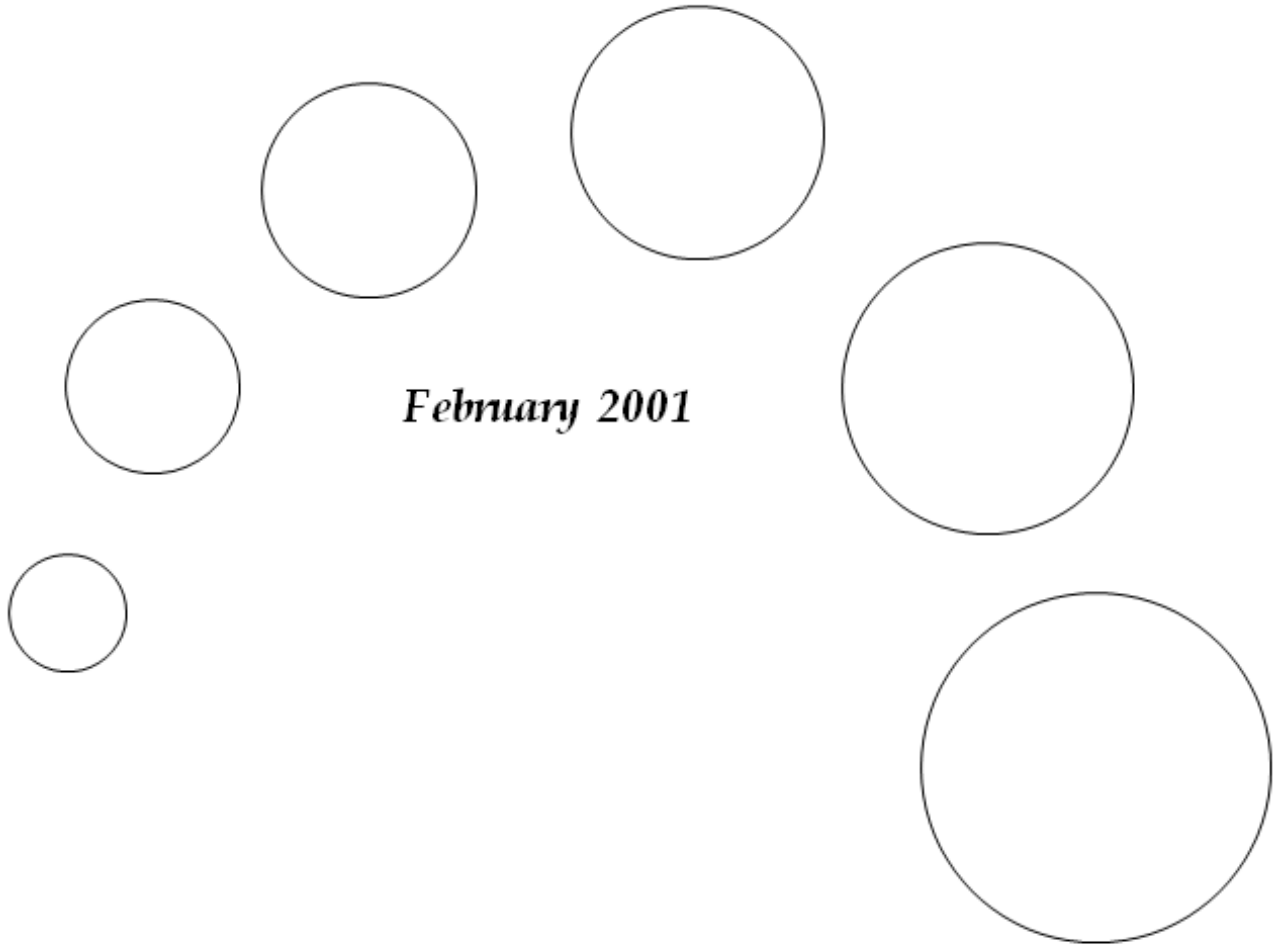
National Industrial
Chemicals Notification and
Assessment Scheme

Triglycidylisocyanurate (TGIC)

Priority Existing Chemical Secondary Notification Assessment Report No. 1S



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Preface

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

The principal aim of NICNAS is to aid in the protection of people at work, the public and the environment from the harmful effects of industrial chemicals, by assessing the risks associated with the manufacture and use of such chemicals.

NICNAS is administered by the National Occupational Health & Safety Commission (NOHSC) and assessments are carried out in conjunction with Environment Australia (EA) and the Therapeutic Goods Administration (TGA), who carry out the environmental and public health assessments, respectively. NICNAS has two major programs: one focusing on risks associated with *new* chemicals, prior to importation or manufacture and the other focusing on *existing* chemicals already in use in Australia.

As there are many thousands of existing industrial chemicals in use in Australia, NICNAS has an established mechanism for prioritising and assessing these chemicals. Such chemicals are referred to as Priority Existing Chemicals.

The scope of priority existing chemical assessments permits recommendations to be made which will assist in the management of the workplace, public health and environmental risks. Recommendations may be directed to industry (employers and employees) and/or other Federal and State/Territory regulatory authorities. NICNAS cannot make regulatory decisions, which fall within the responsibility of other regulatory authorities, and therefore recommendations can only be given effect through consideration of risk management practices and processes by those agencies/authorities charged with regulatory decision-making.

Where further information becomes available after publication of a Priority Existing Chemical report and/or where certain prescribed circumstances occur, as stipulated under Section 64(2) of the Act, the Director (Chemicals Notification and Assessment) may require a reassessment of the hazards of the chemical under 'secondary notification provisions' (Division 6) of the Act. This Full Public Report has been prepared in accordance with these provisions.

Under Section 40 of the Act, a public comment process is also undertaken for secondary notification assessment reports.

For the purposes of Section 78(1) of the Act, copies of Full Public Reports for New and Existing Chemical assessments may be inspected by the public at the library of the National Occupational Health and Safety Commission (NOHSC). Summary Reports are published in the *Commonwealth Chemical Gazette*, which is also available to the public at the NOHSC library.

Copies of this and other priority existing chemical reports are available from NICNAS either by using the prescribed application form at the back of this report, or directly from the following address:

GPO Box 58

Sydney

NSW 2001

AUSTRALIA

International Tel: +61 (02) 9577 9437

Free Call: 1800 638 528

Fax: +61 (02) 9577 9465 or +61 (02) 9577 9465 9244

Other information about NICNAS (also available on request) includes:

- NICNAS Service Charter;
- information sheets on NICNAS Company Registration;
- information sheets on Priority Existing Chemical and New Chemical assessment programs;
- application forms for New Chemical and Priority Existing Chemical assessments;
- application form for the Australian Inventory of Chemical Substances (AICS)
- subscription details for the *Commonwealth Chemical Gazette*; and
- subscription details for the NICNAS *Handbook for Notifiers.*

Priority Existing Chemical and New Chemical Summary Reports together with other information on NICNAS activities can be found on the NICNAS Web site at:

http://www.nicnas.gov.au

Overview

Triglycidylisocyanurate (TGIC) was the subject of an assessment as a Priority Existing Chemical and a full public report was published in April 1994. As a result of new data becoming available, the chemical has been reassessed under the secondary notification provisions of the *Industrial Chemicals (Notification and Assessment) Act 1989* (the Act).

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. A new biodegradability study was also provided. The consequences of the new data on the health and environmental hazard and risk assessments were evaluated.

The original TGIC report, (TGIC-1), concluded that TGIC is a hazardous substance, being toxic by oral and inhalational routes (**R23/25**), a skin sensitiser (**R43**), genotoxic (**R46**) and capable of causing serious eye damage (**R41**).

New human data confirmed that TGIC is a skin sensitiser and also demonstrated that it is a respiratory sensitiser. Repeated dose toxicity studies in animals indicate that TGIC causes severe effects after repeated exposure. The principal effects were significantly lower bodyweight, mastocytosis in lymph nodes and depletion of spleen lymphoid cells. TGIC was not carcinogenic in male rats exposed to TGIC by gavage. However, the carcinogenic potential of TGIC in female rats has not been studied.

