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The Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals

128. Triglycidyl isocyanurate

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Nordic Council of Ministers

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Preface

The Nordic Council is an intergovernmental collaborative body for the five countries, Denmark, Finland, Iceland, Norway and Sweden. One of the committees, the Nordic Senior Executive Committee for Occupational Environmental Matters, initiated a project in order to produce criteria documents to be used by the regulatory authorities in the Nordic countries as a scientific basis for the setting of national occupational exposure limits.

The management of the project is given to an expert group. At present the Nordic Expert Group consists of the following members:

Gunnar Johanson (chairman)	National Institute for Working Life, Sweden
Vidir Kristjansson	Administration of Occupational Safety and Health, Iceland
Kai Savolainen	Finnish Institute of Occupational Health, Finland
Vidar Skaug	National Institute of Occupational Health, Norway

For each document an author is appointed by the Expert Group and the national member acts as a referent. The author searches for literature in different data bases such as Toxline, Medline and Nioshtic. Information from other sources such as WHO, NIOSH and the Dutch Expert Committee on Occupational Standards is also used as are handbooks such as Patty's Industrial Hygiene and Toxicology. Evaluation is made of all relevant scientific original literature found. In exceptional cases information from documents difficult to access is used.

The present document is such an exceptional case. Very few peer-reviewed reports on the toxicology of triglycidyl isocyanurate were found. The Nordic Expert Group therefore decided to admit the inclusion of non peer-reviewed reports on four conditions. Thus, to be included each report must be (1) judged to be reliable and (2) relevant and important for the main conclusions. In addition, (3) the report must have been cited and, thus, critically reviewed by at least one other distinguished international or national body. Finally, (4) the nature of the report should be clearly indicated in the text.

The document aims at establishing dose-response/dose-effect relationships and defining a critical effect based only on the scientific literature. The task is not to give a proposal for a numerical occupational exposure limit value.

The evaluation of the literature and the drafting of this document on triglycidyl isocyanurate was made by M Ph Birgitta Lindell, and Dr Johan Montelius at the National Institute for Working Life, Sweden. The draft document was discussed within the Expert Group and the final version was accepted by the Nordic Expert Group November 20, 2001, as its document.

Editorial work was performed by the Group's Scientific Secretary, Jill Järnberg, and technical editing by Karin Sundström, both at the National Institute for Working Life in Sweden.

We acknowledge the Nordic Council for its financial support of this project.

Jill Järnberg
Scientific Secretary

Gunnar Johanson
Chairman

Abbreviations

ANOVA	analysis of variance
CICAD	Concise International Chemical Assessment Document
CHO	Chinese hamster ovary
CHL	Chinese hamster lung
FEV_1	forced expiratory volume in 1 second
GLP	good laboratory practise
HSE	Health and Safety Executive
LD_{50}	lethal dose for 50% of the exposed animals at single administration
NICNAS	the National Industrial Chemicals Notification and Assessment Scheme
NOAEL	no observed adverse effect level
TGIC	triglycidyl isocyanurate
UK	United Kingdom

Contents

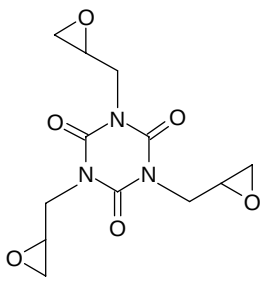
1. Introduction

Triglycidyl isocyanurate (TGIC) is an epoxy compound often used as a hardener. The main use of TGIC is in the manufacture of polyester powder coatings (paints) for metal finishing. Powder coatings usually contain between 4 and 10% TGIC. TGIC has been used in weather-resistant powder coatings in Europe since the 1970s. Powder coated objects include garden steel furniture, car parts, metal fencing, window and door frames but also electrical equipment, refrigerators, washing machines and ovens. TGIC may also be used in inks in the printed circuit board industry. The two-part inks contain approximately 60% TGIC in the hardener component. Furthermore, TGIC has been used as an anti-tumour agent in clinical trials, but owing to its severe local toxicity the use of TGIC was not pursued (15, 20, 29, 33).

Normally, only studies published in peer-reviewed international scientific journals are cited in criteria documents produced by the Nordic Expert Group. However, in the case of TGIC very few peer-reviewed studies were found. Therefore, non peer-reviewed studies have been referred to in this document on condition that they have been cited in a review prepared by an international or national body and are important for the conclusions. It is also indicated if the original report has not been retrieved.

2. Substance identification (15, 16, 29)

IUPAC name	1,3,5-tris (oxiranylmethyl)-1,3,5-triazine-2,4,6(1H,3H,5H)-trione
Common name:	triglycidyl isocyanurate
CAS number:	2451-62-9, 59653-73-5 (α-TGIC), 59653-74-6 (ß-TGIC)
Synonyms:	TGIC; 1,3,5-triglycidyl isocyanurate; 1,3,5-triglycidyl-s-triazinetrione; 1,3,5-tris(2,3-epoxypropyl)-s-triazine-2,4,6(1H,3H,5H)-trione; tris(2,3-epoxypropyl)isocyanurate
Trade names:	TEPIC, Araldite PT 810, TK 10622
Molecular formula:	$C_{12}H_{15}N_3O_6$
Molecular weight:	297.3 g/mol
Structural formula:	



TGIC is manufactured and supplied as technical grade under the trade names TEPIC and Araldite PT 810 (also known as TK 10622) (20, 29). There are two stereoisomeric forms, α-TGIC and ß-TGIC, which differ in the orientation of the glycidyl groups. Technical grade TGIC contains 90% α-and 10% ß-isomer (16).

3. Physical and chemical properties

	α-TGIC	ß-TGIC	TEPIC	Araldite PT 810
Purity (%)			≈90	>97
Melting point (°C)	105	156	90-125	95
Vapour pressure (kPa)				$7.2 \cdot 10^{-9}$ (20°C)
Flash point (°C)			>170	
Autoignition temp. (°C)			>200	
Density (g/cm^3)[a]			1.420	1.460
Solubility in water (g/l)	10 (20°C)	0.53 (20°C)	9 (25°C)	8.7 (25°C)
Partition coefficient (log $K_{o/w}$)			-0.8	

[a] Temperature not given

References for data are 6, 15, 29

TGIC is a solid, which may occur as a white opaque powder or granules or as clear crystals (16). It is an epoxy compound, where three glycidyl groups are coupled to a triazine ring (33). TGIC has a low vapour pressure and no discernible odour at room temperature (16, 20). It is soluble or slightly soluble (25°C) in epichlorohydrin (<22%), methanol (7.3%), toluene (3%), and isopropanol (1%) (20).

Dust explosions may occur if TGIC in powder or granular form is mixed with air. The substance may polymerise after heating to more than 120°C for more than 12 hours, or under the influence of catalysts (20). In its molten state, TGIC reacts easily with various functional groups in the presence of catalysts or promoters (29). Molten TGIC reacts rapidly with primary and secondary amines, carboxylic acids and anhydrides, thiols, phenols and alcohols (20). Combustion products include oxides of nitrogen, carbon monoxide, carbon dioxide, ethene oxide, and acrolein (5, 20).

4. Occurrence, production and use

TGIC does not occur naturally. It is produced industrially by reacting cyanuric acid with excess epichlorohydrin. The worldwide production of TGIC is approximately 7000-8000 tonnes per year (16, 20, 29). The two main technical grades of TGIC used in the manufacture of powder coatings worldwide are

Araldite PT 810 manufactured by Ciba-Geigy and TEPIC manufactured by Nissan Chemical Industries (29).

TGIC is used mainly as a hardener in the thermosetting one-component polyester powder coatings (33). In the manufacture of powder coatings, TGIC granules are mixed with resin, pigments (if pigmented powder coatings), fillers and additives. The mixture is heated until melting occurs and the melt is mixed to ensure homogeneity. It is then extruded into a thin sheet, which cools and solidifies. The solid material is chipped, milled, sieved and packed as a fine powder (29). TGIC is partially cross-linked to the polyester resin. The powder coatings usually contain 4-10% TGIC and are sprayed onto metal objects by an electrostatic process. The coated metal objects are then placed in an oven. At a temperature of about 200°C the resin melts, flows, and chemically cross-links to form a paint film (20, 29). The TGIC in powder coatings after application to metal particles is fully cross-linked and is bound in a solid matrix. The coatings are durable and resist ultraviolet damage and are therefore typically used in out-door applications (16, 20).

In addition, TGIC is used in electrical insulation materials, resin-moulding systems, laminated sheetings, silk-screen printing coatings, tools, inks, adhesives, lining materials, and stabilisers for plastics (33). Solder ”mask” inks used in the printed circuit board industry are two-part inks containing approximately 60% TGIC in a powdered form in the hardener component (16, 20). The inks are applied by curtain coating, electrostatic spraying, or by screen-printing. The coated circuit board is finally passed through an oven at 150°C to complete the curing (20).

