental- and Trace Analysis

Attachment 2

Central Laboratory of Industrial Hygiene

Ambient Monitoring Method for Triglycidylisocyanurate, TGIC,

(Araldite PT 810)

Method No.	AV-052
Revision No.	2
Date	01 / 29 / 93
Page	1 of 7

Author: Th. Kramer / T.Maurer

Matrix	Air (480 L)
MEL	250 µg/m³
Range	6 - 240 µg/sample corresponding to 10-500µg/m³
Accuracy	4 %

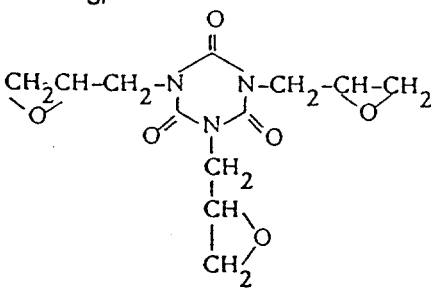
Effective date: 02 / 05 / 93

Approval: M. Joppich

Dr. M. Joppich

1. GENERAL

1.1. Substance Data

Substance	TGIC
Formula	$C_{12}H_{15}N_3O_6$
Molecular weight	297.3 g/mol
Structure	

1.2. Determination Limit

0.4 µg/filter, corresponding to 0.8 µg/m³ for a sampling volume of 480 L air.

1.3. Principle of Procedure

Sampling is performed by collecting the dust on glass fibre filters. After extraction with HPLC eluent, the sample solution is analyzed by HPLC using UV detection.

Ambient Monitoring Method for Triglycidylisocyanurate, TGIC, (Araldite PT 810)	Method No. AV-052
	Revision No. 2
	Date 01 / 29 / 93
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2. CHEMICALS, SOLUTIONS, EQUIPMENT

2.1. Chemicals

TGIC	TGIC technical grade, the content of active epoxides has to be determined by CG method KBB-152/1, september 1989
KOH	Merck # 5033
H_3PO_4 85%	Merck # 573
Acetonitrile (gradient grade)	Merck # 30
Water SQS HPLC Quality	CG Art. 24901

2.2. Solutions

KOH solution	15 M
Phosphate buffer	0.01M H_3PO_4, adjusted to pH 6 with KOH solution (15M)
HPLC eluent	Acetonitrile / Phosphate buffer 10:90
Extraction solution:	HPLC eluent (2 ml)
TGIC-stock solution	240 mg of reference substance in 20 ml HPLC eluent
TGIC-reference solution:	10 µl of TGIC-stock solution added to 2 ml extraction solution;corresponds to 60 µg/ml TGIC

2.3. Equipment

Sampling pump:	Range 1 - 5000 ml/min
Filters:	Glass fibre filters d=37 mm (Milipore AP4003705)
Air monitoring cassettes:	Size: d=37 mm (GELMAN # 4338)
Liquid chromatograph:	Hewlett Packard 1090
Injection volume:	150 µl
Detector:	Kratos 757 UV/VIS
Solvent filters:	ACRODISC CR PTFE, 0.45 µm (GELMAN # 4219)

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3. PROCEDURE

3.1. Sampling Procedure

Sampling volume:	480 L air
Linear flow rate:	1.25 m/s
Sampling speed, time:	1000 ml/min., 480 min.
	4000 ml/min., 120 min.

Calibrated pumps are used. Start and end times of sampling as well as temperature and atmospheric pressure are recorded. After sampling, the filter is transferred to a 4 ml vial for transportation. The samples are stored at 4 C and analyzed within 2 weeks.

3.2. Sample Preparation

For extraction of the substance TGIC from the glass fibre filter, 2 ml of extraction solution is added to each flask. Extraction is accomplished within 25 minutes using an ultrasonic bath. Before the analysis, the solutions are filtered through a Gelman filter ACRODISC CR PTFE; 0,45 µm.