Induction of chromosomal aberrations and cytotoxicity in mouse spermatogonia raised concerns in the original report, regarding potential reproductive effects of TGIC. A recent fertility study in male rats provides some evidence that TGIC does not affect male fertility. However, the potential for TGIC to affect female fertility and offspring growth and fertility has not been tested.

As reported in TGIC-1, TGIC residues released to the environment are expected to rapidly degrade due to the epoxide nature of the compound. The reactivity of TGIC precludes any possibility of bioaccumulation. In the aquatic environment, persistence is expected to be limited.

The occupational risk assessment in TGIC-1 concluded that TGIC is unlikely to cause adverse health effects if appropriate control measures, safe work practices and atmospheric monitoring strategies are implemented. The new data showing that TGIC is a respiratory sensitiser confirms the need to maintain occupational exposure levels to the lowest practicable level. The new repeated dose data goes some way towards predicting the long term health effects of occupational exposure to TGIC. However, there remain several data gaps, and therefore the potential for chronic health effects is not fully understood.

The new data does not change the public health and environment conclusions of the original report. TGIC is unlikely to present a risk to the public or the environment.

Recommendations

Further to the new data provided under this assessment, and in accordance with the health effects criteria detailed in the National Occupational Health and Safety Commission's (NOHSC) *Approved Criteria for Classifying Hazardous Substances* (NOHSC, 1999),

TGIC should be classified with additional risk phrases: 'may cause sensitisation by inhalation' (**R42**) and 'danger of serious damage to health by prolonged exposure if swallowed' (**R48**).

Consistent with good occupational health and safety principles, all occupational control measures including atmospheric monitoring, as recommended in the TGIC-1 report should be adhered to.

It is recommended that employers conduct an assessment of the risks to the health of employees from exposure to TGIC. Where there is a likelihood of sensitisation occurring in workers, then a health surveillance program should be provided.

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7.5 Carcinogenicity

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Acronyms and Abbreviations

CAS	Chemical Abstracts Service
DNA	deoxyribonucleic acid
EA	Environment Australia
FEV_1	forced expiratory volume in the first second
g	gram
h	hour
L	litre
LC_{50}	median lethal concentration
LD_{50}	median lethal dose
LLNA	local lymph node assay
mg	milligram
MSDS	Material Safety Data Sheet
NICNAS	National Industrial Chemicals Notification and Assessment Scheme
NOAEL	no observed adverse effect level
NOHSC	National Occupational Health and Safety Commission
OECD	Organisation for Economic Cooperation and Development
PD_{15}	provocative dose causing 15% depression in FEV_1
PEF	peak expiratory flow
ppm	parts per million
S.I.	stimulation index
TGA	Therapeutic Goods Administration
TGIC	triglycidylisocyanurate
TWA	time-weighted average

1. Introduction

1.1 Declaration and assessment as a Priority Existing Chemical

The chemical triglycidylisocyanurate (CAS Number 2451-62-9), known as TGIC, was declared a Priority Existing Chemical, under the *Industrial Chemicals Notification & Assessment) Act 1989* (the Act) on 5 November 1991. TGIC is used in Australia as a cross-linking agent in powder coatings in the metal finishing industry.

The reasons for the declaration were: (i) 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 also have adverse reproductive effects; and (ii) there were a significant number of workers exposed to TGIC.

A comprehensive evaluation of the available toxicity and exposure data was conducted and a full public report was published in April 1994 (NICNAS, 1994). The assessment concluded that TGIC should be classified as toxic by oral and inhalation routes, a skin sensitiser, mutagenic (category 2 mutagen) and capable of causing serious eye damage. The report recommended an interim occupational exposure limit as guidance for industry until a national exposure standard had been set.

The report also detailed an extensive analysis of control measures to minimise occupational exposure to TGIC. It concluded that TGIC was unlikely to cause adverse human health effects if appropriate control measures (such as full protective equipment) and atmospheric monitoring strategies were in place. However, it noted that the long term health effects in workers exposed to TGIC were difficult to predict in the absence of chronic data. The original assessment report also concluded that TGIC was unlikely to present a risk to the public or the environment.

Publication of the report was initially subject to delays pending an Administrative Appeals Tribunal (AAT) decision regarding the classification of TGIC in the areas of acute toxicity and mutagenicity. An application had been made to the AAT for review of the Director's decision to refuse to vary the assessment report. All decisions of the Director concerning classification were upheld by the AAT.

1.2 Secondary notification

In accordance with Section 62 of the Act, the publication of the full public report revoked the declaration of TGIC as a Priority Existing Chemical. However, under Section 64(2) of the Act, specific circumstances are prescribed where reassessment (secondary notification) of a Priority Existing Chemical, may be warranted. These circumstances include additional information as to the adverse health or environmental effects of the chemical becoming available.

In 1998, one company notified the Director of new information relating to the respiratory sensitising potential of TGIC. As a consequence, notice was provided in the *Chemical Gazette* of 5 January 1999 requiring reassessment of TGIC under Section 65(2) of the Act. All persons who introduced TGIC into Australia, either by import or manufacture, were required to apply for secondary notification, in order for TGIC to proceed to assessment. Secondary notification was given by six companies (see Section 2), who also supplied additional data.

1.3 Objectives

The objectives of this assessment were to review the new data made available since the publication of the original assessment report (TGIC-1) and where appropriate, revise the original assessment with regard to:

- the characterisation of the potential hazards of TGIC;
- the characterisation of the risks of adverse effects to workers, the general public and the environment; and
- the recommendations to control exposures and/or reduce potential risks.

1.4 New data

New data supplied for this assessment were:

i. 13-week oral toxicity/fertility study in male rats

ii. 99-week oral carcinogenicity study in male rats

iii. Contact hypersensitivity study in guinea pigs

iv. 2 human case reports of skin and respiratory sensitisation

v. Biodegradability study

1.5 Background on use of TGIC in Australia

TGIC is a three-dimensional cross-linking or curing agent for powder coatings or polyester resins. 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. Imported technical grade TGIC is mixed with resin, pigments, fillers and additives, at between four and ten percent by weight of the final product. TGIC-containing powder coatings are sprayed onto metal objects, using an electrostatic process, prior to curing in ovens.

1.6 Report format

For easy reference, the general format of this report follows that of TGIC-1. Only sections where new data are available or revisions have been made are included in this report. The following sections in the TGIC-1 report remain unaltered and the reader will need to refer to the original report:

- Methods of detection and analysis
- Use
- Manufacture of TGIC powder coatings

- Occupational exposure
- Public health assessment

1.7 Peer review

During all stages of preparation, the report has been subject to internal peer review by NICNAS, Environment Australia (EA) and the Therapeutic Goods Administration (TGA). Associate Professor Malcolm Simm of the Unit of Occupational & Environmental Health at Monash University reviewed the human case reports relating to TGIC-induced occupational asthma.

2. Applicants

Six companies applied for secondary notification assessment of the chemical. The applicants supplied relevant information for this assessment, including animal toxicity data, human health and environmental data. Under Section 36 of the Act, the applicants were provided with a draft copy of the report for correction of errors and variation of content.