In Sweden, TGIC is imported as technical grade TGIC or as an ingredient of products. 15 products containing TGIC were imported to Sweden in 1999 (including technical grades of TGIC) and the total amount of TGIC imported was 76-91 tonnes. About 31 tonnes was used in the manufacturing of 4 products containing TGIC. Technical grade TGIC was not manufactured in the country. Technical grade TGIC was used as raw material in the paint industry, whereas imported or manufactured products containing TGIC were used in industry for fabricated metal products/industry for the treatment and coating of metals and in the construction industry. Minor uses for products containing TGIC were as solder ”mask” inks or as photoresists (Product Register at the Swedish National Chemical Inspectorate, personal communication). In Norway in the year 2000, TGIC was an ingredient of a few paints used for production of metal products. However, the total amount of TGIC could not be given (Norwegian Product Register, personal communication). In Finland, 9 products containing 1-45% TGIC were used in 2000. Two of these products were used in the manufacturing of electronical components, whereas 7 products were used in painting. The total amount of TGIC could not be given (Finnish Product Register, personal communication). In Denmark, TGIC is imported as technical grade TGIC or as an ingredient of products. In the year 2000, 9 products were reported to contain TGIC and the total amount of TGIC approached 10 tonnes. Technical grade TGIC was used in the manufacturing of painting products. The products containing

TGIC were mainly paints and lacquers used in the iron- and metal industry or in the manufacturing of means of transport (Danish Product Register, personal communication).

The anti-tumour properties of α- and ß-TGIC have been investigated in various transplantable mouse tumour systems. Both stereoisomers displayed a high therapeutic activity, but α-TGIC was superior to the ß-isomer in prolonging the lifespan of treated animals and in inducing long-term survival, probably due to a higher water solubility (3, 4, 11, 14, 36, 39). *In vitro* studies measuring cells killed by the drug indicated that neoplastic cells were more susceptible to α-TGIC than non-neoplastic cells (39). α-TGIC has also been available as an experimental anti-neoplastic agent and was used in human clinical trials in the early 1980s (29). However, it has been suspected that some of the clinical trials were conducted with TGIC mixtures, rather than pure α-TGIC as reported (14).

5. Occupational exposure data

Occupational exposure to TGIC may occur during the manufacture of TGIC and the manufacture and use of products containing TGIC (20). The most likely routes of occupational exposure are inhalational and dermal. A fraction of the inhaled material will be swallowed, and there may also be some oral ingestion (19, 29). Activities likely to cause high levels of exposure during the manufacture of TGIC powder coatings are weighing out of TGIC, filling hoppers, mixing, transfer of powder mixes in open vessels, extrusion, milling, bagging, cleaning-up spills and cleaning equipment. The highest level of exposure to TGIC will occur when handling technical grade TGIC (29). However, particle size data on technical grade TGIC as granules indicate that only very small fractions are respirable. Of TEPIC particles, 99.6% are >400 µm and only 0.003% are <10 µm (29).

Exposure to TGIC during the use of products containing TGIC may occur in factories and paint shops, where TGIC powder coatings are sprayed onto metal objects prior to curing in ovens. There is a considerable potential for airborne dust generation during decanting of the powder in preparation for spraying (filling hoppers). The method of application (spraying) also provides considerable potential for exposure to powder coatings, especially if the area is not fully enclosed and the objects are manually sprayed (29). Furthermore, certain cleaning operations (cleaning-up spills, cleaning equipment, cleaning spray booths) may lead to exposure to large amounts of TGIC (29, 37). Nevertheless, some data indicate that TGIC powder coatings have a low fraction of particles in the respirable range (29). Generally, the particle size of 90-95% of the powder coating is >10 µm (20).

Data describing actual exposure levels at workplaces are limited. No monitoring data are available for the manufacture of TGIC and data for the manufacture and use of TGIC containing products are restricted to powder coatings. These data have shown marked differences in the air levels of TGIC between and within workplaces (Table 1). In an Australian powder coating manufacturing plant the

levels of atmospheric TGIC in July/August 1991 varied between 0.023 and 1.34 mg/m^3 (time-weighted average, TWA). Levels of total dust were up to 24.9 mg/m^3. The data showed that dust levels for different operators performing the same job varied considerably. Later work practices were improved and dust levels were considerable lowered. In October 1991, the levels of TGIC (TWA) were between 0.00001 and 0.03 mg/m^3 (20, 29). In a Japanese powder coating manufacturing plant TGIC levels up to 0.035 mg/m^3 (TWA) and dust levels up to 1.12 mg/m^3 were measured in 1991 (20, 29). In 5 plants manufacturing TGIC-containing powder coatings in the United Kingdom (UK) in 1994, TGIC levels

Table 1. Workplace concentrations of TGIC in various types of industries

Industry	Process/work operation	Exposure level (TWA) (mg/m^3)	Ref
manufacture of powder coatings	make up	0.032-0.19	(20, 29)
	extruder	0.023-0.27	(20, 29)
	mill	0.085-1.34	(20, 29)
	laboratory	0.047	(20, 29)
manufacture of powder coatings	warehouse	0.002-0.007	(20, 29)
	mixing	0.00001	(20, 29)
	extruder	0.003-0.013	(20, 29)
	mill	0.006	(20, 29)
	bulk	0.004	(20, 29)
	laboratory	0.004-0.030	(20, 29)
manufacture of powder coatings	weighing raw materials	0.005*	(20, 29)
	filling raw materials	0.004*	(20, 29)
	mixing	trace*	(20, 29)
	pulverisation	0.002*	(20, 29)
	packing	0.009*	(20, 29)
	cleaning work: mixer	0.006*	(20, 29)
	cleaning work: pulveriser	trace*	(20, 29)
	cleaning work: cyclone	0.009*	(20, 29)
	cleaning work: sieve	0.035*	(20, 29)
	cleaning work: packing hopper	0.005*	(20, 29)
manufacture of powder coatings		0.01-0.44	(16, 20, 37)
		mean: 0.1	(16, 20, 37)
	weighing	mean: 0.27	(16, 37)
	milling	mean: 0.08	(16, 37)
use of powder coatings	spray painting	<0.001-6.5	(20, 29)
use of powder coatings	e.g. spraying	0.001-1.5	(16, 20, 37)
		mean: 0.24	(16, 20, 37)
	cleaning, colour changes	mean**: 0.95	(16, 37)

*determination of TEPIC

**short-term exposure

ranged from 0.01 to 0.44 mg/m^3 with a mean of 0.1 mg/m^3 (8-hour TWAs). Corresponding total inhalable particulate levels were 1.1-64 mg/m^3 (8-hour TWAs). The highest exposures were found during weighing (TGIC mean: 0.27 mg/m^3) and milling (TGIC mean: 0.08 mg/m^3). High exposures were, however, found for all the tasks monitored (weighing, mixing, extrusion, milling, packing, cleaning). The high exposures were generally due to poor working practices (16, 20, 37).

In a survey of 8 spray painting workplaces in Australia in 1991 the TGIC content in dust from 7 workplaces was up to 6.5 mg/m^3 (TWA; personal air monitoring). Total dust levels were up to 132 mg/m^3 (20, 29). The results of a survey of 16 similar workplaces in the UK in 1994 showed TGIC levels between 0.001 and 1.5 mg/m^3 (8-hour TWAs; mean: 0.24 mg/m^3). Corresponding total inhalable particulate levels were 0.2-131 mg/m^3 (8-hour TWAs). Exposures were high during all the tasks measured (spraying, loading, cleaning). Furthermore, high full-shift exposures to TGIC were measured for both manual spray operators and sprayers at automated booths. High short-term exposures were measured during cleaning and colour changes. The high exposure levels of TGIC in the investigated workplaces in the UK were generally attributed to poor working practices (16, 20, 37).

6. Measurement and analysis of workplace exposure

A rough estimate of exposure to free TGIC in coating powders can be made by measuring exposure to total inhalable particulate. After collection on filters and gravimetric analysis, the exposure to free TGIC can be calculated from the composition of the coating powder (17, 18).

A more accurate method for the analysis of TWA concentrations of TGIC, and premix and coating powders containing TGIC in air has been described by the UK Health and Safety Executive (HSE) (18). Premix is defined as formulated and mixed coating powder prior to extrusion in manufacture, and coating powder as the extruded and milled powder supplied by manufacturing companies to users. The method described is suitable for personal sampling in the breathing zone but can also be used for background or fixed location monitoring. Only monomeric TGIC will be measured. Sampling is carried out according to a general method for sampling of total inhalable dust (17), i.e. a measured volume of air (a suitable sample volume is 200 l) is drawn through a silanised glass fibre filter mounted in a sampler for inhalable dust. A gravimetric screening method can be used as a preliminary screening method for TGIC (18). For a more specific analysis high performance liquid chromatography is used. It is important to analyse the samples promptly, as decomposition of TGIC is rapid. For sample volumes of 200 l, the method is validated between 0.01 and 0.2 mg/m^3 pure TGIC and the detection limit is approximately 0.18 µg TGIC per sample corresponding to 0.9 µg/m^3.