3.3 HPLC Conditions

Column:	Nucleosil C18, 5 µm, 100 A; 125 x 4.6 mm (Bischoff)
Eluent:	Acetonitrile / Phosphate buffer 10:90
Flow rate:	1.5 ml/min
Temperature:	40 C
Wavelength:	212 nm
Injection volume:	150 µl

Retention time:	TGIC	7.15 min.	(k'= 9.2)

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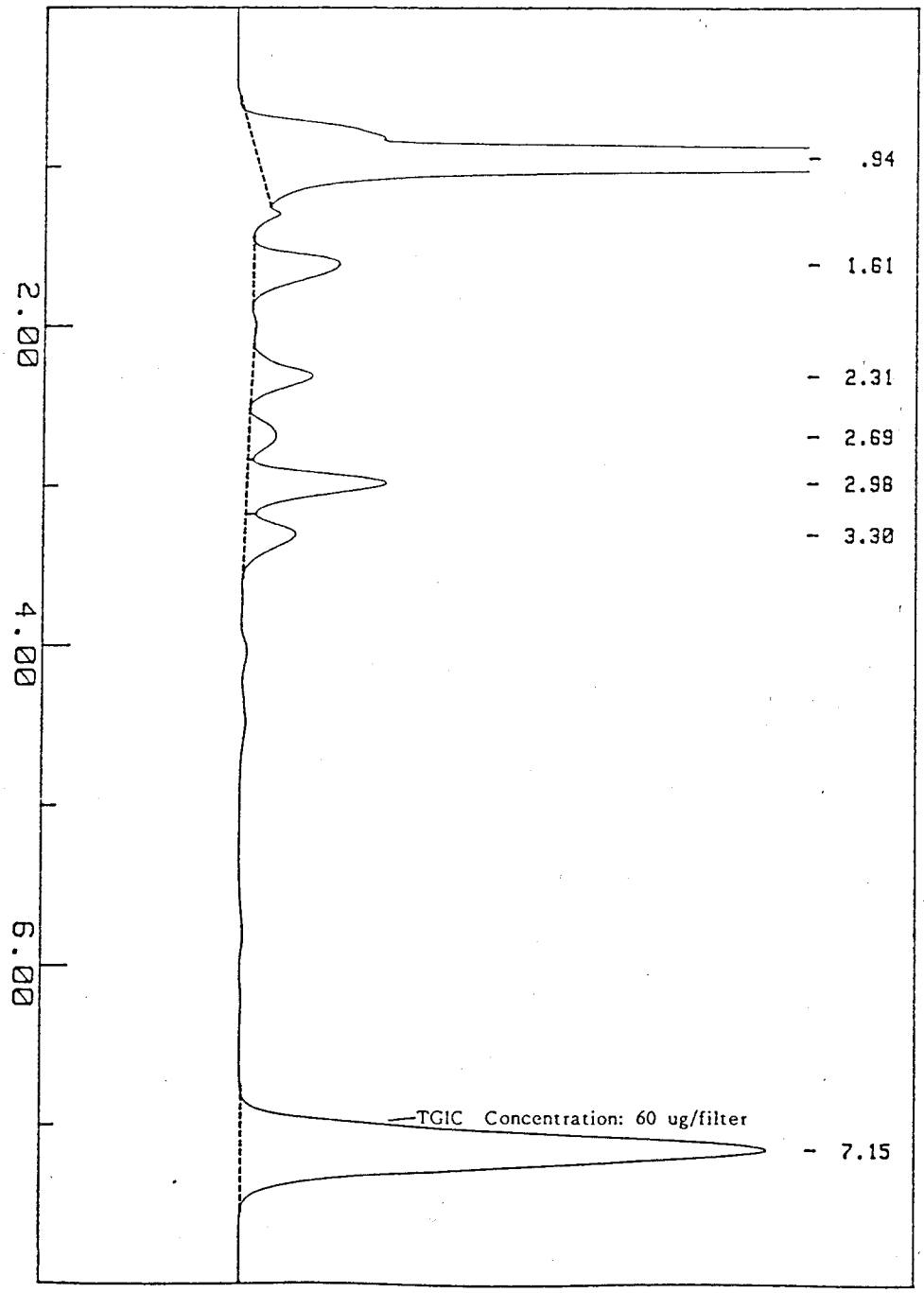
4. CHROMATOGRAM



5. COMPUTATION

5.1 Calculation of the Quantity of TGIC

The quantity of TGIC in the sample solution (Qs) is determined by the external standard method, based on a 5 point calibration.