Applications were received from:

Vantico Pty Limited
235 Settlement Road
Thomastown VIC 3074

Sumitomo Australia Limited
GPO Box 4241
Sydney NSW 2001

Dulux Australia
Powder & Industrial Coatings
51 Winterton Road
Clayton VIC 3168

Jotun Australia Pty Ltd
P.O. Box 105
Altona Nth. VIC 3025

Ameron Coatings
P.O. Box 356
Seven Hills NSW 2147

Interpon Powder Coatings
Akzo Nobel Pty. Limited
P.O. Box 26
Sunshine VIC 3020

3. Chemical Identity and Composition

3.1 Chemical Identity

Chemical Name: Triglycidylisocyanurate

CAS No.: 2451-62-9

Synonyms: 1,3,5-Triglycidyl isocyanurate

TGIC

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

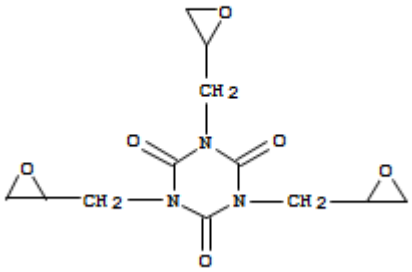
1,3,5-Tris(oxiranylmethyl) 1,3,5-triazine-2,4,6(1H,3H,5H)-trione

Tris(2,3-epoxypropyl) isocyanurate

Trade Names: Araldite PT 810
TEPIC
TK 10622

Molecular Formula: $C_{12}H_{15}N_3O_6$

Structural Formula:



Molecular Weight:

4. Physical and Chemical Properties

TGIC is manufactured and supplied as the technical grades TEPIC and Araldite PT810 (also known as TK 10622). TGIC technical grades are white, granular solids (at 20°C and 101.3 kPa) with no discernible odour. TEPIC has a melting point range of 90 to 125°C, while Araldite PT 810 melts at 95°C. Densities are 1420 and 1460 kg/m^3 respectively.

The water solubility and partition coefficient for TEPIC is 9 g/L at 25°C and log P_{ow} -0.8, respectively.

The reactivity of TGIC in the molten state is well characterised and includes reactions with the following functional groups: primary and secondary amines, carboxylic acids and anhydrides, thiols, phenols, and alcohols (at high temperatures). Molten TGIC may also undergo autopolymerisation.

The conversion factors for TGIC (at 25°C) TGIC are:

- 1 mg/m^3 = 0.082 ppm, and
- 1 ppm = 12.18 mg/m^3

Further details of the physical and chemical properties of TGIC are provided in TGIC-1.

5. Evaluation of animal toxicological data

Animal toxicological studies submitted for secondary notification have been evaluated and are reported below. Full reporting of data evaluated in the original assessment can be found in the TGIC-1 assessment report.

5.1 Skin sensitisation

Guinea pig maximization study

The skin sensitisation potential of TGIC (TK10622) was tested in male Albino Dunkin Hartley guinea pigs (RCC, 1997). The study was conducted according to OECD Guideline No. 406 'Skin Sensitisation' (1992).

Based on pretest data, 30% and 25% TGIC in corn oil were selected as the maximum tolerated dose and highest non-irritant dose concentrations suitable for the induction and challenge phase respectively. The test group (20 animals), were subjected to two induction and challenge phases comprising of:

Induction I: Intradermal injections (0.1ml) of adjuvant and of 5% TGIC (equivalent to 5 mg) in corn oil v/v (day 1)

Induction II: Topical application (approximately 0.3ml) of 30% TGIC (equivalent to 90 mg) in corn oil v/v under occlusion for 48h (day 8)

Challenge I: Topical application (0.2ml) of 25% TGIC (equivalent to 50 mg) (left flank) and corn oil only (right flank), under occlusion for 24h (day 22)

Challenge II: Topical application (0.2ml) of 25% TGIC (right flank) and corn oil only (left flank), under occlusion for 24h (day 29)

Guinea pigs in the control group (10 animals) were treated with vehicle only, and were not subjected to a second challenge. All animals were pre-treated with 10% Sodium-Lauryl-Sulfate (SLS) on day 7, to enhance sensitisation.

Clinical observations, viability/mortality, body weight and macroscopic findings were recorded. Skin reactions were recorded at 24 and 48h after removing the dressing following induction II, challenge I and challenge II. Erythema and oedema were assessed using the Draize numerical grading system. The skin reactions are summarised in Table 1. Only very slight erythema (Draize score 1) was observed in some of the animals. No oedema was observed in any of the animals. One animal in the control group died on day 7.

In a positive control group, 70% (7/10) of animals tested positive at challenge. The positive control was a non-irritating concentration (25%) of alpha-hexylcinnamaldehyde.

In accordance with OECD *Guideline No*. 406 'Skin Sensitisation' (1992), TGIC did not induce skin sensitisation in this study.

Table 1 - Results of skin sensitisation study

		Number of animals presenting with erythema**	
Phase	**Treatment Group**	**24h***	**48h***
Induction II	Control Test (30% TGIC)	4/9 10/20	4/9 10/20
Challenge I	Control Test (25% TGIC)	0/9 4/20	0/9 1/20
Challenge II	Test (25% TGIC)	1/20	1/20
Positive control	Alpha-hexylcinnamaldehyde	7/10	7/10

*Time (h) after treatment
**Each positive response received a Draize score of 1 for erythema.

Local Lymph Node Assay

The murine Local Lymph Node Assay (LLNA), which attributes a stimulation index (S.I.) as a measure of lymphocyte stimulation derived from animal auricular lymph nodes, has been proposed as a predictive test for the identification of sensitising agents, and in particular as a predictor of skin sensitisation potential (NIEHS, 1999).

Lymphocyte proliferation, induced in the lymph nodes of female BALB/c mice (3 per group, including control) exposed to 0.2% to 5% TGIC, (by topical application to the dorsum of both ears), was assessed and a stimulation index (S.I.) determined (Clottens et al, 1996). The LLNA is considered positive if a S.I. of at least 3 is obtained. The maximal S.I. for TGIC was 2.0, with a 2-fold increase in the lymph node cell number (LNC) and a 1.5 fold increase in lymph node weight. Taken together, the data were considerably lower than for the positive control, which provided an S.I. of 37 with a 6.4 fold increase in total LNC. Only an abstract for this study was available. In addition, critical information as defined by NIEHS (1999), was not reported.

5.2 Combined 13-week toxicity and fertility study

A combined oral 13-week toxicity and fertility study was conducted in Sprague Dawley rats (CIT, 1995). The conduct of the study was similar to OECD Guideline No. 408, however females were not exposed to TGIC at any time.

Toxicity study

Male rats (10 per group) were exposed to dose levels of 0, 10, 30 and 100 ppm (0, 0.73, 2.08, 7.32 mg/kg/day) TGIC for 94 days by dietary admixture (supplied *ad libitum*). Examinations for ophthalmology (checked before treatment and at week 13 in control and 100 ppm group), haematology, blood biochemistry and urinalysis (each performed at week 13) were made. Body weight gain and food consumption were checked weekly. At the end of the treatment period the males were killed and

a pathological assessment including organ weight, macroscopic and microscopic examination were made. Microscopic examination was performed in lungs, liver, kidneys, prostate, seminal vesicles, testes and epididymis and lymph nodes (mandibular and mesenteric) of all males.

No treatment-related clinical signs or mortality were observed at the 10 or 30 ppm dose-level. At 100 ppm (7.32 mg/kg/day), treated animals had a consistently lower body weight compared to controls, which was significant throughout most of the treatment period. At the end of the study, treated animals had an 8% mean lower body weight compared to controls. In addition, a significantly lower body weight gain (-16%) over the first 6-week period was observed. Thereafter, the bodyweight gain was similar to the controls. The only other effects observed were hemosiderosis and/or congestion in the mesenteric lymph nodes of 4 animals at 100 ppm.

Fertility study

After the initial 9-week exposure period each male was placed overnight with 2 unexposed females until mating occurred or up to seven days maximum. On day 19 of pregnancy, the females of each group were allocated equally to two subgroups (hysterectomy subgroup or delivery subgroup). Females in the hysterectomy subgroup were killed on day 20, foetuses were removed by Caesarean section and examined. Females in the delivery group were allowed to deliver and rear their progeny until weaning. Between day 22 and 25 post-partum, the females and pups were killed and examined. Females received only untreated diet ad libitum throughout the study.