7. Toxicokinetics

7.1. Uptake

No data have been found in the peer-reviewed literature.

7.2. Distribution

No data have been found in the peer-reviewed literature.

7.3. Biotransformation and excretion

α-TGIC is rapidly metabolised by rat liver. When α-TGIC was incubated (1 mM) with hepatic microsomes, rapid disappearance of the parent drug was observed in the presence or absence of $NADP^+$. When inactivated microsomes were used in the incubation mixture, no loss of α-TGIC occurred. These results suggest that α-TGIC is metabolised by microsomal enzymes other than monooxygenases. Epoxide hydrolysis products were detected in hepatic microsomal incubation mixtures and cyclohexene oxide inhibited α-TGIC metabolism, suggesting that epoxide hydrolase is responsible for the biotransformation. Rat lung preparations did not significantly metabolise α-TGIC (2).

It has been shown that there is considerable variation in epoxide hydrolase activity between individuals in humans (25).

The disposition of α-TGIC following intravenous administration of 3 and 10 mg/kg body weight to rabbits has been studied. At these doses plasma elimination of parent drug was very rapid with a half-time of <5 minutes. When ^{14}C-labeled α-TGIC (10 mg/kg body weight) was intravenously administered to rabbits plasma elimination of radioactivity was much slower than that of parent drug. The radioactivity was equally distributed between plasma and red blood cells. The 24-hour urinary recoveries of parent drug and total radioactivity were <1% and about 65%, respectively. When ^{14}C-labeled α-TGIC (10 mg/kg body weight) was administered to rabbits by stomach tube parent drug was not detected in plasma and plasma concentrations of total radioactivity were lower compared to those observed following intravenous administration. The 24-hour urinary recoveries of radioactivity were about 30%. These data suggest extensive metabolism of TGIC (2).

Disposition of α-TGIC has also been studied in patients. When patients received α-TGIC as intravenous infusions at constant rates (12.5-50 mg/min) plasma concentrations rapidly reached plateau values and remained constant during the infusion. Plasma steady-state concentrations increased and total-body clearance values decreased as the rate of infusion increased. The 24-hour urine recovery of the parent drug was less than 1% for all patients. The mean plasma elimination half-time was 1.4 minutes for 9 patients given 140-500 mg/m^2 body surface for 3-10 minutes (2, 34). In another study a mean half-time of 0.9 minutes was reported following short intravenous infusion of α-TGIC to 5 patients (28).

8. Biological monitoring

No data have been found.

9. Mechanism of toxicity

No information is available concerning the mechanism of toxicity of TGIC.

Considering that TGIC contains three reactive epoxide groups it is plausible that it reacts with macromolecules causing different adverse effects, e.g. inducing mutations by binding to DNA and sensitisation by binding to proteins. Dose-dependent increases in TGIC-DNA adduct formation were reported in a non peer-reviewed study[a] (cited in 15, 20 and 29).

10. Effects in animals and in vitro studies

10.1 Irritation and sensitisation

No peer-reviewed studies concerning eye or skin irritation have been found.

However, there are three non peer-reviewed eye irritation studies from manufacturers. In these studies 0.1 g of TGIC was inserted into the conjunctival sac of rabbits followed by a 7-day observation period. In one of the studies[b] (cited in 29) TGIC was not an eye irritant, but in the other two studies [c d] (both cited in 15, 20 and 29), conducted according to Environmental Protection Agency (1978) guidelines, severe eye reactions were noted (corneal opacity, redness, chemosis, discharge).

No peer-reviewed studies on the potential of TGIC to induce contact allergy in animals have been found.

10.2. Effects of single exposure

The dose that is lethal for 50% of the animals at single administration (LD_{50}) of α-TGIC, evaluated over a 14 days observation period, was 105 mg/kg body weight at intraperitoneal administration in mice. Because of the poor solubility of ß-TGIC, the acute LD_{50} of this isomer could not be determined. All mice survived a single intraperitoneal dose of 650 mg/kg body weight (3).

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[a]Ciba-Geigy, 1990. Potential for DNA binding of Araldite PT 810 (No PS32-01903). Basel, Ciba-Geigy Ltd.

[b]Ciba-Geigy, 1979. Eye irritation in the rabbit after single application of TK 10622 (No.790338). Basel, Ciba-Geigy Ltd. Report not retrieved.

[c]Ciba-Geigy, 1979. Eye irritation in the rabbit after single application of TK10622/3 (No.790341). Basel, Ciba-Geigy Ltd. Report not retrieved.

[d]Ciba-Geigy 1982. Acute eye irritation study in the rabbit with TK10622 (No.820696). Basel, Ciba-Geigy Ltd. Report not retrieved.

10.3. Effects of short-term exposure

The daily dose of α-TGIC causing 50% mortality at intraperitoneal administration, evaluated over a 14 days observation period, was found to be approximately 58 mg/kg body weight when a 9 consecutive days treatment was used in mice. A 50% mortality was obtained with 5 intraperitoneal doses of 350 mg/kg body weight, when the ß-isomer was used (3).

In a non peer-reviewed 13-week toxicity/fertility study[a] (cited in 20 and 30), conducted in compliance with Good Laboratory Practice (GLP) regulations, groups of 10 male rats were given diets containing 0, 10, 30 or 100 ppm TGIC. The dose levels corresponded on average to 0, 0.7, 2.1 or 7.3 mg/kg body weight/day. No exposure-related clinical effects or deaths were observed. However, slightly lower body weight gain was seen at 100 ppm and in 4 animals from this group haemosiderosis and/or congestion in the mesenteric lymph nodes was noted.

10.4. Mutagenicity and genotoxicity

A few peer-reviewed published studies on the *in vitro* mutagenic/genotoxic effects have been found and are described below.

TGIC has been shown to be mutagenic in two strains of *Salmonella typhimurium* (TA98 and TA100) in the Ames test (40) both in the presence and absence of a metabolic activation system (S9). A slight decrease in mutagenic activity was seen in the presence of S9-fractions in both *Salmonella* strains. The purity of the TGIC tested was >79%.

TGIC (purity >79%) was tested for its ability to induce sister chromatid exchanges and chromosomal aberrations in cultured Chinese hamster ovary (CHO) cells using a standard protocol, as part of a National Toxicology Program project to evaluate the relationship between genotoxicity and carcinogenicity (22). TGIC was clearly positive in both test systems. The lowest concentration of TGIC that induced a significant frequency of sister chromatid exchange was 0.066 µg/ml (concentration range tested: 0.066-0.66 µg/ml) in the absence of S9-mix and 1.98 µg/ml (concentration range tested: 1.98-19.8 µg/ml) in the presence of S9-mix. Details of the chromosomal aberration test are described below (35).

TGIC was tested for the induction of chromosomal aberrations in two cultured mammalian cell systems, Chinese hamster lung (CHL) cells and CHO cells, in a study conducted to compare the two test systems (35). TGIC was clearly positive in both cell systems without metabolic activation. In CHL cells, TGIC was tested at 1.2, 2.5 and 5.0 µg/ml for 24 and 48 hours. Chromosomal aberrations (mainly chromatid gaps, chromatid breaks, and chromatid exchanges) were seen at all dose levels except at the two highest doses at 48 hours which were toxic to the cells. In

[a]CIT, 1995. 13-week toxicity study and fertility study by oral route (dietary admixture) in male rats with PT 810 (TGIC) Miserey, Centre Internationale de Toxicologie.

CHO cells chromosomal aberrations (simple and complex aberrations) were seen when the cells were treated with 3.0, 10.0 and 30.0 µg/ml of TGIC for 8 hours. The highest dose tested, 50.0 µg/ml, was toxic to the cells. However, the presence of S9 gave negative results in the CHL cell system when TGIC was tested at the same concentrations as used in the absence of S9 but with a slightly different time schedule. A positive result was obtained in the CHO cell system in the presence of S9 although the effect was slightly reduced at the doses tested (10.0, 30.0 and 100.0 µg/ml). These inconsistent results in the presence of an added metabolic activation system may, according to the authors, be due to the fact that higher doses of TGIC were used in CHO cells than in CHL cells. It could also be the result of differences in treatment protocols (35).

The study of Sofuni et al. (35) has later been repeated in a multilaboratory comparison study where *in vitro* tests for chromosomal aberrations in CHO and CHL cells were tested with the same protocol (13). TGIC gave strong positive results in both cell types with and without metabolic activation in all participating laboratories. The dose levels that gave positive results were higher with S9 than without, suggesting that S9 interferes with the activity of TGIC. The earlier reported negative results in CHL cells in the presence of S9 reported by Sofuni et al. (35) were concluded by the authors to be due to testing with too low concentrations of TGIC (13).

Several non peer-reviewed studies on the *in vivo* mutagenic/genotoxic effects of TGIC (cited in 15, 20, 29) are summarised in Table 2.

10.5. Effects of long-term exposure and carcinogenicity

No peer-reviewed studies were found concerning the carcinogenicity of TGIC.