Range: 6 to 240 µg/sample, corresponding to 10 - 500 µg/m^3 for 480 L sampling volume

Linearity: $r^2 = 0.999$

Quantity of TGIC, Qa [µg]

$$Qa = Qs \cdot EE$$

$$Qa = Qs \cdot 1.053$$

Qs quantity of analyte in sample solution
Qa quantity of adsorbed analyte [µg]
EE extraction efficiency

5.2 Concentration in the Air Sample

Normalized air sampling volume V*

$$V^* = V \cdot \frac{P}{1013} \cdot \frac{293}{T+273}$$

V sampling volume [L]
V* volume normalized to 1013 mbar, 20 C [L]
P atmospheric pressure [mbar]
T air temperature [C]

TGIC-concentration C* in the air sample

$$C^* = \frac{Qa \cdot 1000}{V^*}$$

V* volume normalized to 1013 mbar, 20 C [L]
C* concentration under standard conditions [µg/m^3]
Qa quantity of adsorbed analyte [µg]

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1. APPENDIX

1.1 Linearity

Preparation of stock solutions

(1) TGIC stock solution 1: weigh 480 mg TGIC ad 20 ml HPLC eluent

(2) TGIC stock solution 2: weigh 360 mg TGIC ad 20 ml HPLC eluent

(3) TGIC stock solution 3: weigh 240 mg TGIC ad 20 ml HPLC eluent

(4) dilute stock solution 3 1:10

(5) dilute stock solution 3 1:20

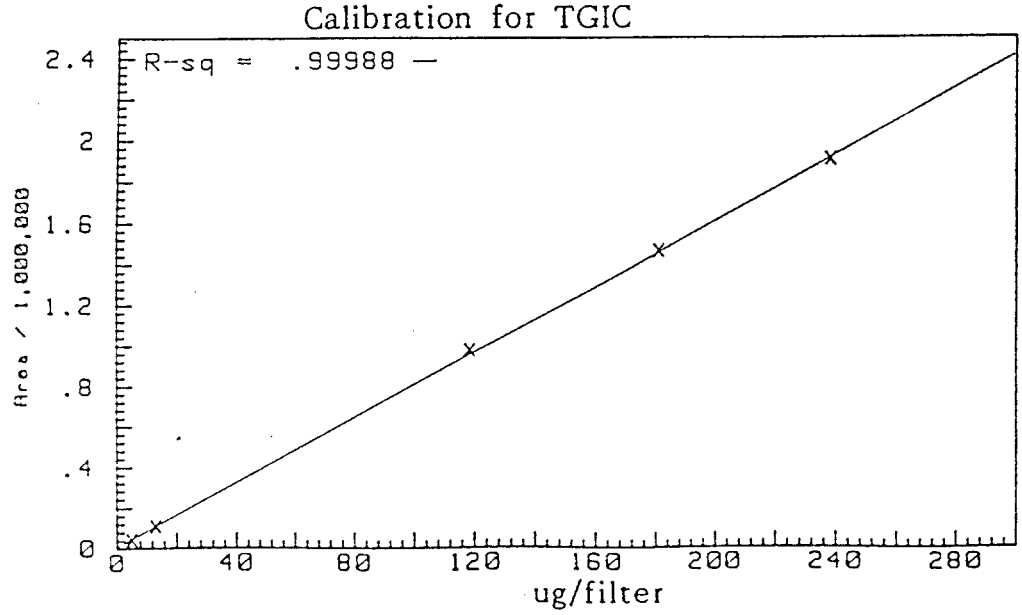
The TGIC is dissolved using an ultrasonic bath (25 min)

TGIC calibration solutions

add 10 µl of (1) respectively (2), (3), (4), (5) in 2 ml extraction solution.