No clinical signs, unscheduled mortality, abortions, differences in body weight or relevant macroscopic findings (at necropsy) were noted in the maternal animals. In the litter of the hysterectomy subgroup, there were no differences in corpora lutea and implantation sites, post-implantation losses, live foetuses and fatal external abnormalities. In the litter of the delivery subgroup, there were no differences in the litter size, pup weight and viability, clinical signs or pup development.

No treatment-related male infertility, as measured by the mating and fertility indices was noted.

A treatment-related decrease in mean number of spermatozoa was noted in males treated with 30 and 100 ppm TGIC, however, further independent statistical analysis of the data (ANOVA) revealed that this was not statistically significant when compared to controls ($p>0.5$). Mean spermatozoa viability was unaffected.

Under the conditions of this study, the no observed adverse effect level (NOAEL) is 7.32 mg/kg/day (100 ppm).

5.3 Carcinogenicity

The carcinogenic potential of TGIC was examined in 50 male Sprague-Dawley rats per dose level over a 99-week exposure (CIT, 1999). The study was conducted according to OECD Guideline No. 451 (OECD, 1981), with the exception that female rodents were not included in the study.

Animals were given by dietary admixture either 0, 10, 30, 100 or 300 ppm TGIC (achieved doses of 0, 0.43, 1.30, 4.36 and 13.6 mg/kg/day, respectively). In

addition, a satellite group (10 males per dose level) were exposed for 26 weeks to 0, 100, and 300 ppm TGIC.

Microscopic examination was performed in all tissues, macroscopic lesions and palpable masses from control and high-dose (300 ppm) animals at the end of the treatment period in the principal and satellite groups. Additionally, similar examination of the intermediate dosed (100 ppm) animals of the principal study group was conducted at the end of the treatment period.

a) Principal Group

Due to the high level of mortality and marked signs of toxicity at 300 ppm, treatment was stopped at week 63 for this group, and the animals were sacrificed.

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

At 100 ppm, terminal body weight was lower (-9%) as well as mean food consumption in treated animals compared to controls, however the differences were not statistically significant. A slight increase in hepatocellular adenoma (6/50 vs. 4/50 for controls) and carcinomas (3/50 vs. 0/50 for controls) was noted, however the incidence was not dose-related and was within the range of historical controls.

Treatment-related effects observed in the 300 ppm group include:

- Poor clinical condition (including round back, piloerection and emaciation) was noted as early as week 34.
- At week 52, a higher mean neutrophil count (+41%) and mean monocyte count (+50%) was noted, while at week 63, a lower lymphocyte count (-33%), and a lower mean total leukocyte count (-23%) at week 63 ($P<0.01$) was noted.
- A significantly higher incidence of mastocytosis in the mesenteric lymph nodes, hemosiderosis, splenic lymphoid depletion and sinusal haemorrhage.
- A high incidence of dilated lumen in the duodenum, jejunum and ileum. In addition, a higher incidence of hyposecretion and small tubulo-alveolar units in the prostate.
- Onset of mortality occurred significantly earlier (week 45).
- At 52 weeks, the survival rate was lower (56% in 300 ppm group compared to 90% in controls.)
- A marked decrease in body weight gain persisted throughout the study period, and by week 62 was 68% lower ($p<0.01$) than controls for the same period.
- A consistently lower mean food consumption, which was statistically significant.

b) Satellite Toxicity Group

No treatment-related clinical signs or mortality were observed in the satellite toxicity group, and no adverse effects were observed at 100 ppm. High dose (300 ppm) treated animals revealed the following changes:

- Body weight gain was markedly lower (-77%) than controls during the initial 8-week treatment period and less marked by the end of the 16-week treatment period (-43%).
- Significantly decreased mean food consumption level throughout the 16-week treatment period.
- Slightly lower mean total leukocyte count (-35%, $p<0.01$), and a slightly higher thrombocyte count (+19%, $p<0.05$).
- Slightly lower mean total protein level (attributable to a slightly lower globulin level) was most marked at week 27 (-9%) when compared to controls.
- Increased relative mesenteric lymph nodes (88%, $p<0.01$), associated with hemosiderosis, plasmacytosis, mastocytosis and sinusal haemorrhages. Statistical significance as determined by the Kruskal-Wallis test, was attributed to the mesenteric lymph node data alone.
- Lower absolute weights of thymus (-24%, $p>0.05$) and spleen (-37%, $p>0.05$), associated with lymphoid depletion.
- Lower absolute weights of prostate (-27%, $p>0.05$), and seminal vesicles (-36%, $p>0.05$), associated with moderate hyposecretion.

Conclusion

In conclusion, there were no adverse effects in animals treated up to 100 ppm. TGIC failed to induce an increase in tumours in a dose-dependent manner in males, at doses up to 100 ppm.

At the highest dose (300 ppm), the principal effects were decrease in body weight, mastocytosis in the lymph nodes and depletion of the spleen lymphoid cells in both study groups. Increased mortality resulted in the group being sacrificed at week 63. The authors concluded that marked mastocytosis in the mesenteric lymph node, together with sinusal haemorrhage, indicate that a histamine-related hypotension might have been the cause of death in this group.

The NOAEL for non-neoplastic effects in this study is 100 ppm (4.36 mg/kg/day).

6. Human Health Effects

6.1 Case reports

Two recent case reports were available for assessment.

The first published case report (Piirila et al., 1997) describes a male spray painter exposed to powder paints containing TGIC (4% v/v), for periods extending 5 – 8h daily over 7 years. The worker suffered from eczema on his hands, face and body, symptoms of dyspnoea, particularly during and after workdays, and from dyspnoea, coughing and wheezing at night and during exercise. The authors state that 'no atopic tendency had been verified' prior to working as a spray painter. Protective clothing and a motorised breathing protector were used during painting. TGIC-induced contact dermatitis was diagnosed, following positive patch testing with polyester paint containing 10% and 3.2% TGIC, or 1%, 0.32% or 0.1% TGIC in petroleum.

Skin prick tests to TGIC and tests for IgE specific to TGIC were negative, however total serum IgE was elevated. Peak flow follow-up revealed a regular 20% diurnal variation, reducing to less than 10% following a 3 month budesonide treatment, and significant bronchodilatation responses of 17 – 20%. The lactose-control challenge test was negative. Moderate bronchial hypersensitivity (PD_{15} 0.33 mg), as measured by the provocative dose causing 15% depression in FEV_1, was observed following a histamine challenge test. A challenge test with paint containing 4% TGIC, induced a 15% fall in peak expiratory flow (PEF) 30 minutes after exposure, together with tightness in the chest. Additionally, there was a late fall of 23% in the forced expiratory volume in the first second (FEV_1) and 17% in PEF, at 11h and 16h after challenge, respectively.

When challenged with 4% TGIC containing lactose (1:1), an immediate 17% fall in PEF (within 15 minutes) was observed. In addition, a late 16% fall in PEF and 19% in FEV_1 (both 6h post exposure), and a 16% fall in PEF and 15% in FEV_1 (both 13h post exposure) was observed. When the histamine challenge test was repeated post challenge, moderate bronchial hyper-reactivity was observed, with the PD_{15} significantly lower.

The second published case report (Meuleman et al., 1999) describes a spray painter (without pre-existing atopic disease) exposed to polyester powder pigments, containing 1–7% w/w TGIC, over a three-year period. Although he wore a protective mask, but not protective gloves, he developed sustained erythematous, papular, and plaque-like lesions on his arms and legs, as well as the axillae and upper part of the back. Respiratory symptoms including, rhinitis, dyspnoea, cough and wheezing, appeared shortly after the skin lesions. A decrease in symptoms during weekends provided a clear association with his occupational activities. Positive patch test results, to TGIC (0.5% and 5% in petroleum) and one of the pigment powder samples, were observed 2 to 3 days post exposure.

