National Industrial Chemicals Notification and Assessment Scheme

Priority Existing Chemical No. 3

Glutaraldehyde

Full Public Report

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Preface

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

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

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

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

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

On publication of the Summary Report in the Chemical Gazette of 7 June 1994, the chemical will no longer be a Priority Existing Chemical in accord with Section 62 of the Act.

Copies of the full public report can be obtained by contacting the Chemical Safety Group .

For the purposes of subsection 78(1) of the Act, copies of full public reports may be inspected by the public at the Library, Plaza level, Alan Woods Building, 25 Constitution Avenue, Canberra, ACT 2600, between 9am and 5pm weekday except on public holidays.

A pamphlet giving further details of the PEC program is available from NOHSC. Contact the Chemicals Assessment Branch at:

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1. Introduction

The chemical glutaraldehyde (CAS No. 111-30-8) was declared by the Minister for Industrial Relations as a priority existing chemical (PEC) under the *Industrial Chemicals* (*Notification and Assessment*) Act 1989 (Cwlth) (the Act) by notice in the *Chemical Gazette* of 2 March 1993.

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

In summary these grounds were that:

- the use of glutaraldehyde in a number of industries in Australia had led to widespread occupational exposure; and

- exposure of workers in Australia to glutaraldehyde had resulted in significant skin, respiratory and eye irritation and, in some cases, skin sensitisation.

In accordance with the Act, importers of glutaraldehyde applied for the assessment of the chemical as a PEC. Information for the assessment was received from importers, end-users, State and Territory governments, other interested persons, and from a comprehensive literature search.

2. Background

2.1 Early use of glutaraldehyde

The early use and synthesis of glutaraldehyde has been summarised by Russell and Hopwood.[1] The first report of the synthesis of glutaraldehyde appeared in 1908, but its first commercial use, as a tanning agent, was not recognised until about 30 years ago. Commercial availability led to other uses, namely as a fixative in electron microscopy, as a cross-linking agent for proteins and enzymes, and then in the early 1960s as a disinfectant for instruments used in the health care industry.[2] Concerns about the health risks associated with the use of formaldehyde in the early 1970s led to a further impetus in glutaraldehyde use.

2.2 Health issues

Following the increasingly widespread use of glutaraldehyde, particularly as a disinfectant, concerns arose about the irritant effects of the chemical. Contact dermatitis and eye and respiratory problems were observed in nurses who were regularly exposed to glutaraldehyde during the disinfection of instruments such as endoscopes and bronchoscopes, and radiologists, who used glutaraldehyde as a fixative in their x-ray developing solutions.

2.3 The Australian perspective

By 1990, glutaraldehyde was used widely in Australia in a number of industries, with an increasing number of workers reporting adverse health effects after exposure to glutaraldehyde, especially in the health care industry.

In response to widespread concern, Worksafe Australia issued a Hazard Alert in October 1991, warning workers and their employers of the health hazards associated with glutaraldehyde use. The two main results from the Hazard Alert were:

- a greater awareness of the hazards of glutaraldehyde, particularly in the health care industry, with immediate improvements in control measures to reduce exposure to glutaraldehyde in the workplace; and
- a decline in the use of glutaraldehyde in some other industries, particularly animal housing.

The Hazard Alert also generated interest in potential alternatives to glutaraldehyde. Unfortunately in some cases, glutaraldehyde was replaced with an unsuitable or more hazardous substitute, for example, formaldehyde.

Glutaraldehyde is not manufactured in Australia, but it is currently imported by a number of companies included in the list of 13 applicants for this assessment (see Chapter 3, Applicants).

2.4 The international perspective

Internationally, some countries, for example, the United Kingdom and New Zealand, have taken action to regulate and/or improve the controls required in the use of glutaraldehyde, particularly in the health care industry.

Glutaraldehyde is listed on Phase 4 of the Organisation for Economic Cooperation and Development (OECD) High Production Volume (HPV) Program for chemicals where there is high risk of exposure to humans or the environment because production volumes are in excess of 1000 te/yr. As Australia is sponsoring glutaraldehyde in the HPV program, this report will be forwarded to the OECD as part of the screening information data set (SIDS) requirements of the program.

No known major international reviews of glutaraldehyde have been conducted.

3. Applicants

AGFA-Gevaert Ltd
372 Whitehorse Road,
Nunawading Vic 3131

BASF Australia Ltd
500 Princes Highway,
Noble Park Vic 3174

Du Pont (Australia) Ltd
168 Walker Street,
North Sydney NSW 2060

Hanimex Pty Ltd
108 Old Pittwater Road,
Brookvale NSW 2100

ICI Australia Operations Pty Ltd
1 Nicholson Street,
Melbourne Vic 3000

Ilford (Australia) Pty Ltd
cnr Ferntree Gully and Foster Road,
Mount Waverley Vic 3149

Johnson and Johnson Medical Pty Ltd
1-5 Khartoum Road,
North Ryde NSW 2113

Kodak (Australasia) Pty Ltd
173 Elizabeth Street,
Coburg Vic 3058

Pfizer Agricare Pty Ltd
38-42 Wharf Road,
West Ryde, NSW 2114

Phoenix Medical Pty Ltd
Unit C, 6 Lyon Park Road,
North Ryde NSW 2113

T R (Chemicals Australia) Pty Ltd
195 Briens Road,
Northmead NSW 2152

Union Carbide Chemicals (Australia) Pty Ltd
Site 1, 1st floor,
1-7 Jordan Street
Gladesville NSW 2111

Whiteley Chemicals Australia Pty Ltd
82-84 Ivy Street,
Chippendale NSW 2008

4. Chemical identity

4.1 Chemical name

Glutaraldehyde is listed on the Australian Inventory of Chemical Substances (AICS) as pentanedial.

The IUPAC name is 1,5-pentanedial.

The Chemical Abstracts Service (CAS) number is 111-30-8.