Calibration range: 6 to 240 µg/sample, corresponding to 10 - 500 µg/m³ for 480 L sampling volume

$r^2 = 0.99988$



1.2 Extraction Efficiency (EE)

24 mg TGIC are dissolved in 20 ml acetone, using an ultrasonic bath (25 min). A glass fibre filter is placed in a monitoring cassette and 50 µl of this solution (60 µg/filter corresponding to 125 µg/m^3) are placed onto the filter. After 480 L of air are sucked through the loaded cassette, further sample preparation is performed following the procedure on page 3.

-TGIC EE: 95% n=3 (std. dev.: 4%)

1.3. Humidity and Storage Test

2 mg of the pure substance are applied onto a glass fibre filter and placed in a monitoring cassette. After 480 L of air of known relative humidity are sucked through the loaded cassette, further sample preparation is performed following the procedure on page 3. For storage tests, the vial with filter is stored at room temperature for the indicated time.

Humidity Test

Sampling volume and relative humidity of air used: 480 L, 50% humidity

- TGIC Recovery: 101% / 104% n=2

Two Weeks at Room Temperature

Sampling volume and relative humidity of air used: 480 L, 50% humidity

- TGIC Recovery: 99% - 100% n= 3

Page x of Total y
Date of Issue

MATERIAL SAFETY DATA SHEET

COMPANY DETAILS

Company Name

Address

Telephone Number

Emergency Telephone Number

Telex and Fax Numbers

IDENTIFICATION

Chemical Name: 1,3,5-Triglycidyl isocyanurate

Other Names: Tepic, Tepic-G, Araldite PT 810, TGIC

Manufacturer's Product Code:

UN Number: none allocated
Dangerous Goods Class/Subsidiary Risk: none allocated

Hazachem Code: none allocated

Poisons Schedule Number: none allocated

Use: Curing agent used in the manufacture of powder coatings for electrostatic spray painting.

PHYSICAL DESCRIPTION/PROPERTIES

Appearance: White granule

Melting Point: 90 - 125 $^{-}$C

Vapour Pressure: Approx 10^{-6} Pa at 20˚C

Specific Gravity: 1420 - 1460 kg/m^3

Flashpoint: > 170 $^{-}$C (Closed Cup Method)

Flammability Limits: Not available

Solubility in Water: 0.9 - 2.0%
Will vary depending on ratio of mix of isomers of α and βTGIC.

OTHER PROPERTIES

Reactivity: Hazardous autopolymerisation occurs following heating to > 120 C for more than 12 hours.

Autoignition Temperature: > 200°C

Solubility in Organic Solvents:
At room temperature, >10% in dimethyl formamide, dimethyl sulphoxide, epichlorohydrin, tetrachloro ethane and acetonitrile.

INGREDIENTS (check all ingredients)

Chemical Entity: TGIC, α and βisomers

CAS Number: 2451-62-9

Proportion: 100%

HEALTH HAZARD INFORMATION

HEALTH EFFECTS

Acute

Swallowed: Toxic

Eye: Severe eye effects

Skin: Skin sensitiser

Inhaled: Toxic by inhalation. Will irritate mucous membranes and may cause nosebleeds.

Chronic

Susceptible individuals may develop allergic reactions such as dermatitis or asthma-like symptoms on a single significant skin exposure or may become sensitised on repeated contact.

TGIC has been shown to be genotoxic in a number of tests with isolated cells and whole animals. TGIC has been shown to reach reproductive organs in test mammals exposed to it and damage genetic material in sperm cells. There is limited animal data to show other adverse effects on reproductive organs.