However, the carcinogenic potential of TGIC was examined in a non peer-reviewed study[a] (cited in 30) performed in compliance with GLP. In this study TGIC was administered by dietary admixture to groups of 50 male rats at concentrations of approximately 0, 10, 30 and 100 ppm (corresponding to 0, 0.4, 1.3 and 4.4 mg/kg body weight/day) for up to 99 weeks or 300 ppm (13.6 mg/kg body weight/day) for 63 weeks. The animals in the 300 ppm group were killed at week 63 due to the high level of mortality (the cause of death was possibly a histamine-related hypotension). TGIC did not show a carcinogenic potential at any dose level. At 300 ppm lower food consumption and a marked decrease in body weight gain was recorded as well as poor clinical condition.

Histopathological investigations (300 ppm) revealed a significantly higher incidence of mastocytosis, haemosiderosis and sinusal haemorrhage in the mesenteric lymph nodes and lymphoid depletion in the spleen and a high incidence of dilatation of some intestinal segments. In addition, a higher incidence of hyposecretion and small tubulo-alveolar units in the prostate was found.

[a]CIT, 1999. Carcinogenicity study in male rats with TGIC (1,3,5-triglycidyl isocyanurate). Miserey, Centre Internationale de Toxicologie.

Hematological changes (week 52: a higher neutrophil count and monocyte count, lower lymphocyte count; week 63: lower total leukocyte count) were also noted. These findings were attributed to treatment. No indication of treatment-related non-neoplastic changes was seen in the 10, 30 and 100 ppm groups and the no observed adverse effect level (NOAEL) in the study was considered to be 100 ppm.

In a satellite study[a] (cited in 30) the subchronic toxicity of TGIC was evaluated over a 26-week treatment period. Groups of 10 male rats were given 0, 100 or 300 ppm (0, 5.8 or 16.7 mg/kg body weight/day) TGIC in the diet. No mortality or clinical signs considered as substance-related occurred during the treatment period, and no adverse effects were observed at 100 ppm. At 300 ppm, the principal signs of toxicity were markedly lower body weight gain and food consumption. Other effects reported at this dose level were lymphoid depletion of spleen and thymus and hyposecretion of prostate and seminal vesicles, all correlating with lower organ weights ($p>0.05$). Furthermore, a higher weight of the mesenteric lymph nodes, associated with haemosiderosis, plasmocytosis, mastocytosis and sinusal haemorrhages, was seen. A slightly lower mean total leukocyte count was also found at 300 ppm.

10.6. Reproductive and developmental studies

No information concerning reproductive and developmental effects of TGIC was found in the peer-reviewed literature.

A non peer-reviewed toxicity/fertility study[b] (cited in 20 and 30) conducted in compliance with GLP is available, but it should be noted that the highest concentration used in this study was not the maximum tolerated dose. Groups of 10 male rats were given diets containing 0, 10, 30 or 100 ppm TGIC, corresponding to 0, 0.7, 2.1 or 7.3 mg/kg body weight/day (mean) for 13 weeks. After 64 days of treatment each male was placed with two untreated females for mating. Decreases in the mean number of spermatozoa in treated groups (5%, 13% and 23% compared to the control group) were reported, but without any statistical analysis. According to the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) (30) the decreases were not significant when analysed by analysis of variance (ANOVA), but no details on the statistical procedures were given. Reanalysis of the raw data, performed by the Nordic Expert Group during the elaboration of the present criteria document, confirmed that there was no statistically significant difference between the dose groups (ANOVA, SPSS software, v.10.0). However, the test for linear trend showed a significant ($p=0.015$), dose-related decrease in sperm count. The mean spermatozoa viability

[a]CIT, 1999. Carcinogenicity study in male rats with TGIC (1,3,5-triglycidyl isocyanurate). Miserey, Centre Internationale de Toxicologie.

[b]CIT, 1995. 13-week toxicity study and fertility study by oral route (dietary admixture) in male rats with PT 810 (TGIC) Miserey, Centre Internationale de Toxicologie.

Table 2. *In vivo* genotoxic effects caused by TGIC; + = positive result, - = negative result

Species (test system)	End-point	Route of exposure	Dose	Results	Reference (see footnote)
Chinese hamster bone marrow	Nuclear anomalies	Oral	0, 140, 280, 560 mg/kg bw	+	a
Chinese hamster bone marrow	Sister chromatid exchange	Oral	0, 35, 70, 140 mg/kg bw	-	b
		Oral	0, 140, 280, 560 mg/kg bw	+	c
Mouse spermatogonial cells	Chromosomal aberrations	Oral	0, 43, 128 mg/kg bw	+	d
		Oral	0, 30, 125, 350 mg/kg bw	+	e
		Oral	0, 29, 58, 115 mg/kg bw	+	f
		Oral	115 mg/kg bw	+	g
		Inhalation	0, 7.8 mg/m^3	-	g
		Inhalation	0, 2.5, 10, 50 mg/m^3	Equivocal	h
Mouse spermatocytes	Chromosomal aberrations	Oral	0, 32, 96 mg/kg bw	-	i
Mous spot test	Gene mutation	Intraperitoneal	13.5, 27, 54 mg/kg bw	-	j
Mouse	Dominant lethal mutations	Oral	0, 160, 480 mg/kg bw	Equivocal*	k
		Oral	0, 138, 275, 550 mg/kg bw	-*	l
		Inhalation	0, 2.5, 10, 50 mg/m^3	-	m
Mouse stomach, liver, and testis	DNA binding	Oral	5, 17, 200 mg/kg bw	+	n
Rat liver	DNA binding	Oral, intraperitoneal	20 mg/kg bw	+	o

*Mating period included only first 3 weeks post-treatment.

[a]Ciba-Geigy, 1983. Nucleus anomaly test in somatic interphase nuclei of Chinese hamster with TK 10622 (No. 820931). Basel, Ciba-Geigy Ltd (cited in 15, 20, 29).

[b]Ciba-Geigy, 1984. Sister chromatid exchange studies on somatic cells of Chinese hamster (No. 830989). Basel, Ciba-Geigy Ltd. Report not retrieved (cited in 15, 20, 29).

[c]Ciba-Geigy, 1983. Sister chromatid exchange studies on somatic cells of Chinese hamsters (No. 820932). Basel, Ciba-Geigy Ltd (cited in 15, 20, 29).

[d]Ciba-Geigy, 1986. Chromosome studies on male germinal epithelium of mouse spermatogonia (No 850067). Basel, Ciba-Geigy Ltd. Report not retrieved (cited in 15, 20, 29).

[e]Hazelton, 1989. Mutagenicity test on PL88-810 in the mouse spermatogonial cell cytogenetic assay (No. 10386-0-474). Kensington, MD, Hazleton Laboratories America Inc. (cited in 15, 20, 29).

[f]Hazelton, 1991. Study to evaluate the chromosome damaging potential of TK 10622 (PT 810 [TGIC, 97%]) by its effects on the spermatogonial cells of treated mice. Heslington, York, Hazleton Microtest (cited in 15, 20, 29).

[g]Safepharm, 1992. TGIC technical and TGIC ten per cent powder: Chromosome analysis in mouse spermatogonial cells, comparative inhalation study (No. 14/75) [draft]. Derby, Safepharm Laboratories Ltd. Report partly retrieved (cited in 20, 29).

[h]Bushy Run, 1992. PL90-810: Chromosomal aberrations assay in mouse spermatogonial cells (No. 54-520). Export, PA, Bushy Run Research Center (cited in 15, 20, 29).

[i]Ciba-Geigy, 1986. Chromosome studies on male epithelium mouse spermatocytes (No. 850068) with TK 10622. Basel, Ciba-Geigy Ltd. Report not retrieved (cited in 15, 20, 29).

[j]Ciba-Geigy, 1986. Mammalian spot test, mouse, 8 weeks (No. 850070) with TK 10622. Basel, Ciba-Geigy Ltd. Report not retrieved (cited in 15, 20, 29).

[k]Ciba-Geigy. 1986. Dominant lethal test, mouse, three weeks (No. 850069). Basel, Ciba-Geigy Ltd. Report not retrieved (cited in 15, 20, 29).

[l]Hazelton, 1989. Mutagenicity test on PL88-810 in the mouse dominant lethal assay (No.10386-0-471). Kensington, MD, Hazleton Laboratories America Inc. (cited in refs. 15, 20, 29).

[m]Bushy Run, 1992. Dominant lethal assay of inhaled PL 90-810 dust in CD-1 mice (No. 54-515). Export, PA, Bushy Run Research Center (cited in 15, 20, 29).

[n]Ciba-Geigy, 1990. Potential for DNA-binding of Araldite PT 810 (No. PS32-01903). Basel, Ciba-Geigy Ltd. (cited in 15, 20, 29).