Specific bronchial provocation tests involving inhalation of aerosolised 0.05% TGIC (in lactose) induced a progressive decrease in FEV_1 to –22% by 6h. The following day, a second challenge test using 0.1% TGIC (in lactose) was mounted, the response was clearly positive with a maximal decrease in FEV_1 of –31% at 4 h after exposure. The worker experienced coughing, wheezing, dyspnoea and itching during the night following the provocation test. Skin prick tests with TGIC were inconclusive. Serum IgE levels were measured before the bronchial provocation tests and found to be elevated.

Taken together, the data provide evidence of allergic contact dermatitis and occupational asthma as a result of exposure to TGIC.

6.2 UK SWORD Notification System

The UK Surveillance of Work-Related & Occupational Respiratory Disease (SWORD) is a national scheme for the reporting of new cases of occupational respiratory diseases (including asthma) by thoracic and occupational physicians. Since the Scheme began in 1989, eleven cases of asthma have been attributed to TGIC exposure (approximately 2 cases per year from 1994-2000) (McDonald JC (2000), personal communication).

7. Human Health Hazard Assessment and Classification

This section integrates data on animal toxicity and human health effects in order to characterise potential human health hazards from exposure to TGIC and classify these hazards. The classification criteria used throughout are the NOHSC *Approved Criteria for Classifying Hazardous Substances* (the Approved Criteria) (NOHSC, 1999).

Only those toxicity endpoints where new data were available for this assessment are considered. The hazard assessment of these endpoints takes into account the new data (described and evaluated in Section 6) and relevant data from the TGIC-1 report.

7.1 Skin sensitisation

In TGIC-1, animal and human health data concerning the skin sensitisation potential of TGIC were available. A summary of the data is as follows:

Animal studies

In 2 studies, the skin sensitisation potential of TGIC was assessed in male and female guinea pigs (Ciba-Geigy Ltd, 1988, Safepharm Laboratories Ltd,1988). In the studies, a two-stage induction process was followed by 1 or 2 challenge phases. The duration of exposure to TGIC during the challenge phase was limited to 24h. The challenge phase concentrations of TGIC were 20 mg (Ciba Geigy Ltd, 1988a) or 50-100 mg (Safepharm Laboratories Ltd, 1988). TGIC tested positive for sensitisation in both studies.

Human studies

Three case studies reported TGIC-induced contact dermatitis. In each case the worker had been exposed to TGIC or TGIC powder coatings, and complained of dermatitis. The workers were patch-tested with TGIC and the results were positive. ICI Dulux also provided a summary of the health status of employees at an Australian powder coating manufacturing plant, whereby, two employees had allergic dermatitis (confirmed positive by TGIC patch-test analysis).

New animal and human data, concerning the skin sensitisation potential of TGIC are summarised as follows:

Animal studies

A negative study was reported, examining the skin sensitisation potential of TGIC in a group of 20 male guinea pigs. A murine LLNA was negative however only an abstract was available for assessment, and essential information was not reported.

Human studies

Two recently published case reports were available for this assessment. In both studies, spray painters using TGIC powder coatings for extended periods of time reported dermatitis. Clinical examination revealed eczema in both workers, and returned positive patch-tests to TGIC and TGIC powder coatings.

In summary, there are now 5 human case reports of skin sensitisation, 2 positive and 1 negative guinea pig maximisastion studies and 1 negative murine LLNA (abstract only). The recent sensitisation study in guinea pigs was negative, which is in contrast with the findings of 2 similar studies reported in TGIC-1. Although there are small differences in dose at induction and challenge in these animal studies, they are unlikely to account for the differences in results. In fact, the methodology adopted by Safepharm Laboratories Ltd (1991) is the same as the latest study (Ciba-Geigy Ltd, 1997), with the exception of the slightly lower doses at the second induction (90 mg in the Ciba study c.f. 100-150 mg in the Safepharm study).

Classification status

Based upon available animal and human data, TGIC satisfies the Approved Criteria for classification as a substance causing sensitisation by skin contact.

7.2 Respiratory sensitisation

TGIC-1 reported that ICI Dulux had provided a summary of the health status of employees at an Australian powder coatings plant. In 1991, two separate incidents of TGIC-aggravated intrinsic asthma were reported (no further details provided). Shortly after, twenty-eight employees were given medical examinations, and respiratory irritation was present or reported in five employees. No TGIC exposure monitoring data was provided (this data was not used for classification because of the lack of reporting detail).

New respiratory sensitisation data is limited to two human case reports (Piirila et al., 1997; Meuleman et al., 1999), each demonstrating positive bronchial provocation test data. The studies report on two spray painters, who, after working with TGIC powder coatings (1-7% w/w) for extended periods of time, reported respiratory symptoms including rhinitis, dyspnoea, cough and wheeze.

In both cases, occupational asthma was diagnosed following bronchial provocation tests, involving challenges to aerosolised TGIC. The time taken to reach a greater than 20% reduction in FEV_1 was considerably longer in the Piirila report (11h vs 6h) and the concentration of TGIC used during bronchial provication was much higher (4% vs 0.05%). These clinical differences may reflect patient-specific differences and are considered not to weaken the evidence for the positive causal relationship between TGIC and occupational asthma. Skin prick tests to unconjugated TGIC however, were negative in one (Piirila et al., 1997), and inconclusive in the other (Meuleman et al., 1999).

As there are currently no known published epidemiological studies, rates of occupational asthma in TGIC-exposed populations remain unclear. However, under the UK SWORD notification system, eleven cases of asthma have been attributed to TGIC since 1989.

Classification status

The classification system prescribed in the Approved Criteria states that a chemical meets these criteria if there is evidence that the substance can induce specific respiratory hypersensitivity. As is the case with TGIC, this evidence is usually human data. In considering the human evidence for TGIC, the explanatory notes regarding the use of R42 have been taken into account as follows:

- Two case reports show positive bronchial challenge on exposure to TGIC and thus provide sufficient evidence for classification on their own. (paragraph 4.63 of the Approved Criteria)
- In the two case studies, exposure to TGIC resulted in respiratory hypersensitivity, that is, the clinical condition of asthma (in addition to dyspnoea and rhinitis). There is no data to show that the asthma elicited by TGIC is a result of respiratory irritation in bronchial hyper-reactive individuals. There was no evidence that the asthma was caused by irritation in hyper-reactive individuals. Similar to other low molecular weight substances known to cause respiratory sensitisation, no immunological mechanism has been demonstrated. (paragraphs 4.59 and 4.64)
- Both case studies provide relevant clinical history (medical and occupational information) to support a relationship between exposure to TGIC and the development of respiratory hypersensitivity. Lung function tests, including serial peak flow measurements and assays for bronchial hyper-responsiveness to histamine, provide further evidence. (paragraph 4.62)

Supporting evidence

- Case reports do not give an indication of the incidence of respiratory sensitisation amongst TGIC workers and no epidemiological studies have been conducted. Because of the other known adverse health effects of TGIC, the wearing of personal protective equipment (including respiratory protection) is recommended by manufacturers and distributors of TGIC and TGIC products and is common practice in workplaces. Therefore, the number of cases reported as a function of population size would be expected to be low. However, in addition to the 2 case studied discussed in the report in detail, under the UK SWORD notification scheme 11 cases of occupational asthma have been attributed to TGIC exposure. (paragraph 4.60)
- TGIC is structurally related to isocyanates and has reactive epoxide side groups, which suggests TGIC may have the potential for sensitisation. (paragraph 4.61)

7.3 Repeated dose toxicity

No long-term repeated dose studies were available for assessment for TGIC-1. Only short-term repeated dose (5 or 7 day) studies in rodents were available. Results of these short-term studies are described below.