TGIC, as well as being a genotoxin, has structural similarities with carcinogenic epoxides and may be regarded as a possible human carcinogen. There is no animal carcinogenicity data on which to base an exposure standard.

FIRST AID

Swallowed: Rinse mouth with water. Give plenty of water to drink. If more than 15 minutes from a hospital induce vomiting using fingers in the throat or Ipecac Syrup APF. Seek immediate medical assistance.

Eye: Immediately irrigate with copious quantities of water for at least 15 minutes. Eyelids to be held open. Seek immediate medical assistance.

Skin: Wash contaminated skin with plenty of soap and water. Remove contaminated clothing and wash before re-use.

Inhaled: Remove victim from exposure - avoid becoming a casualty. Remove contaminated clothing and loosen remaining clothing. Allow patient to assume most comfortable position and keep warm. Keep at rest until fully recovered. Effects may be delayed. Seek medical advice.

First Aid Facilities:

ADVICE TO DOCTOR

Advice to Doctor: Treat symptomatically.

PRECAUTIONS FOR USE

Exposure Standards: None. The Director, National Industrial Chemicals Notification and Assessment Scheme has recommended an interim occupational exposure of 0.08 mg/m^3 and also recommends that the National Occupational Health and Safety Commission establish an exposure standard.

Engineering Controls

During powder coating formulation, processes should, where possible be segregated from non-involved personnel. All vessels involved in mixing, blending and extrusion should be

enclosed. All materials should be transferred to or from vessels by mechanical means. Local exhaust ventilation should capture liberated dust at source during all operations in which it is liberated.

PERSONAL PROTECTION

A respirator offering a minimum protection factor of 100+ for mechanically generated particulates as outlined in Australian Standard AS 1715-1991 should be worn. The respirator should include full head covering and eye protection.

Impervious gloves conforming to Australian Standard AS 2161-1978 should be worn. Protective clothing conforming to Australian Standard AS 3765.1-1990 should be worn.

FLAMMABILITY

As with most organic solids a flammable dust cloud may be generated and this should be avoided.

SAFE HANDLING INFORMATION

Storage and Transport

Storage should be in a restricted area. Temperature variation in the store should range from 5 - 35°C. There are no particular storage incompatibilities.

SPILLS AND DISPOSAL

Care should be taken not to puncture containers when moving pallets with forklift. In the event of a spill do not use a broom or air blower. Vacuuming is recommended. Personal protective equipment as noted in the appropriate section above should be worn. Dispose of to landfill in accordance with local and State regulations.

FIRE/EXPLOSION HAZARD

Hazardous autopolymerisation may occur following heating to more than 120˚C for more than 12 hours. Dust explosion hazard. Use CO_2, foam and dry powder only for extinguishing.

OTHER INFORMATION

Toxicity

Toxicity is likely to vary with the ratio of the isomers α:β

Acute Oral:	LD_{50} <100 mg/kg male rats, 250 mg/kg female rats, 155 mg/kg male/female
Acute Dermal:	LD_{50} >2000 mg/kg
Acute Inhalational:	LC_{50} 650 mg/m^3
Skin Irritation:	slight irritant to rabbit skin
Eye Irritation:	severe irritant to rabbit eye
Skin sensitisation:	positive skin sensitiser in guinea pigs

Genotoxicity

There are 21 genotoxicity studies for TGIC. The overall profile shows that TGIC is capable of reaching reproductive organs and breaking chromosomes. In animals exposed to TGIC, it was distributed to stomach, liver and testes and found to bind to the genetic material (DNA) in cells (DNA alkylation) at these sites and produce toxicity.

Ecological Information

Zebra fish, 96h LC_{50}: 77 mg/L
Daphnia magna immobilisation 24h EC_{50}: 100 mg/L

Not readily biodegradable: 9.1% at 10 mg/L, 48% at 20 mg/L (modified Sturm test)

Limited persistance in the environment

CONTACT POINT

Title

Telephone Number