4.2 Other names

1,3-diformylpropane

Glutaral

Glutardialdehyde

Glutaric dialdehyde 1,5-

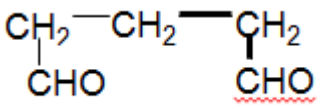
pentanedione

Potentiated Acid Glutaraldehyde

4.3 Molecular and structural formula

The molecular formula is C5H8O2.

The structure is



The molecular weight is 100.11.

4.4 Trade names

Actisan

Aidal, Aidal Plus

Aldecyde 28

Aldespray 15

Aqucar 545

Biomate 733, Biomate 5792

Cidex, Cidex Long-Life

Cronex, Cronex HSD/R

Derugan 2000, Derugan 2020

DSD (Dodge sterilant & disinfectant)

Duraflo RT Developer Replenisher

Formula 936N, Formula 9365N, Formula 9465N

G135 Developer Part C

Germ-Out

Glutaral

l GPC 8

Ilfotec RT Developer Replenisher

Industrex Developer Replenisher

Keymix Glutacide

Microcide

Nalco 7338

Neoquat LA

Parvocide

Piror Slimicide 825

Protectol GDA, Protectol GDA 25%

Protosan

Relugan GT 25, Relugan GT 50

RD III Developer/Replenisher

RP X-Omat Developer/Replenisher

Safeguard

Sepacid GA 50

Sonacide

Ucarcide 125, 225, 250

Ucarsan

Ucar Tanning Agent G50

Uconex 350

Wavicide 01

4.5 Chemical composition

Glutaraldehyde is used mainly as an aqueous solution, ranging in concentration from 50% w/w to less than 1% w/w.

Glutaraldehyde tends to polymerise in solution, with differing proposals advocated for its chemical composition in solution. It has been reported that commercial glutaraldehyde may contain numerous species, including oligomers, unsaturated derivatives and cyclic aldehydes.[1]

Some glutaraldehyde-containing products contain other chemicals, for example, disinfectants activated with sodium bicarbonate and x-ray film developers containing sodium bisulfite.

Glutaraldehyde can be characterised by infra-red spectroscopy, nuclear magnetic resonance spectroscopy and gas chromatography/mass spectroscopy.

5. Physical and chemical properties;

5.1 Physical state

Glutaraldehyde is a colourless oily liquid. In Australia glutaraldehyde is commercially available as a clear aqueous solution at concentrations up to approximately 50% w/w. Commercial samples may have a slightly coloured tint and an odour of rotten apples.

In the vapour state, glutaraldehyde has a pungent odour, with an odour threshold of 0.04 ppm.

5.2 Physical properties

Where information has been available, the physical properties for glutaraldehyde as a pure chemical have been listed below. Where data for some properties was available only for aqueous solutions of glutaraldehyde, for example, vapour pressure, this has been indicated.

Table 1

Physical properties of glutaraldehyde

Property	*50%*	*100%*
Freezing point	-21°C	-14°C
Boiling point	101°C	188°C
Density (water = 1)	1.13	0.72
Vapour density	n.a.	4.1 g/L
Relative density (air = 1)	n.a.	3.4
Vapour pressure (20°C)	2.03 Pa	–
pH	mildly acid	n.a.
Refractive index (at 25°C, 589 nm)	1.421	1.4338
Flash point	n.a.	unknown
Flammability limits	n.a.	unknown

n.a. *Not applicable.*

5.3 Chemical properties

Table 2

Chemical properties of glutaraldehyde

Property	*Description*
Solubility	Soluble in all proportions in water and ethanol; soluble in benzene and ether.
Hydrolysis	Stability decreases with increasing pH.[3] • pH 5, half-life 508 days. • pH 7, half-life 102 days. • pH 9, half-life 46 days.
Partition Coefficient (n-octanol/water)	log P = -0.01[4] (50% solution).
Dissociation constant	Not applicable, as glutaraldehyde is non-ionic and would not be expected to dissociate in water.
Adsorption/ Desorption	The soil mobility of gluaraldehyde was determined[5] in sandy loam, silty clay loam, loamy sand and a sandy sediment, which were equilibrated with glutaraldehyde solutions (0-10 ppm) by shaking for 24 hours. The respective organic content and pH values for each soil are at Table 3. Significant losses due to metabolism were observed during the equilibration, with unchanged glutaraldehyde representing between 62% and 84% of radiolabel, dropping to below 20% in the loamy sand. However, data obtained were well correlated with the Freundlich equation. Derived Freundlich coefficients were normalised for organic carbon content, and indicate organic sorption to, and moderate mobility in, the four soils, grading to weak sorption and high mobility in the sandy sediment (K_{oc} values at Table 3). Desorption coefficients could not be determined because of the instability of glutaraldehyde under the test conditions. Little or no desorption occurred during a 24-hour desorption phase.

Table 3

Adsorption/desorption in soils

Soil type	*% organic carbon*	*pH*	K_{oc}
Sandy loam	1.0	6.8	210
Silty clay loam	1.0	5.7	500
Silt loam	1.4	6.7	340
Loamy sand	0.24	5.8	460
Sandy sediment	0.5	8.1	120

Glutaraldehyde is an aliphatic dialdehyde that undergoes most of the typical aldehyde reactions to form acetals, cyanohydrins, oximes, hydrazones and bisulfite complexes. Glutaraldehyde in solutions is susceptible to aerial oxidation to give the corresponding carboxylic acid.

Glutaraldehyde reacts with proteins by a cross-linking reaction which is mainly between the NH_2 groups, and which depends upon time, pH and temperature. The reaction is less efficient under alkaline conditions.

Glutaraldehyde polymerises in water to a glassy form which regenerates the dialdehyde on vacuum distillation. In solution, glutaraldehyde partially polymerises to oligomers to give a mixture of variable composition. The degree of polymerisation increases with pH and temperature. Above pH 9, polymerisation proceeds comparatively rapidly and solutions eventually lose their sporicidal activity.