Male rats were administered 0, 54 or 216 mg/kg/day TGIC, and females administered 0, 43 and 172 mg/kg/day by gavage for 7 days (Shell Research Ltd, 1971). No abnormal clinical signs or symptoms were observed. Minor

cytoplasmic vacuolation of distal convoluted tubule epithelia were observed in males in the low dose group. In the high dose groups, renal tubular damage, and haemorrhagic and degenerative changes of the gastric and duodenal mucosa were observed.

Male mice were administered 0, 10, 40 or 140 mg/m^3 TGIC for five days (Safepharm Laboratories Ltd, 1991). No adverse effects were observed in mice exposed to 10 mg/m^3 TGIC. However, adverse clinical signs, increased bodyweight losses and higher mortality occurred at inhaled dose levels of 40 and 140 mg/m^3 TGIC.

Male mice were exposed nose-only to 7.8 mg/m^3 or orally to 115 mg/kg/day, TGIC, for five days (Safepharm Laboratories Ltd, 1992). No adverse clinical signs or deaths were observed and bodyweight gain was unaffected.

In this report, a 13-week toxicity study was assessed (CIT, 1995). Exposure to 0,10, 30 or 100 ppm (0, 0.72, 2.08 or 7.32 mg/kg/day) TGIC by dietary admixture in male rats was well tolerated. At the highest dose, treated animals exhibited a statistically significant lower body weight, the only effect observed.

Additionally, data on the non-neoplastic effects of TGIC can be obtained from the new 99-week carcinogenicity study in male rats exposed to 0, 10, 30, 100 or 300 ppm (0, 0.43, 1.30 or 4.36 and 13.6 mg/kg/day) (CIT, 1999). Principal effects seen at the highest dose studied (300 ppm) included, decrease in body weight, mastocytosis in the lymph nodes and depletion of the spleen lymphoid cells. However, increased mortality within the group meant these animals were sacrificed at week 63. There were no treatment-related non-neoplastic changes observed in lower dosed groups.

Classification status

Reduced body weight was observed in the 13-week toxicity study at 100 ppm (7.32 mg/kg/day) and in a carcinogenicity study (CIT, 1999) a rapid onset of mortality and other severe effects were observed at 300 ppm (13.6 mg/kg/day) TGIC. TGIC is classified as 'Harmful' for severe effects after repeated or prolonged exposure.

7.4 Fertility

While no standard fertility studies were available for assessment for TGIC-1, genotoxicity studies indicated that TGIC induced chromosomal aberrations and cytotoxicity in mouse spermatogonia and reduced fertility in males in a dominant lethal test. These findings raised the possibility of reproductive effects of TGIC. Studies in male mice included exposure of TGIC by nose-only inhalation (Safepharm Laboratories Ltd, 1992), and oral administration (Ciba-Geigy Ltd, 1986; Hazleton Laboratories America Inc, 1989; and Hazleton Microtest, 1991).

The nose-only inhalation study established that exposure of mice to 7.8 mg/m^3 TGIC (only dose tested) over 5 days did not induce chromosomal aberrations or cytotoxicity in spermatogonial cells, or adverse clinical effects. In the oral studies, chromosomal aberrations were seen at the lowest dose tested, 28.5 mg/kg/day and cytotoxicity at 57.5 mg/kg/day and above.

In a dominant lethal study in which TGIC did not induce mutations, reduced fertility was observed in males at the highest dose, 50 mg/m^3. The reductions in

fertility were consistent with effects on mature sperm, maturing spermatids and Type-B spermatogonia.

In this report, a combined, 13-week fertility study was assessed (CIT 1995). Exposure to 0, 10, 30 or 100 ppm (0, 0.72, 2.08 or 7.32 mg/kg/day) TGIC by dietary admixture in male rats was well tolerated. A slight treatment-related decrease in the mean number of spermatozoa was noted at the 30 and 100 ppm doses; however, this was not statistically significant when compared to controls.

There was no treatment-related infertility in males or changes in embryonic and pup development. However, females were not exposed in this study. The NOAEL is considered to be 7.32 mg/kg/d.

Classification status

The potential effects of chromosomal damage in spermatogonia in mice were not demonstrated as infertility in male rats, or developmental effects when males were exposed to repeated, lower doses of TGIC. The effects of TGIC on female fertility and developmental effects as a result of maternal exposure to TGIC have not been investigated.

There is insufficient data to classify TGIC with respect to effects on fertility or developmental toxicity.

7.5 Carcinogenicity

Although no carcinogenicity studies were available for assessment for TGIC-1, the mutagenic potential of TGIC was assessed, and categorised as a 'Category 2 mutagen' accordingly. TGIC was positive in a number of short-term *in vivo* and *in vitro* genotoxicity studies and shown to covalently bind to DNA. The results raise the question of potential carcinogenic effects of TGIC.

In this report, the carcinogenic potential of TGIC was examined in male Sprague-Dawley rats over a 99-week exposure period. Animals were given by dietary admixture either 0, 10, 30, 100 or 300 ppm (0, 0.43, 1.30, 4.36 and 13.6 mg/kg/day) TGIC. The 300 ppm dosed group was sacrificed at week 63 due to high mortality and adverse clinical signs.

The NOAEL for non-neoplastic effects is 4.36 mg/kg/d. This NOAEL is approximately equivalent to an inhalation exposure level of 23.2 mg/m^3 over 6-hours (assuming a rat body weight of 0.215 kg and inhalation rate of 0.161 m3/d). TGIC failed to induce an increase in the incidence of tumours at doses up to 100 ppm in male rats.

Non-neoplastic effects were not observed at 100 ppm and females were not investigated. Notwithstanding the positive mutagenicity potential of TGIC reported in TGIC-1, additional data is required before classification for the carcinogenic potential of TGIC can be made.

Classification status

There is insufficient data to classify the carcinogenic potential of TGIC.

8. Environmental Assessment

8.1 Environmental exposure

As highlighted in the initial assessment of TGIC, the chemical is an epoxide where any residues released to the environment are expected to be rapidly degraded, either through microbal action or abiotic hydrolysis. In the aquatic environment, persistence is expected to be limited (half-life expected to be less than 10 days in fresh water) with hydrolysis proceeding more rapidly in the marine environment. Studies provided showed TGIC is not readily biodegradable using the modified Sturm test, with 48% degradation from a solution containing TGIC at 20 ppm after 28 days. However, in a modified Zahn-Wellens test, the compound was inherently degradable.

Since the original TGIC-1 assessment, the ready biodegradability of TGIC has been further assessed in a CO_2 evolution (28 day Modified Sturm) Test in accordance with EEC Directive 92/69 and OECD Guideline No. 301 B (Grutzner, 1997). Exposure was prolonged to 43 days because the chemical showed no sign of biodegradation by exposure day 28. The inoculum was activated sludge from a domestic waste water treatment plant. Concentrations in the test solution appeared to be around 33 ppm, with 100 mg of TGIC added to test flasks containing 3 litres of medium. Only one concentration was tested for biodegradability. To determine whether the compound had any toxic effect on the microorganisms, a toxicity control was established where 51 mg of TGIC was added along with 39 mg of the reference compound, aniline, to a flask containing 3 litres of test medium, giving a concentration of around 17 ppm. This concentration was around half of that used to test biodegradability, and the reason for this is not made clear in the study. The outcomes of this study showed TGIC to be nonbiodegradable and nondegradable (in the absence of activated sludge) over the 43 days exposure with zero degradation recorded. Likewise, the abiotic control containing TGIC and sterile test medium showed no abiotic degradation. While the toxicity control showed no inhibitory effect (around 44% degraded after 28 days, although it is not clear whether this was solely due to the aniline), the effective concentration of TGIC was around half that used in the degradation strudy. However, as an earlier test showed 48% degradation from a solution containing TGIC at 20 ppm after 28 days (see above), an inhibitory effect at 33 ppm must be considered.