[o]Ciba-Geigy, 1993. Hazard assessment with Araldite PT 810: Inactivation by subcellular liver fractions and binding to liver DNA, Project No. 924004. Basel, Ciba-Geigy Ltd. Report not retrieved (cited in 20, 29).

in treated groups was similar to that in the control group and the decrease in the number of spermatozoa did not impact fertility outcomes or embryonic and pup development. No changes or effects were seen compared to controls in a number of parameters studied (pre- and post-implantation losses, number of live foetuses, foetal body weights, sex ratios, number of live born, viability 4 and 21 days post-partum, pup weight day 1-21, external anomalies, malformations, physical and reflex development of pups).

In a non peer-reviewed oral study[a] (cited in 20 and 29) chromosomal aberrations and cytotoxicity have been reported in mouse spermatogonial cells at 115 mg TGIC/kg body weight.

In a non peer-reviewed inhalation study[b] (cited in 15, 20 and 29) effects on mouse spermatogonial cells were measured by the induction of chromosomal aberrations. Mice were exposed to 0, 2.5, 10 or 50 mg TGIC/m^3 (purity not stated; particle size range 2.5-3.5 µm) for 6 hours per day for 5 consecutive days. The results of this study were inconclusive since the number of analysable spermatogonial metaphase cells in the two highest dose groups was too small. Furthermore, the number of chromosomal aberrations in the control was unexpectedly high. The study indicates that TGIC was cytotoxic to spermatogonial cells at the two highest dose levels but the cytotoxic ratio was not calculated.

A reduction in male fertility, i.e. number of sperm-positive and pregnant females, has been reported in a non peer-reviewed dominant lethal mutation study[c] (cited in 20 and 29). Male mice were exposed by inhalation to 0, 2.5, 10 or 50 mg TGIC/m^3 (purity not stated; particle size range 2.5-3.5 µm) for 6 hours per day for 5 consecutive days. General toxicity was observed at 50 mg/m^3 and included death (10%), reduction in body weight during exposures (persisting through the 2nd mating week), and persistent ocular discharge and swelling. After exposure the male mice were bred to naive females. Females were replaced weekly for a total of 8 weeks. A reduction in male fertility was observed in the highest dose group for the first 3 mating weeks and for mating week 6. At 10 mg/m^3 a reduction in male fertility was observed for the 3rd mating week. The authors conclude that effects observed during this period of the mating regime correspond to effects on mature sperm, maturing spermatids and Type B spermatogonia. The NOAEL for general toxicity was 10 mg/m^3 and the NOAEL for effects on fertility was 2.5 mg/m^3. There were no observable dominant lethal effects following exposure.

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[a]Safepharm, 1992. TGIC technical and TGIC ten per cent powder: Chromosome analysis in mouse spermatogonial cells, comparative inhalation study (No. 14/75) [draft]. Derby, Safepharm Laboratories Ltd. Report partly retrieved.

[b]Bushy Run, 1992. PL90-810: Chromosomal aberrations assay in mouse spermatogonial cells (No. 54-520). Export, PA, Bushy Run Research Center.

[c]Bushy Run, 1992. Dominant lethal assay of inhaled PL 90-810 dust in CD-1 mice (No. 54-515). Export, PA, Bushy Run Research Center.

11. Observations in man

11.1. Irritation and sensitisation

11.1.1. Irritant and allergic (type IV allergy) contact dermatitis

No studies on the irritant effect of TGIC in humans have been found in the peer-reviewed literature.

Seventeen cases of allergic contact dermatitis to TGIC, verified by patch testing, have so far been described in the literature; 1 in the production of TGIC, 9 from the manufacturing of powder paints containing TGIC, 5 from the use of TGIC-containing powder paints, and 2 from contact with TGIC containing hardeners for epoxy acrylate ink. A weakness in these studies is that in most cases the purity of TGIC used in patch testing is not stated. The studies are summarised in Table 3.

11.1.2. Occupational asthma

A case of occupational asthma has been described by Piirilä et al. (33). The patient was a healthy 36-year-old non-smoking man who had worked mainly as a spray painter, using a polyester powder paint containing 4% TGIC as a hardener. After 4 years of work with the powder paint an allergic contact dermatitis to TGIC was diagnosed (see Table 3). A year later he had symptoms of dyspnoea, especially during and after workdays and also suffered from wheezing dyspnoea at night and during exercise. The symptoms were relieved during weekends. Spirometry showed slight obstruction, the blood eosinophils and serum total IgE levels were elevated, and a histamine challenge test showed slight bronchial hyperreactivity. A skin-prick test to TGIC as well as a measurement of TGIC specific IgE were negative. A challenge test with paint containing 4% TGIC induced a late 23% fall and a test with 4% TGIC (stated to be “pure”) in lactose induced a late 19% fall in forced expiratory volume in 1 second (FEV_1). Both immediate and late reactions were seen in peak expiratory flow. A lactose control challenge test was negative. The patient’s respiratory disease was diagnosed as occupational asthma caused by TGIC used as a hardener in the polyester powder paint. No conclusion could be drawn about the underlying mechanism(s) for the patient’s asthma.

An additional case of occupational asthma has been reported (26). The patient, a 38-year-old man, first presented with an allergic contact dermatitis to TGIC (see Table 3). For 3 years he had been working with polyester powder pigments. Shortly after the cutaneous signs appeared he developed respiratory symptoms, i.e. rhinitis, cough, dyspnoea, and wheezing. His symptoms decreased during weekends and cleared completely on vacation. Histamine challenge tests showed bronchial hyperreactivity and the total serum IgE level was elevated. The occupational asthma was confirmed by bronchial provocation testing: two challenges to an aerosol of lactose containing 0.05 and 0.1% TGIC (approximate

Table 3. Case reports of allergic contact dermatitis caused by TGIC

Exposure situation	No. of cases (sex)	Length of exposure	Effects and patch test results	Ref.
Spray painting	1 (male)	2 months	Severe dermatitis of the ears, forehead, perioral skin and cheeks near the eyes. The outbreak of dermatitis came two weeks after a new clean-up procedure was introduced that involved entering the spray booth. Patch testing with 1% of the powder paint (containing approximately 5% TGIC) and 0.5% TGIC (technical grade) in petrolatum, produced positive reactions. 3 volunteer controls without dermatitis were negative.	(23)
TGIC production	1 (male)	Shortly after transfer to TGIC production department	Itchy, scaly, erythematous lesions in the face and the dorsa of hands. Patch testing with TGIC (purity not stated) from 2% down to 0.1% in petrolatum, gave positive reactions when read at 48 and 72 hours. 10 control subjects showed negative results when patch tested in the same manner.	(31)
Cleaning up after spray painting	1 (male)	1 month	Eczema on the face, neck, behind the ears, and forearms. Patch testing with different powder paints (as is), containing approximately 5% TGIC, gave no reactions. However, patch test with TGIC (purity not stated) 5% in petrolatum and saturated solution in alcohol (<5%) gave positive reactions. 5 control subjects were tested in a similar manner with negative results.	(9)
Spray painting	1 (male)	3 months	Recurrent attacks of acute dermatitis of the forehead and wrists. Patch testing with 1% TGIC (purity not stated) in petrolatum, was positive.	(24)
Spray painting	1 (male)	4 years	Eczema on hands, arms, face, and neck. Patch testing with the paint, 10% and 3.2% in petrolatum, as well as TGIC (purity not stated), 1%, 0.32% and 0.1% in petrolatum, gave strongly positive reactions. The patient subsequently developed an occupational asthma against TGIC (see 11.1.2).	(33)

Table 3. Cont.

Exposure situation	No. of cases (sex)	Length of exposure	Effects and patch test results	Ref.
Manufacture of powder paints	3 (male)	Not stated	Recurrent periorbital eczema and swelling. Patch testing with TGIC (purity not stated) gave positive reactions. Testing of 10 control subjects gave no reactions. The authors state that the detection of 3 cases over a short period at a single workplace, with about 80 employees potentially at risk, indicates significant allergenicity.	(27)
Manufacture of powder paints	5 (male)	Within 12 months	Eczema. All 5 patients had positive reactions to two tested hardeners, both of which were commercial preparations of TGIC. 20 tested control subjects showed no reaction.	(12)
Manufacture of powder paints	1 (male)	3 years	Persisting rhinitis and eczema of the face and forearms. A positive patch test reaction was obtained with 5% of the hardener used in the production of the powder paints, Araldite PT 810 (>99.9% TGIC) in methyl ethyl ketone. 10 unexposed control subjects were tested in a similar manner with negative results.	(38)
Manufacture of circuit boards	1 (female)	12 years	Mild dermatitis on wrists and lower arms that 3 years later developed into severe dermatitis on the face and eyelids. Patch testing with 2% hardener (containing <60% TGIC) and 0.1, 0.3, 1 and ≥3% TGIC (purity not stated) in petrolatum, gave positive reactions. The patient also showed positive patch test reactions to several acrylates, methacrylates and epoxy compounds.	(21)
Manufacture of circuit boards	1 (male)	Not stated	Dermatitis of the hands, forearms and face. Patch testing with TGIC (>99% pure) 0.1% in petrolatum gave a positive reaction whereas 25 control subjects showed no reaction. The patient also showed positive patch test reactions to several acrylates and epoxy resins.	(7)
Spray painting	1 (male)	Not stated	Dermatitis in the elbow and knee folds that later spread to the forearms, face, axilla and upper back. The patient showed positive patch test reactions to freshly prepared TGIC and a commercially available test preparation of TGIC (0.5% in petrolatum). This study stresses the importance of using freshly prepared test preparations. The patient also suffered from respiratory symptoms, i.e., cough, dyspnoea, and wheezing (see 11.1.2).	(10)

purity 90%) led to a maximal decrease in FEV_1 of 22 and 31% after 6 and 4 hours, respectively. A control test using an aerosol of lactose powder was negative.