When heated to elevated temperatures (> 400°C), glutaraldehyde in aqueous solution will decompose thermally to form carbon oxides and hydrocarbons. In standard thermal stability tests in the laboratory, aqueous glutaraldehyde showed no exothermic decomposition when heated to 340°C.[6]

6. Methods of detection and analysis

6.1 Sampling

All methods of detection and analysis must include reliable sampling procedures.

In the determination of glutaraldehyde in air, sampling is usually carried out by drawing air through an adsorption tube by means of a small pump at a known flow-rate. Sampling can be carried out at a fixed location or on the worker (personal sampling). In personal sampling, air should be drawn through an adsorption tube attached in the breathing zone of the worker. Sampling pumps need to be regularly calibrated to ensure that the flow-rate is constant during the sampling period.

Further guidance on sampling by solid adsorption techniques is available in Australian Standard AS 2986.[7]

In the sampling of aqueous glutaraldehyde solutions, clean dry sampling containers should be used so that cross-contamination is avoided.

6.2 Glutaraldehyde in air

A number of analytical test methods are available for the determination of low levels of glutaraldehyde in the atmosphere. The national exposure standard for glutaraldehyde is 0.2 ppm v/v (peak limitation),[8] so the methods should have detection limits comfortably below that level, for example, 0.05 ppm. Results may be affected by other chemicals in the workplace, for example, alcohols and other aldehydes, so the methods should be designed to avoid interference. Some of the methods used are listed below.

6.2.1 Thermal desorption/gas chromatographic analysis

Air is sampled by pump and drawn through an adsorption tube packed with Tenax-GC. The tube, which also acts as the separation column, is then connected to the gas chromatograph equipped with a flame ionisation detector, with the contents thermally desorbed and separated using temperature programming. The method is quick (approximately 15 minutes), accurate and very sensitive.

6.2.2 OSHA method 64 – High performance liquid chromatographic analysis

Samples are collected (by pump) on 37 mm glass fibre filters treated with 5% dinitrophenyl-hydrazine hydrochloride (DNPH), and then desorbed in acetonitrile. The solution is analysed by injection into an HPLC equipped with an ultra-violet absorption detector. The detection limit for glutaraldehyde is approximately 0.1 µg.

6.2.3 NIOSH method 2531

The United States-based National Institute of Occupational Safety and Health (NIOSH) method 2531 is similar, except that the sample is collected on washed XAD-2 tubes treated with DNPH. The detection limit is approximately 0.3 µg.

6.2.4 Silica gel adsorption/gas chromatographic analysis

Samples are collected by pump on adsorption tubes filled with silica gel and then desorbed with acetone. The resulting solution is injected into a gas chromatograph equipped with flame ionisation detection. For a 30 litre air sample, the detection limit for glutaraldehyde is 0.02 ppm. The method is suitable for 15-minute exposures.

6.2.5 Alumina adsorption/gas chromatographic analysis

Samples are collected by pump on adsorption tubes filled with alumina and then desorbed with a phosphate buffer solution. The resulting solution is injected into a gas chromatograph equipped with a Tenax-GC column and a flame ionisation detector.

6.2.6 Colorimetric determination using MBTH

As glutaraldehyde is readily soluble in water, air can be drawn through impingers containing distilled water, for example, by means of a reciprocating air pump operating at flow rates up to 1 L/min. Glutaraldehyde absorbed in the water is then determined by colorimetric analysis with 3-methyl-2-benzothiazolinone hydrazone (MBTH) solution (see section 6.3). The method is sensitive and quick, but other aldehydes and ketones may interfere.

6.2.7 Direct-reading instruments

From information received during the assessment, only one direct-reading instrument is commercially available for the monitoring of glutaraldehyde in air. The Lion Glutaraldemeter* has a fuel cell sensor which enables glutaraldehyde to undergo catalytic oxidation to produce an electrical response proportional to the quantity of glutaraldehyde in air. The detection range is 0.05 to 5 ppm v/v. The instrument is simple and convenient to use, but readings are subject to interference from compounds such as alcohols and other aldehydes. Regular calibration of the instrument is essential. Monitoring with the Glutaraldemeter should therefore be carried out by trained personnel and with regular verification by more specific analytical procedures such as those listed above.

In a study which compared Glutaraldemeter results with those obtained using OSHA method 64 (see above),[9*] it was recommended that the meter not be used in x-ray film processing establishments, due to the presence of interfering chemicals, and that it be used with caution in disinfection units, especially if alcohols or other aldehydes are present.

6.3 Glutaraldehyde in aqueous solution

It has been reported that the purity of glutaraldehyde solutions can be determined by measuring the ratio of the ultra-violet absorbances at 235 nm and 280 nm.[10]

The standard method for the determination of glutaraldehyde in aqueous solutions at high concentrations, for example, 10% to 50% w/w, is titration with 0.5N hydroxylamine hydrochloride. A potentiometric titration method is available.

* Comments in this report on commercial equipment do not constitute an endorsement by Worksafe Australia

A number of analytical test methods are available for the determination of low levels of glutaraldehyde in water, for example, below 5000 ppm w/v. Some of these are listed below.

6.3.1 Colorimetric determination using MBTH

The water sample is added to a solution of MBTH and the absorbance measured at 605 or 610 nm. Possible interference by ketones and other aldehydes is overcome by sampling water before the addition of glutaraldehyde to the system. The method is suitable for 0.5 to 10 ppm w/v glutaraldehyde in water and can be used in the field.

6.3.2 Titration after reaction with sodium bisulfite

Glutaraldehyde in water is determined by reaction of the carbonyl groups with sodium bisulfite and then titration of hydroxyl ions with standardised sulfuric acid. The range of the method is 25 to 5000 ppm w/v, but ketones and other aldehydes interfere, and a correction is needed for acids and bases in the sample.