9. Summary and Conclusions

Triglycidylisocyanurate (TGIC) is a triepoxy compound used as a cross-linking or curing agent for polyester resins. In Australia, TGIC is only imported, and is used principally as an ingredient in polyester powder coatings in the metal finishing industry. TGIC is either imported as technical grade TGIC for the manufacture of powder coatings or imported in powder coatings formulated overseas. An electrostatic process is used to spray powder coatings onto metal objects, such as steel furniture, car parts, metal fencing, window and door frames.

TGIC was assessed by NICNAS as a priority existing chemical in 1994. The availability of significant new data has led the chemical to be reassessed (secondary notification). New data supplied for secondary notification assessment included contact hypersensitivity, repeated dose toxicity, fertility and carcinogenicity animal data, human health effects data and an environmental biodegradability study.

The new data was assessed and considered together with the health assessment data in original TGIC report. The major impact of the new data relates to respiratory sensitisation, and effects due to prolonged exposure. The data, considered as a whole, are summarised below.

The human health effects reported in the literature are skin and respiratory sensitisation. Several case reports of allergic dermatitis and occupational asthma in workers exposed to TGIC or TGIC powder coatings have been published. Patch tests with TGIC, to confirm skin sensitisation of these workers, were positive. Positive bronchial challenge tests confirmed respiratory sensitisation. Other health effects reported amongst workers in Australia include nasal, eye and throat irritation, skin rash and nose bleeds.

In animals, TGIC is acutely 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, including renal, lung and gastric/duodenal damage.

TGIC is genotoxic, *in vitro* and *in vivo* in mice. TGIC induced chromosomal aberrations in mouse spermatogonia following oral administration. TGIC was also positive in *in vivo* nucleus anomaly assays and induced sister chromatid exchanges in a number of *in vitro* genotoxicity studies. The evidence for induction of dominant lethal mutations by TGIC is equivocal. TGIC was shown to bind to rat liver DNA *in vivo* following oral and intraperitoneal administration. Genotoxicity studies indicated that inhalation of TGIC resulted in cytotoxicity and chromosomal aberrations in spermatogonial cells of mice. In a dominant lethal study, TGIC showed reduced fertility following inhalation in some but not all cases studied. This data raised concerns that there may be a risk of reproductive effects from exposure to TGIC. In a recent study, effects on male fertility and developmental effects were not observed when male rats were exposed to TGIC up to the maximum dose tested (100 ppm). However, even at the highest dose, apart from a slightly lower body weight gain, no other effects were observed. Effects on female

fertility and developmental effects as a result of maternal exposure, have not been tested.

The only available chronic data indicate that the NOAEL in male rats is 100 ppm, with severe effects occurring at 300 ppm. TGIC did not induce an increase in tumours up to 100 ppm in these animals. Principal effects at 300 ppm included decrease in body weight, mastocytosis in the lymph nodes, depletion of the spleen lymphoid cells and death. Females were not tested.

The sources of occupational exposure during manufacture of TGIC powder coatings include weighing out of TGIC, filling hoppers, mixing, transfer of powder mixes in open vessels, extrusion, milling, bagging, cleaning up spills, and cleaning equipment. Sources of occupational exposure during use of TGIC powder coatings include filling hoppers, spraying, cleaning up spills, cleaning equipment and cleaning spray booths.

Based upon all the available data, and in accordance with NOHSC Approved Criteria, TGIC should be classified as:

- toxic by inhalation and if swallowed.
- may cause sensitisation by inhalation.
- risk of serious damage to eyes.
- may cause sensitisation by skin contact.
- 'harmful' for severe effects after repeated or prolonged exposure.
- may cause heritable genetic damage (Category 2 mutagen).

As a result of the original toxicity assessment, TGIC-1 noted that there were a number of critical data gaps and recommended studies to examine the chronic toxicity, carcinogenicity and reproductive toxicity of TGIC.

The impact of new data on the recommendations for further toxicity testing, as outlined in TGIC-1, is summarised accordingly:

- The oral carcinogenicity in male rats provides some evidence for lack of tumour development (up to 4.36 mg/kg/day). However, females were not tested. Additional data is required before classification for the carcinogenic potential of TGIC can be made.
- The combined 13-week toxicity/fertility study provides some information on reproductive toxicity. The study established a NOAEL (7.32 mg/kg/day) for male rats (including fertility), reporting no treatment-related infertility in males or change in embryonic and pup development following exposure of males to TGIC. However, females were not exposed to TGIC and potential effects on the next generation were not studied. Therefore, the study did not adequately address potential effects on the offspring (as a result of male or female reproductive toxicity) or female fertility.

At the time of writing the TGIC-1 report, no national occupational exposure standard for TGIC had been adopted. TGIC-1 acknowledged that a national occupational exposure standard should be predicated on chronic data, but in its absence concluded the genotoxic potential of TGIC as the critical determinant in establishing an occupational exposure standard. Accordingly, TGIC-1

recommended that NOHSC set an exposure standard. Subsequently, a time-weighted average exposure standard for TGIC of 0.08 mg/m^3 was set by NOHSC (adopted December, 1995). The exposure standard was based on the Safepharm 6-hour inhalation study (Safepharm Laboratories Ltd , 1992), where the lowest no effect level was 7.8 mg/m^3.

The NOAEL for non-neoplastic effects in a recent 99-week oral study in male rats was 100 ppm (4.36 mg/kg/d). This NOAEL is approximately equivalent to a 6-hour exposure level of 23 mg/m^3 (based on a rat body weight of 215 g and an inhalation rate of 0.161 m^3/d). Based on the chronic data, review of the occupational exposure standard is not warranted.

The new data demonstrates that TGIC is a respiratory sensitiser and like all sensitisers, exposure levels should be kept to a minimum. This is consistent with the conclusion in TGIC-1; that is, TGIC is a sensitiser and is genotoxic, and therefore, occupational exposure levels should be maintained at the lowest levels practicable. Experience has shown that exposure levels of 0.08 mg/m^3 can be achieved and maintained in powder coating manufacturing plants and spray paint workshops.

The conclusions of the earlier report still stand, that TGIC is unlikely to cause adverse human health effects if appropriate control measures (including personal protective equipment where necessary), safe work practices and atmospheric monitoring and health surveillance strategies (when necessary) are implemented.

Additional biodegradability data for TGIC confirms the findings of the TGIC-1 assessment, that is, TGIC is not expected to accumulate in soil or sediment because of high mobility and limited persistence. Persistence in the aquatic environment is also expected to be limited. The reactivity of TGIC precludes any possibility of bioaccumulation.

Finally, TGIC is unlikely to present a risk to the public or the environment under the current use conditions.

10. Recommendations

10.1 Classification and labelling

In the TGIC-1 report, TGIC was classified as toxic by oral and inhalation 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 *Approved Criteria for Classifying Harzardous Substances* (NOHSC, 1999).

This secondary notification assessment has shown no data to change TGIC-1 recommendations and in addition, new data indicate that TGIC should also be classified as a **respiratory sensitiser** and **'harmful' for severe effects following repeated exposure**.

Based on the classification of its health effects and in accordance with the Approved Criteria (NOHSC, 1999), TGIC is considered to be a hazardous substance.

The complete requirements for the labelling of hazardous substances are detailed in the *National Code of Practice for the Labelling of Workplace Hazardous Substances* (NOHSC, 1994a). The following risk phrases and appropriate safety phrases apply to the present report and 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 for the Control of Workplace Hazardous Substances* (NOHSC, 1994b) have been met.

Risk phrases

- **R23/25** Toxic by inhalation and if swallowed.
- **R41** Risk of serious damage to eyes.
- **R42** May cause sensitisation by inhalation.
- **R43** May cause sensitisation by skin contact.
- **R46** May cause heritable genetic damage.
- **R48/22** Danger of serious damage to health by prolonged exposure if swallowed.

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 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 label where possible).