11.2. Effects of single and short-term exposure

α-TGIC was used in human clinical trials as an anti-tumour agent in the early 1980s (15, 20, 29). In these cases the drug was infused intravenously to cancer patients and was administered with a variety of dosing schedules. Toxic signs included myelosuppression (leukopenia, thrombocytopenia), nausea and vomiting, but the main dose-limiting toxic effect was thrombophlebitis at the injection site, sometimes associated with cutaneous flare reactions over the vein (8, 28, 32, 34). However, these data were derived from patients that were seriously ill and some of the systemic effects seen may have been the result of previous chemotherapy treatment. Furthermore, the studies involved the rapid intravenous infusion of α-TGIC. Thus, these studies are of limited relevance for the occupational setting.

11.3. Effects of long-term exposure

No data have been found.

11.4. Genotoxic effects

No data have been found.

11.5. Carcinogenic effects

No data have been found.

11.6. Reproductive and developmental effects

No data have been found.

12. Dose-effect and dose-response relationships

12.1. Single/short-term exposures

Very few peer-reviewed data concerning effects of TGIC in animals after single/short-term exposures have been found (Table 4). A non peer-reviewed inhalation study reports reduced fertility in male mice at an exposure level of 10 and 50 mg/m^3, 6 hours/day for 5 consecutive days. No effect on fertility was seen at 2.5 mg/m^3. Another non peer-reviewed study indicate a dose-related decrease in the number of spermatozoa in rat at peroral administration of TGIC for 13 weeks, in dose levels ≥ 0.7 mg/kg body weight/day. Lower dose levels were not tested (Table 4).

12.2. Long-term exposures

There are no long-term exposure data available for TGIC in the peer-reviewed literature.

In a non peer-reviewed study a marked decrease in body weight gain and remarkably high incidences of non-neoplastic histopathological changes were recorded in male rats receiving doses of 300 ppm TGIC (approximately 13.6 mg/kg body weight/day) in the diet for 63 weeks. The principal findings were increased mortality, mastocytosis in the lymph nodes and depletion of the spleen lymphoid cells. Some hematological changes were also observed at this dose level. No adverse effects were seen at lower dose levels, when TGIC was given in the diet for up to 99 weeks. The NOAEL in the study was considered to be 100 ppm (approximately 4.4 mg/kg body weight/day) (Table 4).

13. Previous evaluations by national and international bodies

The UK HSE published a toxicity review on TGIC in 1992 (15). Most of the information was derived from non peer-reviewed studies. The major conclusions were: A number of reports indicate that TGIC is capable of causing skin sensitisation in occupationally exposed workers. One study in guinea pigs indicates that the compound has skin sensitisation potential. TGIC appears to be of moderate acute toxicity to rats. Kidney damage has been found after repeated exposure. TGIC has been shown to cause severe eye irritation in rabbits. It is mutagenic *in vitro* and has shown genotoxic effects in rodents *in vivo*. Clastogenic effects in bone-marrow cells and cytotoxicity and chromosomal aberrations in male germ cells have been observed. A decrease in male fertility has been shown in one study in mice. In a Summary Criteria for Occupational Exposure Limits (16) based on the HSE review (15) the basis for setting a limit was stated: TGIC is a direct-acting genotoxic substance capable of expressing this activity *in vivo*. Given the chemically reactive nature of TGIC, there are concerns for mutagenic effects at site of contact tissues. The same report suggests that the mutagenic effects of TGIC are non-threshold phenomena, and consequently it is not possible to set a health-based occupational exposure limit for such substances (16).

An assessment of TGIC made under the Australian NICNAS, mainly based on non peer-reviewed studies, was published in 1994 (29). From the assessment of the hazards of TGIC it was concluded that the chemical is a hazardous substance, is toxic by oral and inhalational routes, a skin sensitiser, genotoxic and capable of causing serious eye damage. From the assessment of the known hazards of TGIC, overseas experience and air monitoring data, it was stated 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. As a result of new data becoming available, a second assessment of

Table 4. Effects of TGIC in animals

Exposure level	Exposure regimen	Route	Species (sex) m=male	Effect	Reference (non-peer reviewed studies given as footnotes)
2.5 mg/m^3	6 hours/day, 5 days	inhalation	mouse (m)	no observed effects	a
10 mg/m^3	6 hours/day, 5 days	inhalation	mouse (m)	reduced male fertility	a
50 mg/m^3	6 hours/day, 5 days	inhalation	mouse (m)	general toxicity including death; reduced male fertility	a
0.7 mg/kg bw/day	daily, 13 weeks	oral	rat (m)	non-significant 5% decrease in sperm count, compared to control*	b
2.1 mg/kg bw/day	daily, 13 weeks	oral	rat (m)	non-significant 13% decrease in sperm count, compared to control*	b
7.3 mg/kg bw/day	daily, 13 weeks	oral	rat (m)	slightly lower body weight gain mesenteric lymph nodes: congestion, haemosiderosis non-significant 23% decrease in sperm count, compared to control*	b
4.4 mg/kg bw/day	daily, 99 weeks	oral	rat (m)	NOAEL	c
5.8 mg/kg bw/day	daily, 26 weeks	oral	rat (m)	NOAEL	c
13.6 mg/kg bw/day	daily, 63 weeks	oral	rat (m)	death, decrease in body weight gain mesenteric lymph nodes: mastocytosis, haemosiderosis, sinusal haemorrhage spleen: lymphoid depletion prostate: hyposecretion, small tubulo-alveolar units intestinal segments: dilatation hematological changes	c

Table 4. Cont.

Exposure level	Exposure regimen	Route	Species (sex) m=male	Effect	Reference (non-peer reviewed studies given as footnotes)
16.7 mg/kg bw/day	daily, 26 weeks	oral	rat (m)	lower body weight gain mesenteric lymph nodes: increased weight, mastocytosis, plasmocytosis, haemosiderosis, sinusal haemorrhage spleen and thymus: lymphoid depletion prostate and seminal vesicles: hyposecretion lower total leucocyte count	c
58 mg/kg bw/day**	daily, 9 days	intraperitoneal	mouse	50% mortality	(3)
105 mg/kg bw**	single dose	intraperitoneal	mouse	LD_{50}	(3)
350 mg/kg bw/day***	daily, 5 days	intraperitoneal	mouse	50% mortality	(3)

*Analysis of variance, test for linear trend, showed a significant, dose-related decrease (p=0.015)
**α-TGIC
***ß-TGIC
[a]Bushy Run, 1992. Dominant lethal assay of inhaled PL 90-810 dust in CD-1 mice (No. 54-515). Export, PA, Bushy Run Research Center (cited in 20 and 29).
[b]CIT, 1995. 13-week toxicity study and fertility study by oral route (dietary admixture) in male rats with PT 810 (TGIC). Miserey, Centre Internationale de Toxicologie (cited in 20 and 30).
[c]CIT, 1999. Carcinogenicity study in male rats with TGIC (1,3,5-triglycidyl isocyanurate). Miserey, Centre Internationale de Toxicologie (cited in 30).

TGIC was published by NICNAS in 2001 (30). This assessment has evaluated new animal studies including oral toxicity/fertility, carcinogenicity and contact hypersensitivity studies, in addition to human case reports of respiratory sensitisation. It was stated that new human data confirmed that TGIC is a skin sensitiser and also demonstrated that it is a respiratory sensitiser. Furthermore, it was concluded that animal studies indicate that TGIC causes severe effects after repeated exposure. The principal effects were lower body weight, mastocytosis in lymph nodes and depletion of spleen lymphoid cells. TGIC was also regarded not carcinogenic in male rats. Further, NICNAS stated that a recent fertility study in rats provides some evidence that TGIC does not affect male fertility. However, it was also stated that several data gaps remain.

A Concise International Chemical Assessment Document (CICAD) on health effects of TGIC was published by the International Programme on Chemical Safety, World Health Organization in 1998 (20). The most important conclusions from the evaluation of health effects (mainly based on the NICNAS document (29) and non peer-reviewed studies) were as follows: The only reported health effects in humans are contact dermatitis and one case of respiratory sensitisation. TGIC produces serious eye irritation and is a skin sensitiser in animals. Animal studies have revealed renal, lung, gastric/duodenal and sperm cell damage. The chemical has produced positive results in *in vitro* genotoxicity studies. Genotoxic effects have also been observed *in vivo* in somatic cells and germ cells in the testes. The demonstrated ability for TGIC to cause genetic damage raises concern over potential carcinogenic and reproductive effects. Owing to its genotoxic and sensitisation effects, workplace exposures should be maintained at the lowest practicable level. According to the CICAD (20) TGIC is a direct-acting mutagen, and it is not possible to identify a level of exposure below which there would be no risk to human health.