6.3.3 Gas chromatographic analysis

The water sample is injected into a gas chromatograph equipped with a Tenax-GC or Porapak PS column and a flame ionisation detector. The range of the method is 1 to 2500 ppm w/v.

7. Uses

7.1 Introduction

Glutaraldehyde has a wide variety of uses throughout the world with its use spread over a number of different industries. It is used primarily as a biocide but it also has wide use as a fixative, and some use as a therapeutic agent. In Australia, glutaraldehyde is similarly used in a number of different industries. The main uses of glutaraldehyde in Australia are:

- as a cold disinfectant in the health care industry;
- as a hardener in x-ray film processing;
- in tanning as a fixative;
- as a biocide in water treatment;
- in animal housing for disinfection;
- as a preservative in industrial oils;
- as a biocide in sanitary solutions for aircraft and portable toilets;
- in small quantities as a disinfectant for air ducts;
- as a tissue fixative in electron and light microscopy and in histochemistry;
- as a biocide in aquaculture;
- in small quantities as an embalming agent; and
- as a therapeutic agent.

Table 4

Estimated distribution of glutaraldehyde in end-use products in Australia

Use	*Percentage**
Cold disinfectant	55%
X-ray film processing	20%
Animal housing	5%
Water treatment	10%
Tanning	5%
Preservative/general biocide and other uses	5%

* Approximate.

Glutaraldehyde has been reported to be used overseas as:

- an intermediate in the production of pharmaceuticals, pesticides and crop protection agents;
- as a water-resistant in the manufacture of wallpaper and paper towelling;
- as a cross-linking agent for microencapsulation; and
- as a preservative in cosmetics.

These uses have not been reported in Australia.

7.2 Cold disinfectant

Aqueous glutaraldehyde solutions are used throughout the health care industry in Australia to disinfect instruments such as endoscopes, surgical instruments and dental equipment. For proper effect, the solutions are made alkaline, for example, with sodium bicarbonate at approximately 0.3% w/v. Normally the 1% or 2% solutions are used, although in recent years the trend throughout the industry has been towards the 1% solution, due to the increased occupational hazard associated with higher concentrations of glutaraldehyde.

Disinfection is usually carried out by soaking the instruments in glutaraldehyde solution for a fixed period, and then rinsing the equipment with clean water.

The advantages of buffered glutaraldehyde as a disinfectant are:

- its broad spectrum of activity;
- its rapid microbiocidal action; and
- its non-corrosivity (at lower concentrations) to most materials, including metals, rubbers and lenses.

The main disadvantages are its adverse health effects and its irritating odour.

7.3 X-ray film processing

Glutaraldehyde is incorporated into developing solutions for black-and-white x-ray photography as a hardening (or cross-linking) agent to shorten the drying cycle in film processing. The developers containing glutaraldehyde are generally used in high temperature, automated film processing, mainly in the medical x-ray processing field and, to a lesser extent, in engineering applications such as the non-destructive testing of welds.

X-ray developers are usually supplied as a concentrate containing up to 50% w/w glutaraldehyde, and are diluted to working solutions containing glutaraldehyde at less than 2%.

7.4 Tanning

Aqueous solutions of glutaraldehyde are used to soften leathers and to improve their resistance to water, alkalis and mould. Depending on the type of leather or pelt to be treated, an amount of 25% or 50% w/w glutaraldehyde solution is added to a mixing vessel to soak the leathers, giving a final concentration of approximately 0.5 to 2% in the mixing vessel.

Tanning with glutaraldehyde can be achieved over a wide pH range, but the amount of glutaraldehyde bound by collagen and the rate of fixation increase with pH. Glutaraldehyde is bound irreversibly to the collagen molecule and severe acid hydrolysis is required to release it by the breaking of peptide bonds within the collagen rather than the actual glutaraldehyde binding site.[1]

7.5 Water treatment;

Aqueous glutaraldehyde solutions at 45-50% w/w are used as microbiocides for the treatment of water in evaporative recirculating cooling towers such as those in industry, shopping malls and large air-conditioned commercial buildings. The glutaraldehyde solutions are also used in air washers and brewery pasteurisers. In some cases, glutaraldehyde is fed to the water treatment system in a more dilute form, for example, at less than 10%.

Glutaraldehyde helps to control the slime and algae deposits which tend to cause fouling of cooling equipment, adverse health effects, metal corrosion and poor heat transfer.

Microbiocides are usually administered in slugs as shock kill doses for maximum effect. This can be done manually or by the use of automatic dosing equipment. The final concentration of glutaraldehyde in cooling tower water after dosing is approximately 50 to 100 ppm w/v.

7.6 Animal housing

Aqueous glutaraldehyde solutions are used to disinfect animal and bird houses such as pig and poultry sheds, aviaries, hatcheries, kennels, catteries, stables and veterinary hospitals.

Dilute solutions at approximately 0.1 to 0.3% w/v glutaraldehyde are sprayed, washed or foamed onto the walls, floors and other surfaces to clean and disinfect. In the fogging of sheds, usually with automatic or semi-automatic equipment, a more dilute solution of approximately 400 ppm is used.

Glutaraldehyde solutions at approximately 750 ppm are also used to sanitise egg shells to assist in the removal of dirt and debris. Sanitising is followed by rinsing with clean water.

7.7 Preservative/biocide

Glutaraldehyde is used as a preservative or general biocide in a number of applications.

In Australia it is used as a 5% w/v aqueous solution as a biocidal additive in conveyor chain lubricants. The solution is fed continuously from a 25 L container to the lubricant via an automatic feed system.

Glutaraldehyde is also used as a 2% w/v disinfectant in sanitary solutions used in aircraft and portable toilet systems.