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

Table 2 - Concentration limits and classifications for TGIC as an ingredient in mixtures/preparations

Concentration limit	Classification
25% ≤ C	Toxic; **R23/25, R48/22, R41, R42/43, R46**
10% ≤ C < 25%	Harmful; **R20/22, R41, R42/43, R46, R48/22**
5% ≤ C < 10%	Harmful; **R20/22, R41, R42/43, R46**
3% ≤ C < 5%	Harmful; **R20/22, R42/43, R36, R46**
1% ≤ C < 3%	Harmful; **R42/43, R36, R46**
0.5% ≤ C < 1%	Harmful; **R36, R46**
0.1% ≤ C < 0.5%	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 *Approved Criteria for Classifying Hazardous Substances* (NOHSC, 1999) for further guidance.

10.2 Further studies

The data gaps and recommended further studies noted in TGIC-1 still apply and are as follows:

- Chronic toxicity and carcinogenicity data (such as a combined chronic inhalation/carconogenicity study in a mammalian species).
- Reproductive and developmental toxicity (such as a multigeneration reproduction study).

10.3 Health Surveillance

A workplace assessment is required by the *National Model Regulations for the Control of Workplace Hazardous Substances* (NOHSC, 1994b) of the risks to health consequent upon exposure to a hazardous substance. According to the NOHSC *Guidelines for Health Surveillance* (NOHSC, 1995) an employer must consider if use of a hazardous substance in the workplace presents a significant risk to health and, if so, establish an appropriate health surveillance program.

As TGIC is a respiratory and skin sensitiser, particular attention should be paid to worker exposure via skin contact and inhalation of TGIC powder coatings. A medical practitioner appointed by the employer can assist in deciding if the health surveillance is required, and if so, design an appropriate a program.

10.4 Material Safety Data Sheets

The NOHSC *National Code of Practice for the Preparation of Material Safety Data Sheets* (NOHSC, 1994c) provides guidance for the preparation of MSDS.

It is recommended that suppliers amend their MSDS, taking into account the new health effects data and the classification and cut-off levels recommended in Section 11.1. In particular, the MSDS should reflect the new information on chronic health effects and respiratory sensitisation. Some suggested wording is provided in the sample MSDS at Appendix 1.

10.5 Atmospheric monitoring and control of occupational exposure

Recommendations in TGIC-1 in relation to atmospheric monitoring and occupational control measures are considered to be appropriate. For information, a copy of the relevant sections from TGIC-1 is provided in Appendix 2.

11.Secondary Notification

Under Section 65 of the Act, the secondary notification of TGIC may be required, where an applicant or other introducer (importer) of TGIC, becomes aware of any circumstances which may warrant a reassessment of its hazards and risks. Specific circumstances include:

a) The function or use of TGIC has changed, or is likely to change, significantly;

b) The amount of TGIC introduced into Australia has increased, or is likely to increase significantly;

c) Manufacture of TGIC has begun in Australia; or

d) Additional information has become available to the applicant/notifier as to the adverse health and/or environmental effects of TGIC.

The Director must be notified within 28 days of the introducer becoming aware of any of the above circumstances.

Appendix 1

Sample Material Safety Data Sheet for Triglycidylisocyanurate

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Triglycidylisocyanurate is classified as Hazardous according to the National Occupational Health and Safety Commission's *Approved Criteria for Classifying Hazardous Substances* [NOHSC:1008(1999)].

Company details

Company name	
Address	
State	Postcode
Telephone number	Emergency telephone number
Facsimile number	Telex number

SAMPLE

Identification

Product name	Triglycidylisocyanurate
Other names	1,3,5-Triglycidyl isocyanurate TEPIC, TEPIC-G Araldite PT 810 TGIC
Manufacturer's product code	
UN number	None allocated
Dangerous goods class and subsidiary risk	None allocated
Hazchem code	None allocated
Poisons Schedule number	None allocated
Use	Curing agent used in the manufacture of powder coatings for electrostatic spray painting.

Physical description and properties

Appearance
White granule

Melting point
90 - 125°C

Boiling point
Not available

Vapour pressure
Approx 10^{-6} Pa at 20°C

Density
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 α and β TGIC

SAMPLE

Other properties

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

Auto ignition temperature: > 200°C

Solubility in Organic Solvents: At room temperature, > 10% in dimethyl formamide, dimethyl sulphoxide, pichlorohydrin, tetrachloroethane and acetonitrile.

Ingredients

Chemical Name: 1,3,5-Triglycidyl isocyanurate

Chemical Entity: TGIC, α and β isomers

CAS Number: 2451-62-9

Proportion: 100%

Health hazard information

HEALTH EFFECTS

Acute

Swallowed: No evidence for humans. In animals, TGIC is toxic if swallowed.

Eye: Severe eye effects.

Inhalation: Toxic by inhalation in animals. Will irritate mucous membranes and may cause nose bleeds.

Sensitisation

Skin: Animal and human evidence of sensitisation by skin contact.

Inhalation: Human evidence of sensitisation by inhalation. Susceptible individuals may develop respiratory hypersensitivity reactions including asthma and rhinitis on a single significant skin exposure or may become sensitised on repeated contact.

Chronic

Animal studies indicate that repeated exposure could result in effects in the kidneys, liver, lungs and gastrointestinal tract.

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 and damage genetic material in sperm cells, with no verifiable evidence of effects on male fertility, when exposed to repeated, lower doses. At present there is insufficient carcinogenicity data to establish the carcinogenic potential of TGIC.

SAMPLE

FIRST AID

Inhalation: Remove from exposure to fresh air immediately. Allow patient to assume most comfortable position and keep warm and at rest until fully recovered. Effects may be delayed. If breathing is laboured and patient cyanotic (bluish colouration of skin and mucus membranes) give oxygen. If the victim is not breathing, clear airway and apply artificial respiration. Seek medical advice immediately.

Skin: Remove contaminated clothing. Wash affected area immediately with copious quantities of water and non-abrasive soap (at least 15 minutes). Seek medical attention if irritation develops.

Eye: Irrigate immediately with copious quantities of water or normal saline for at least 15 minutes. Eyelids to be held open. Seek immediate medical attention.

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

Contact a *Poisons Information Centre* for further information.

ADVICE TO DOCTOR

Treatment is symptomatic and supportive.

Precautions for use

EXPOSURE STANDARD

Australian Exposure Standard: 0.08 mg/m^3 TWA, sensitiser

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.

SAMPLE

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 be within the range of 5 – 35°C (41 - 95°F). 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 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

Animal toxicity data:

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 Inhalation: LD_{50} 650 mg/m^3

Environmental data:

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 (28 day Modified Sturm) test.

Limited persistence in the environment.

Further information:

National Industrial Chemicals Notification and Assessment Scheme (1994) Priority Existing Chemical No.1: Triglycidylisocyanurate (TGIC): Full Public Report. Canberra, AGPS.

National Industrial Chemicals Notification and Assessment Scheme (2001) Triglycidylisocyanurate (TGIC): Priority Existing Chemical Secondary Notification Assessment Report No. 1S. Sydney, NICNAS.

SAMPLE

Contact point

Contact name	Telephone number
Position title	
Address	
State Postcode Country	

Appendix 2

RECOMMENDATIONS FOR ATMOSPHERIC MONITORING AND CONTROL OF OCCUPATIONAL EXPOSURE (adapted from the TGIC-1 report)

A2.1 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 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 exposure 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 as 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.

A2.2 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 exposure limit of 0.08 mg/m^3 for TGIC.

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* Attachments 1 and 2 are not reproduced in this appendix – refer to TGIC-1 report.

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 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.

A2.2.1 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 over spray 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;
- implementing 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 Device*s, and used in accordance with AS 1715 1991 -*Selection, Use and Maintenance of Respiratory Protective Device*s;
- 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.

A2.2.2 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 process or leakage will increase worker exposure. Any manual process will also increase worker exposure.

Local exhaust ventilation should be provided when filling the hoppers, when 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, which is described above.

The most likely activities where workers may be exposed are:

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

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