The American Conference of Governmental Industrial Hygienists (ACGIH) published a documentation of TGIC in 2001 (1). The major conclusions were: Hematopoietic effects were observed in humans, mice and dogs as a result of repeated intravenous infusions with α-TGIC. Dose levels below 2.3 mg/kg body weight did not result in hematopoietic effects to human subjects. Repeated inhalation exposures in mouse spermatogonial chromosome aberration studies resulted in cytotoxicity to spermatogonial cells and increased incidence of chromosomal aberrations. Spermatogonial cell cytotoxicity was the most sensitive index of toxicity with NOAELs of 7.8 mg/m^3 (nose-only) and 2.5 mg/m^3 (whole-body). Fertility effects in mice were observed in an inhalation-exposure dominant lethal assay; marginal effects were noted at 10 mg/m^3 with a NOAEL of 2.5 mg/m^3.

14. Evaluation of human health risks

14.1. Assessment of health risks

Very little information has been found in the peer-reviewed literature on the toxic effects of TGIC. Several cases of allergic contact dermatitis have been reported subsequent to occupational exposure. However, no relevant peer-reviewed experimental studies that explore the potency of TGIC to induce allergic contact dermatitis have been found. This renders assessment of the sensitising potential of TGIC problematic. Two cases of occupational asthma have been described but the significance of these findings remains to be clarified.

TGIC has been shown to produce mutations *in vitro* in bacterial test systems and chromosomal aberrations in CHO and CHL cells. In addition, there are non peer-reviewed *in vivo* studies in male mice that demonstrate induction of chromosomal aberrations in germ cells. Thus, even though TGIC has not been shown to be carcinogenic in experimental animals or in humans, genotoxic effects of TGIC may have relevance for reproductive and developmental toxicity. In line with these observations is the finding that TGIC causes a dose-dependent reduction in the number of spermatozoa in rats and reduced male fertility in mice.

The toxic effects of TGIC of concern are its sensitising properties, genotoxicity and effects on reproduction. In addition TGIC may cause serious eye damage.

14.2. Groups at extra risk

Based on the data evaluated, no identification of groups or individuals at extra risk in the human population can be made.

14.3. Scientific basis for an occupational exposure limit

TGIC has a genotoxic potential both *in vitro* and *in vivo,* it reduces the number of spermatozoa in rats, reduces male fertility in mice and causes allergic contact dermatitis. These effects are relevant to reproduction toxicity and development through a genotoxic mechanism, and sensitisation. At the present state of knowledge it is not possible to identify a dose or exposure level at which these adverse effects do not occur.

15. Research needs

In view of the potential hazards of TGIC there is a remarkable lack of peer-reviewed data with respect to mutagenicity, genotoxicity and carcinogenicity. Further studies are also needed to clarify the reproductive toxicity of TGIC. Data on absorption of TGIC following inhalation and dermal exposure would be of interest. The sensitising potential of TGIC should be experimentally determined in relevant animal tests and in epidemiological studies in man.

16. Summary

Lindell B, Montelius J. *Triglycidyl isocyanurate.* Arbete och Hälsa 2001;18:1-30.

Triglycidyl isocyanurate (TGIC) is a solid, slightly soluble in water. It has a very low vapour pressure, and will therefore occur as dust at the workplace. TGIC is an epoxy compound containing three epoxy groups. Technical TGIC is a mixture of the α- and ß-isomer. TGIC is often used as a hardener. The main use is in the manufacture of polyester powder coatings for metal finishing. The powder coatings usually contain between 4 and 10% TGIC. There is little information found with respect to the toxicokinetics of TGIC. However, some data on α-TGIC indicate that TGIC is rapidly and extensively metabolised.

TGIC may cause allergic contact dermatitis in humans. Several cases have been reported subsequent to occupational exposure. However, the contact sensitising potential of TGIC remains to be established. TGIC has been shown to be mutagenic/genotoxic *in vitro.* Furthermore, there are data that demonstrate a genotoxic potential of TGIC *in vivo*. A reduction in male fertility and a dose-related decrease in the number of spermatozoa has also been reported in animals. Experimental animal studies indicate that TGIC instilled into the eyes may cause severe eye damage.

The major concerns for human health are contact allergy, mutagenicity/genotoxicity and reproductive toxicity. At the present state of knowledge it is not possible to identify a dose or exposure level at which these adverse effects do not occur.

Keywords: allergic contact dermatitis, eye damage, genotoxicity, occupational exposure limits, mutagenicity, powder coating, reproductive toxicity, risk assessment, TGIC, toxicity, triglycidyl isocyanurate.

17. Summary in Swedish

Lindell B, Montelius J. *Triglycidyl isocyanurate.* Arbete och Hälsa 2001;18:1-30.

Triglycidylisocyanurat (TGIC) är ett fast ämne, något lösligt i vatten. Det har mycket lågt ångtryck och förekommer därför som damm i arbetsmiljön. TGIC är en epoxiförening och innehåller tre epoxigrupper. Tekniskt TGIC är en blandning av α- och ß-isomeren. TGIC används ofta som härdare, framför allt vid tillverkning av pulverlacker av polyestertyp avsedda för ytbehandling av metall. Pulverlackerna innehåller vanligen mellan 4 och 10% TGIC. Informationen om upptag och omsättning av TGIC är sparsam, men data gällande α-TGIC antyder att metabolismen av TGIC är snabb och omfattande.

TGIC kan förorsaka allergiskt kontakteksem hos människa. Åtskilliga fall har rapporterats i samband med yrkesmässig exponering, men ämnets kontaktsensibiliserande potential återstår att fastställa. TGIC har visats vara mutagent/genotoxiskt *in vitro*. Andra data visar att TGIC är genotoxiskt *in vivo.* Minskad fertilitet och en dos-relaterad minskning av antalet spermier har också rapporterats hos handjur. Djurexperimentella studier indikerar att TGIC kan förorsaka svåra ögonskador vid instillation i ögat.

De toxiska effekter som framför allt inger oro vid yrkesmässig exponering för TGIC är kontaktallergi, mutagenicitet/genotoxicitet och reproduktionstoxicitet. Med dagens kunskap är det inte möjligt att identifiera en dos eller exponeringsnivå vid vilken dessa effekter inte uppträder.

Nyckelord: allergiskt kontakteksem, genotoxicitet, gränsvärden, mutagenicitet, pulverlacker, reproduktionstoxicitet, riskbedömning, TGIC, toxicitet, triglycidylisocyanurat, ögonskada.

18. References

1. ACGIH. 1,3,5-Triglycidyl-s-triazinetrione. *Documentation of the threshold limit values for chemical substances*. 7th ed. Cincinnati: American Conference of Governmental Industrial Hygienists, 2001, 8 pp.
2. Ames MM, Kovach JS, Rubin J. Pharmacological characterization of teroxirone, a triepoxide antitumor agent, in rats, rabbits, and humans. *Cancer Res* 1984;44:4151-4156.
3. Atassi G, Spreafico F, Dumont P, Nayer P, Klastersky J. Antitumoral effect in mice of a new triepoxyde derivative: 1,3,5-triglycidyl-s-triazinetrione (NSC 296934). *Eur J Cancer 1980*;16:1561-1567.
4. Atassi G, Dumont P, Fischer U, Zeidler M, Budnowski M. Preclinical evaluation of the anti tumour activity of new epoxyde derivatives. *Cancer Treat Rev* 1984;11:99-110.
5. Audisio G, Severini F, Maccioni AM, Traldi P. Electron impact mass spectrometry and pyrolysis gas chromatography/mass spectrometry of triglycidyl isocyanurate. *Biomed Environ Mass Spectrom* 1986;13:519-521.
6. Budnowski M. Preparation and properties of the diastereoisomeric 1,3,5-triglycidyl-s-triazinetriones. *Angew Chem Internat Edit* 1968;7:827-828.
7. Craven N, Bhushan M, Beck M. Sensitization to triglycidyl isocyanurate, epoxy resin and acrylates in a developmental chemist. *Contact Dermatitis* 1999;40:54-55.
8. Dombernowsky P, Lund B, Hansen HH. Phase-1 study of α–1,3,5–triglycidyl-s-triazinetrione (NSC 296934). *Cancer Chemother Pharmacol* 1983;11:59–61.
9. Dooms-Goossens A, Bedert R, Vandaele M, Degreef H. Airborne contact dermatitis due to triglycidyl isocyanurate. *Contact Dermatitis* 1989;21:202-203.
10. Erikstam U, Bruze M, Goossens A. Degradation of triglycidyl isocyanurate as a cause of false-negative patch test reaction. *Contact Dermatitis* 2001;44:13-17.
11. Fischer H, Zeidler U, Budnowski M, Atassi G, Dumont P, Venditti J, Yoder OC. Investigation of the antitumor activity of new epoxide derivatives. *Arzneim-Forsch/Drug Res* 1984;34:543-547.
12. Foulds IS, Koh D. Allergic contact dermatitis from resin hardeners during the manufacture of thermosetting coating paints. *Contact Dermatitis* 1992;26:87-90.
13. Galloway SM, Sofuni T, Shelby MD, Thilagar A, Kumaroo V, Kaur P, Gulati D, Putman DL, Murli H, Marshall R, Tanaka N, Anderson B, Zeiger E, Ishidate Jr M. Multilaboratory comparison of in vitro tests for chromosome aberrations in CHO and CHL cells tested under the same protocols. *Environ Mol Mutagen* 1997;29:189-207.
14. Hempel A, Camerman N, Camerman A. Crystallographic resolution and crystal and molecular structures of stereoisomers of 1,3,5-triglycidyl-s-triazinetrione. *J Med Chem* 1989;32:648-651.
15. HSE. *Toxicity review 27-part 1:Triglycidyl isocyanurate.* Health and Safety Executive, HSE Books, Sheffield, United Kingdom, 1992.
16. HSE. Triglycidyl isocyanurate (TGIC). *EH64 summary criteria for occupational exposure limits.* Health and Safety Executive, Sudbury, Suffolk, United Kingdom, 1997.
17. HSE. General methods for sampling and gravimetric analysis of respirable and total inhalable dust. *Methods for the Determination of Hazardous Substances, MDHS 14/2.* HSE Books, Sudbury, Suffolk, United Kingdom, 1997:1-8.
18. HSE. Triglycidyl isocyanurate (and coating powders containing triglycidyl isocyanurate) in air. *Methods for the Determination of Hazardous Substances, MDHS 85.* Health and Safety Executive. HSE Books, Sudbury, Suffolk, United Kingdom, 1997:1-7.