It is also used as a disinfectant for air ducts. A 2% w/v solution can be sprayed or fogged directly into the air ducts; if the level of contamination in the duct is low, the solution can be diluted to approximately 0.2%. After application, the ventilating system is run at maximum flow rates to disperse the solution. The solution may also be mixed with a sealing solution before spraying or fogging, but this procedure is not recommended in heavily contaminated ductwork.

7.8 Dentistry

Glutaraldehyde is used in dentistry as a disinfectant for dental instruments as a 1% or 2% solution. It has also been used therapeutically in dentistry as a pulpotomy medicament and in dentin bonding.

In Australia, the use of glutaraldehyde in dentistry has been gradually reduced in recent years, to the extent that in some regions it is not used at all, for example, the South Australian Dental Service has reported that they discontinued use in 1992.

7.9 Electron and light microscopy

Glutaraldehyde is used in electron and light microscopy and in histology as a tissue fixative, generally as a 3% to 6% aqueous solution. Glutaraldehyde is an effective cross-linking agent for proteins and polyhydroxy compounds. Experiments showed that tissues fixed in glutaraldehyde had excellent morphological preservation, superior to that obtained with formaldehyde, since swelling and disruption were regularly absent. Glutaraldehyde gave the best general preservation of cellular fine structure.

7.10 Aquaculture

Glutaraldehyde is used, generally in conjunction with wetting agents, to control viruses and other micro-organisms in the aquaculture industry in some States.[11] Farming of finfish rather than crustacea consumes most of the chemicals used in aquaculture.

7.11 Therapeutic agent

Glutaraldehyde has been used as a therapeutic agent as following:

- the topical treatment of hyperhidrosis (sweating);
- the topical treatment of onychomycosis (fungal nail infection);
- in friction blister prevention in soldiers, athletes and ballet dancers; and
- in dentistry, for example, in pulpotomy and dentin bonding.

7.12 Other uses

A 2% aqueous solution of glutaraldehyde has been used in embalming, but it is believed that usage for this purpose is low in Australia.

In overseas countries, glutaraldehyde has been used as a preservative in cosmetics, for example, in hair conditioners, but there was no evidence during the assessment period of any such application in Australia.

8. Import and production

8.1 Importation

Glutaraldehyde as a pure chemical is not manufactured in Australia, nor are there any known plans for manufacture over the next five years. It is imported into the country by a number of companies (among the applicants in this assessment), mostly as a 25%, 45% or 50% w/w aqueous solution, but also as end-use products such as x-ray developers, tanning solutions and low concentration (1% or 2%) disinfecting solutions.

The total volume of glutaraldehyde imported into Australia per year has been in excess of 100 tonnes in recent years (for concentrations 12-50% w/w).

8.2 Production

Glutaraldehyde end-use products in Australia are manufactured by dilution of a glutaraldehyde concentrate, usually provided as a 25%, 45% or 50% w/w aqueous solution in 200 litre drums.

Concentrate is pumped, generally via a closed system, into a large mixing vessel, for example, 2000 litre capacity, for blending of the ingredients in the end-use product. Water is added during mixing and, in some cases, at the completion of the process to achieve the required concentration of glutaraldehyde. The blended material may be either pumped to a holding tank for intermediate storage and/or final blending or it may be packed directly into containers for end-use. Quality control samples are taken for analysis from the mixing vessels or holding tanks.

In general, blending is carried out in a closed system. However, in some cases mixing is carried out by the direct emptying of 200 litre drum contents into a mixing tank, followed by blending with water and other ingredients to give the end-use product. Rather than being a closed system, the mixing process may be carried out using local exhaust ventilation.

In some cases a simple repacking of glutaraldehyde concentrate is carried out, for example, into an end-user's labelled container or into equipment suitable for end-use, for example, a feeding system in water treatment.

9. Kinetics and metabolism

9.1 Absorption and disposition

9.1.1 Material balance study[12]

A material balance study was carried out in male and female Fischer 344 rats and New Zealand White rabbits by the intravenous injection and dermal application of aqueous ^{14}C-glutaraldehyde solutions. The following doses were administered:

Table 5
Material balance study– doses used

Test	*volume (mL)*	*% glutaraldehyde*
Rat		
intravenous	0.2	0.075, 0.75
dermal	0.2	0.075, 0.75, 7.5
Rabbit		
intravenous	2.5	0.075, 0.75
dermal	2.5	0.75, 7.5

In the dermal studies, glutaraldehyde was kept in contact with the skin under an occlusive dressing for 24 hours.

For both routes of administration, the animals were sacrificed after 24 hours and the tissues and carcasses examined for radioactivity.

The results from intravenous injection showed that exhaled CO2 was the major metabolite in both species (rat 65-80%, rabbit 30-70%), with approximately 80% of it collected over the first four hours. CO_2 excretion was proportionally less at the higher dose, especially in rabbits. Recovery measurements were also made in urine (approx. 10% of administered dose for the rat, 20% for the rabbit), faeces (4%, <1%), tissues (5%, 8%) and carcass (7%, 25%), with higher absorption at the higher concentration for both the rat and rabbit.

The dermal studies resulted in much lower CO_2 excretion (rat 1-2% of administered dose, rabbit 5-15%). There was a much higher recovery on the skin, especially for the rat, where only approximately 5% of the applied dose was absorbed. In the rabbit, approximately 30-50% was absorbed, with 20-30% recovered in the carcass. For the dermal studies in rats, the total recovery ranged from 61 to 75% of the administered dose, whereas for the studies in rabbits, the recovery ranged from 71-100%.

There were no significant differences in the results between corresponding male and female animals in the study.

9.1.2 Pharmacokinetic studies[12]

Pharmacokinetic investigations were also carried out on rats and rabbits using the same doses and routes of administration as those used in the material balance study (see section 9.1.1). Blood was sampled at various intervals between one minute and 24 hours, with results showing that the dermal absorption rate was low (absorption rate constants 0.2-2hr) in both species. The terminal half-lives ($t_{0.5}$) for elimination were long for both intravenous injection (rat 10hr, rabbit 15-30 hr) and dermal application (rat 40-110hr, rabbit 20-100hr), possibly due to the binding of glutaraldehyde to protein and the slow excretion of metabolites.