19. HSE. *Controlling exposure to coating powders.* Health and Safety Executive, Sudbury, Suffolk, United Kingdom, 2000.
20. IPCS. *Concise international chemical assessment document No. 8. Triglycidyl isocyanurate*. International Programme on Chemical Safety, World Health Organisation, Geneva, 1998, 21 pp.
21. Jolanki R, Kanerva L, Estlander T, Tarvainen K. Concomitant sensitization to triglycidyl isocyanurate, diaminodiphenylmethane and 2-hydroxyethyl methacrylate from silk-screen printing coatings in the manufacture of circuit boards. *Contact Dermatitis* 1994;30:12-15.
22. Loveday KS, Anderson BE, Resnick MA, Zeiger E. Chromosome aberration and sister chromatid exchange test in Chinese hamster ovary cells *in vitro.* V: Results with 46 chemicals. *Environ Mol Mutagen* 1990;16:272-303.
23. Mathias CGT. Allergic contact dermatitis from triglycidyl isocyanurate in polyester paint pigments. *Contact Dermatitis* 1988;19:67-68.
24. McFadden JP, Rycroft RJ. Occupational contact dermatitis from triglycidyl isocyanurate in a powder paint sprayer. *Contact Dermatitis* 1993;28:251.
25. Mertes I, Fleischmann R, Glatt HR, Oesch F. Interindividual variations in the activities of cytosolic and microsomal epoxide hydrolase in human liver. *Carcinogenesis* 1985;6:219-223.
26. Meuleman L, Goossens A, Linders C, Rochette F, Nemery B. Sensitization to triglycidylisocyanurate (TGIC) with cutaneous and respiratory manifestations. *Allergy* 1999; 54;752-756.
27. Munro CS, Lawrence CM. Occupational contact dermatitis from triglycidyl isocyanurate in a powder paint factory. *Contact Dematitis* 1992;26:59.
28. Neidhart JA, Derocher D, Grever MR, Kraut EH, Malspeis L. Phase 1 trial of teroxirone. *Cancer Treat Rep* 1984;68:1115-1119.
29. NICNAS. *Priority existing chemical no 1 – triglycidyl isocyanurate (TGIC), full public report.* National Industrial Chemicals Notification and Assessment Scheme. Australian Government Publishing Service, Canberra, 1994.
30. NICNAS. *Priority existing chemical, secondary notification assessment report no 1S.* National Industrial Chemicals Notification and Assessment Scheme. Governmental Publication Office, Sydney, 2001.
31. Nishioka K, Ogasawara M, Asagami C. Occupational contact allergy to triglycidyl isocyanurate (TGIC, Tepic®). *Contact Dermatitis* 1988;19:379-380.
32. Piccart M, Rozencweig M, Dodion P, Cumps E, Crespeigne N, Makaroff O, Atassi G, Kisner D, Kenis Y. Phase 1 clinical trial with alpha 1,3,5-triglycidyl-s-triazinetrione (NSC-296934). *Eur J Cancer Clin Oncol* 1981;17:1263-1266.
33. Piirilä P, Estlander T, Keskinen H, Jolanki R, Laakkonen A, Pfäffli P, Tupasela O, Tuppurainen M, Nordman H. Occupational asthma caused by triglycidyl isocyanurate (TGIC). *Clin Exp Allergy* 1997;27:510-514.
34. Rubin J, Kovach JS, Ames MM, Moertel CG, Creagan ET, O´Connell MJ. Phase 1 study of two schedules of teroxirone. *Cancer Treat Rep* 1987;71:489-492.
35. Sofuni T, Matsuoka A, Sawada M, Ishidate Jr M, Zeiger E, Shelby MD. A comparison of chromosome aberration induction by 25 compounds tested by two Chinese hamster cell (CHL and CHO) systemes in culture. *Mutat Res* 1990;241:175-213.
36. Spreafico F, Atassi G, Filippeschi S, Malfiore C, Noseda S, Boschetti D. A characterization of the activity of α -1,3,5-triglycidyl-s-triazinetrione, a novel antineoplastic compound. *Cancer Chemother Pharmacol* 1980;5:103-108.
37. Stear M, Cooke M. Controlling worker exposure to coating powders. *Pigment Resin Technol* 1999;28:223-229.
38. Wigger-Alberti W, Hofmann M, Elsner P. Contact dermatitis caused by triglycidyl isocyanurate. *Am J Contact Dermat* 1997;8:106-107.

39. Wu FY, Pecq JB. Mechanistic studies of a novel antitumor drug, α-1,3,5-triglycidyl-s-triazinetrione. *Mol Pharmacol* 1982;23:182-189.
40. Zeiger E, Anderson B, Haworth S, Lawlor T, Mortelmans K. Salmonella mutagenicity tests: Results from the testing of 311 chemicals. *Environ Mol Mutagen* 1992;19:2-141.

19. Data bases used in the search for literature

The following data bases were used in the search for literature:
- Arbline
- Chemical Abstracts
- CISDOC
- HSELINE
- Medline
- MHIDAS
- NIOSHTIC
- RILOSH
- Toxline

Last search was performed 2001-11-22.

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Appendix 1

Occupational exposure limits for triglycidyl isocyanurate in air.

Country	mg/m^3	Comments	Year	Ref
Denmark	-	-	2000	1
Finland	-	-	1998	2
Germany		-	2000	3
Iceland	-	-	1999	4
Netherlands	0.1	-	2001	5
Norway	-	-	2001	6
Sweden	-	-	2000	7
United Kingdom	0.1	-	1998	8
USA (ACGIH)	0.05	-	2001	9
(NIOSH)	-	-	2000	10
(OSHA)	-	-	2000	10

References

1. *Grænsverdier for stoffer og materialer.* København: Arbejdstilsynet, 2000 (At-anvisning Nr. C.0.1).
2. HTP-arvot 1998. Tampere: Työministeriö, 1998 (Turvallisuustiedote 25).
3. *MAK- und BAT-Werte-Liste 2000.* Weinheim: Wiley-VCH, 2000. ISBN 3-527-27594-0.
4. Mengunarmörk og aðgerðir til að draga úr mengun á vinnustöðum. Vinnueftirlit ríksins, 1999.
5. *Nationale MAC-lijst 2001*. Den Haag: Sdu Uitgevers 1999. ISBN 90-12-08899-2.
6. *Administrative normer for forurensning i arbeidsatmosfære.* Veiledning til arbeidsmiljøloven. Oslo: Direktoratet for Arbeidstilsynet, 2001 (Bestillingsnr. 361).
7. *Hygieniska gränsvärden och åtgärder mot luftföroreningar.* Stockholm: Arbetarskyddsstyrelsen, 2000 (AFS 2000:3) ISBN 91-7930-357-9.
8. *Occupational exposure limits 2000.* EH40/00. Health and Safety Executive, United Kingdom, 2000, ISBN 0-7176-1730-0.
9. *2001 TLVs and BEIs.* Cincinnati, Ohio: American Conference of Governmental Industrial Hygienists, 2001. ISBN 1-882417-40-2.
10. *NIOSH Pocket Guide to Chemical Hazards.* Washington: U.S. Department of Health and Human Services, 2000.