9.1.3 Other studies

The absorption of glutaraldehyde in a number of species has been reported in the literature. *In vitro* studies using human skin tissue[13] showed that glutaraldehyde did not penetrate the thick skin tissue of the sole, but 3-14% penetrated the stratum corneum of the chest and abdomen and 3-4% penetrated the epidermis. In a more recent study, < 1% of applied glutaraldehyde penetrated the skin of humans, rats, mice, rabbits and guineapigs.[10]

9.2 Metabolism

In the material balance and pharmacokinetic studies described above, the metabolites were not identified. However the report[12] proposed that the metabolism of glutaraldehyde probably involved initial oxidation to the corresponding carboxylic acids by aldehyde dehydrogenase, and then further oxidation via an acidic intermediate to CO_2.

The glutaric acid formed by oxidation is probably metabolised by synthesis of a Coenzyme A thioester to give glutaryl CoA, which is then oxidised by glutaryl CoA dehydrogenase to give glutaconyl CoA, leading to eventual degradation to acetate and then to CO_2.[10,14]

9.3 Reactivity

9.3.1 Reaction with proteins

Glutaraldehyde reacts readily with proteins as a cross-linking agent, the reaction being rapid and pH-dependent (rate increases at pH > 9). Glutaraldehyde initially reacts with amino acids to give Schiff bases with reactive amino groups. Further reaction occurs to give a number of complex reaction products, with the mechanism of the cross-linking process not yet fully understood.[1,10]

9.3.2 Reaction with DNA

Little information is available on the interaction between glutaraldehyde and DNA. It has been reported[15] that glutaraldehyde only reacts with DNA at >60°C. It has also been reported[10] that only some components of DNA react with glutaraldehyde.

9.4 Summary

The results of the material balance and pharmacokinetic studies with solutions of glutaraldehyde up to 7.5% showed that prolonged skin contact can lead to absorption via the skin. This is supported by the results of in vitro testing with human skin tissue.

The pharmacokinetic studies indicated that the dermal absorption rates were low and that the elimination times of absorbed glutaraldehyde were long. The material balance studies did not identify any specific target site for distribution.

Glutaraldehyde is metabolised principally to CO_2 via oxidation to glutaric acid, but the mechanism for complete metabolism and the identification of all metabolites is yet to be determined.

As a cross-linking agent, glutaraldehyde reacts readily with proteins, with a number of complex reaction products formed by a mechanism not yet fully understood.

10. Effects on experimental animals and in vitro test systems

10.1 Acute toxicity

10.1.1 Oral

Acute oral toxicity in the rat[16]

The oral LD_{50} for UCARCIDE Antimicrobial 250 (50% w/w glutaraldehyde) in the rat was determined using groups of five male and five female Sprague-Dawley albino rats. The procedure was based on the United States Environmental Protection Agency's (US EPA) guidelines 40 CFR parts 158 and 798.

In preliminary testing with groups of two male and three female rats, all five animals at 200 and 100 mg (glutaraldehyde)/kg body weight died, and all at 50, 25 and 12.5 mg/kg survived.

In the definitive study, groups of five males were administered by gavage 50, 100, or 200 mg (glutaraldehyde)/kg body weight, with all five at 200 mg/kg dying on the first day, and one at 100 mg/kg on the second day. Groups of five female rats were administered 50, 70 or 100 mg/kg, with two in the high-dose group dying on the first day, and two on the second day. At 70 mg/kg, two females died on the first day. Necropsy findings on those that died included damage and discolouration of the lungs, stomach and intestines, with two of the females also suffering kidney damage.

Signs of toxicity during the study included sluggishness, lacrimation, diarrhoea and encrustation around the nose. All survivors recovered within four to five days of dosing, and were then sacrificed after 14 days, with no significant gross lesions detected.

Under the conditions of the study, the oral LD_{50} results for Antimicrobial 250 (50% glutaraldehyde) were:

- male: 246 mg/kg body weight (95% confidence limits 179-339), or 123 mg glutaraldehyde/kg;
- female: 154 mg/kg (116-206), or 77 mg glutaraldehyde/kg; and
- combined male and female: 200 mg/kg (157-255).

LD_{50} at various concentrations[12]

In a separate study in male and female rats with various strengths of solution, the results are listed in Table 6. The full report of this study was not available for assessment.

Table 6
Oral LD_{50} at various concentrations

		LD_{50}		
Conc. (% w/w)	*Sex*	*(mL soln/kg)*	*(mg soln/kg)*	*(mg gluta/kg)*
50	male	1.3	1466	733
45	male	1.2	1344	605
25	male	1.9	1988	497
	male	1.5	1636	409
15	male	1.2	1220	183
	female	0.9	913	137
10	male	1.6	1680	168
	female	1.1	1110	111
5	male	3.3	3300	165
	female	1.3	1320	66
1	male	12.3	12300	123
	female	9.9	9900	99
0.5	male	>16	>32000	>160
	female	>16	>32000	>160

Conc. Concentration used in test.

The results in the table above show that the LD*50*s for glutaraldehyde in the range 5-50% are similar, leading to relatively larger amounts of glutaraldehyde being required to produce mortality at the higher concentrations. This is contrary to what is expected.

Findings on necropsy of the animals that died included congestion and distension of the stomach and intestines, haemorrhage and congestion of the lungs, and congestion of the liver, spleen, kidneys and adrenals. Signs of toxicity in the tests included piloerection, sluggishness, rapid breathing, diarrhoea and encrustation around the eyes and nose. The surviving animals usually recovered within five days. Some of the animals sacrificed after the 14-day observation period showed a mild thickening of the stomach wall, but there were no other gross pathological findings. The findings were consistent with those of the study described in section 10.1.1, Acute oral toxicity in the rat.

Other studies

A number of other acute oral toxicity studies in various species have been carried out, with LD_{50}s listed in Table 7.

Table 7
Other oral LD_{50}s

				LD_{50}	
Species	*Sex*	*Reference no.*	*% Gluta. tested*	*mg soln/kg*	*mg gluta./kg*
Rat					
		17	n.r.	–	134-820
	male	18	n.r.	–	134
	female	18	n.r.	–	165
	male	18	2%	4800	96
	female	18	2%	5650	113
	male	19	10%	1530	153
	female	19	10%	1680	168
	male	20	1%	10000	100
	female	20	1%	10000	100
Mouse					
		17	n.r.		100-352
	male	18	n.r.	–	100
	female	18	n.r.	–	110
	male	18	2%	6100	122
	female	18	2%	10450	209
Guinea pig					
		17	n.r.	–	50

n.r. *Not reported.*

The results are similar to those reported in the rat studies in the previous two sections, with similar signs of toxicity observed.

10.1.2 Dermal

Acute dermal toxicity at various concentrations[12]

In a study in rabbits summarised by Ballantyne, with various strengths of aqueous solution, the results were as follows:

Table 8
Dermal LD_{50} at Various Concentrations

Conc. (% w/w)	Sex	LD_{50} (mL soln/kg)	LD_{50} (mg soln/kg)	LD_{50} (mg gluta/kg)
50	male	2.5	2860	1430
	male	1.6	1800	900
45	male	2.0	2200	1000
	female	2.7	3020	1360
25	male	12.8	12170	3045
	male	8.0	8520	2130
15	male	no deaths at 16 mL/kg		
	female	1 death at 16 mL/kg		

conc. Concentration used in test.

There were no deaths with 16 mL/kg of 10% and 5% solutions. The tests indicated that the acute percutaneous toxicity was influenced more by the concentration of glutaraldehyde than the amount of glutaraldehyde applied. At necropsy, the only consistent pathological findings were congestion of the liver, lungs, kidney and spleen.

The full report of the study was not available for assessment.

Other studies

A number of other acute dermal toxicity studies in various species have been carried out, with LD_{50}s in Table 9 below.

Table 9

Dermal LD_{50} of glutaraldehyde

Species	*LD_{50} (mg/kg)*	*Reference no.*
Rabbit	640-2000	17
Rat	> 2500	17
Mouse	> 4500	17

In a study[21] carried out with a 10% glutaraldehyde solution, 2 mL/kg body weight (equivalent to 200 mg glutaraldehyde /kg body weight) was applied to the intact and abraded skin of albino rabbits. There were no deaths, so the LD_{50} could not be calculated.

In a similar study[21] with a 1% solution, 2 mL/kg body weight (equivalent to 20 mg glutaraldehyde /kg body weight) was applied. Again there were no deaths, so the LD_{50} could not be calculated.

10.1.3 Inhalation

Four-hour LC_{50} inhalation study on rats[22]

A dynamic inhalation study was conducted to determine the acute toxic effects in rats and to derive a four-hour LC_{50} value. The protocol conformed with the requirements of OECD Test Guideline 403 and the study complied with the standards of Good Laboratory Practice.

In the study, groups of six male and six female Fischer 344 rats were exposed to glutaraldehyde vapour concentrations of 10.6, 23.0 or 42.7 ppm v/v. A similar group of controls was exposed to room air only. The vapour was generated by metering a 5% glutaraldehyde solution into a rotating evaporator tube, where hot air (65°C) was exhausted into the inhalation chamber. The vapour concentrations were regulated by adjusting the sample liquid flow-rate or the air exhaust flow-rate.

Mortality during the study was as follows:

Male

- 42.7 ppm
  One during exposure, two on day 1 after exposure, two on day 2, one on day 3.
- 23.0 ppm
  Two on day 1.

Female

- 42.7 ppm
  Two on day 1, one on day 3.
- 23.0 ppm
  One on day 1, one on day 7.

There were no deaths in control animals or those exposed to 10.6 ppm.

Clinical observations during the four-hour exposure and immediately afterwards included excess lacrimation and salivation, audible and mouth breathing, and wetness and encrustation around the eyes. Wetness and encrustation around the nose and mouth were observed in the animals exposed to the two higher doses. A slow righting reflex was observed during exposure in one male and one female rat exposed to 42.7 ppm, and decreased motor activity was observed during the 14-day post-exposure period in all surviving animals in the 23.0 and 42.7 ppm groups. During exposure, body weights and food and water consumption were reduced compared with the control group. All symptoms decreased or disappeared during days 8-14 of the post-exposure period.

The cause of death was apparently lung damage. Breathing difficulties were observed in most animals during exposure, and at necropsy, colour changes of the lungs were noted in the male and female rats exposed to 42.7 and 23.0 ppm. No gross lesions of the nasal

cavity, larynx or trachea were observed at necropsy.

Under the conditions of the study, a four-hour LC_{50} of 23.5 ppm v/v (96 mg/L) resulted for the male rats (with 95% confidence limits 16.8-32.8 ppm), and 40.1 ppm (164 mg/L) for the females (confidence limits 15.2-105.8 ppm). This high toxicity of glutaraldehyde was attributed partly to the presence of more toxic higher molecular weight species formed during vapour generation, but no supporting evidence has been submitted to substantiate this claim.

Static and dynamic acute vapour inhalation toxicity study in rats[23]

A recent static and dynamic inhalation study was conducted with UCARCIDE Antimicrobial 250 (an approximately 50% w/v aqueous glutaraldehyde solution) to determine the acute toxic effects of glutaraldehyde in rats after a four-hour exposure to the 'maximum' vapour concentrations achievable at ambient temperature. Groups of five male and five female Sprague-Dawley albino rats were used in the study. The method was similar to the limit test in OECD Test Guideline 403 except for the recommended seven-hour exposure period. The study met the generally accepted standards of Good Laboratory Practice.

In the static study, the animals were exposed to a mean vapour concentration of 3 ppm, ranging from a peak of 6.6 ppm to less than the detection limit (2 ppm). The vapour was generated by placing an open tray of the 50% glutaraldehyde solution above the animals in the inhalation chamber. No deaths resulted, but eye irritation was observed. No gross lesions were noted at necropsy after 14 days.

In the dynamic study, two tests were carried out, one at a mean glutaraldehyde vapour concentration of 16.3 ppm (range 10-24 ppm during exposure) and the other at 14.5 ppm (range 12-17 ppm). The vapour was generated by passing compressed air at ambient temperature through a bubbler containing the 50% glutaraldehyde solution. No deaths resulted and the symptoms included those observed in the static test plus wetness and encrustation around the nose and the eyes. No gross lesions were noted at necropsy after 14 days.

Under the conditions of the study, no mortality resulted from exposure to the glutaraldehyde vapours generated statically and dynamically. However the 'maximum' ambient concentrations achieved in this study are inconsistent with those obtained in other similar studies (see below), and the considerable variation in concentration during the tests raised doubts about the reliability of the vapour generation process.

Other studies summarised by Ballantyne[12,24]

In addition to the above two studies, the results of a number of other acute inhalational studies were reported (in summary form) for rats exposed to glutaraldehyde vapour generated from various strengths of solution.

In the early studies between 1961 and 1977,[24] groups of six rats were exposed for eight hours to atmospheres saturated with vapour generated either statically or dynamically from glutaraldehyde solutions, but no measurements of the glutaraldehyde vapour concentration were made. No animals died during the studies and no signs of toxicity were reported.

The results of other later acute inhalational studies are in Table 10.

Table 10

Other Acute Inhalational Studies summarised by Ballantyne

Study type	*Rats*	*Hours*	*Soln (%)*	*Gluta. vapour (ppm)*	*Ref*	*Results*
Static	6f	6	50	4 or 48*	24,25	No deaths
						Eye, respiratory irritation
Static	6f	6	50	5	12,24	No deaths
				(2-11)		Eye,respiratory irritation
Dynamic	5m,5f	4	14.5	8	24	No deaths
						Eye irritation
Dynamic	5m,5f	4	43.6	22	24	No deaths
						Eye, respiratory irritation
						Increased motor activity

Gluta. Glutaraldehyde.
* Disagreement between two sets of analyses.

In the dynamic studies tabled above, the vapour was generated at room temperature by the bubbler method.

Other studies

A study[18] in rats and mice exposed to approximately 20 ppm v/v (82 mg/L) glutaraldehyde resulted in the following exposure times required to produce death in half the animals.

Table 11

50% mortality exposure times (minutes)

Animal	*Male*	*Female*
Rats	60	86
Mice	51	94

Marked hyperaemia was observed in the lungs of both rats and mice. During the study, observations included sluggishness, breathing rate increase, changes in grooming behaviour, and drooping of the eyelids, with nose bleeding in the rats only. The glutaraldehyde vapour for the study was generated by drawing glutaraldehyde solution into an ultrasonic nebuliser, the resultant vapour passing into the animal chamber.

Other values for the rat LC_{50} of glutaraldehyde are in Table 12.

Table 12

Other LC_{50}s for glutaraldehyde

			LC_{50}	
Conc.	*Exposure time (h)*	*Reference no.*	*(mg soln/L)*	*(mg gluta/L)*
–	4	26	–	0.48
–	4	27	–	20.5
–	8	28	–	12.6
1	1	20	>31.7	0.32
10	1	19	>6.67	0.67

A study[29] in mice exposed to 133 mg/L glutaraldehyde vapour for 24 hours resulted in toxic hepatitis.

In a study by St Clair[30], the acute toxicity of glutaraldehyde to the nasal epithelium of male Fischer 344 rats was determined by instilling 40 mL of 10, 20 and 40 mM glutaraldehyde into a nostril. The minimum dose to induce nasal lesions was 20 mM, with severe lesions at 40 mM. In the study, glutaraldehyde was shown to be approximately 10 times more toxic to the nasal epithelium of rats than equivalent doses of formaldehyde.

10.1.4 Evaluation

From information available from the one study submitted during the assessment period and from values quoted in the scientific literature, the oral LD_{50} in the rat for glutaraldehyde is in the range 77-820 mg/kg body weight. A number of measurements have been carried out with various concentrations of glutaraldehyde from 1-50%. In the only oral LD_{50} study submitted,[16] the values for a 50% glutaraldehyde solution for male and female rats respectively were 246 mg/kg body weight (95% confidence limits 179-339) and 154 mg/kg (116-206), whereas the value reported from an earlier study[12] was much higher at 1466 mg/kg. The LD_{50} values in the latter study were comparatively higher for the higher concentrations (25%, 45% and 50%); as the study was not submitted for assessment, no evaluation of this finding is possible. At 0.5%, no signs of toxicity were observed by the oral route.

No full studies on the acute dermal toxicity of glutaraldehyde were made available for assessment. However, data from summaries indicated that the LD_{50} for glutaraldehyde by this route is above 1000 mg/kg. Aqueous solutions of 10% showed no signs of acute toxicity by skin contact, but the results for 45% and 50% aqueous solutions indicated that skin absorption can occur at these higher concentrations. Material balance studies on the rat and rabbit support this finding. Findings on the animals that died consisted of congestion of the lungs, liver, kidneys and spleen.

Many of the acute inhalational studies were carried out at low vapour concentrations which were too low to produce mortality, resulting in mainly irritant effects being observed in the test animals. From the results of the studies that produced mortality, glutaraldehyde has a high acute inhalational toxicity, with lung damage observed in rats and mice that died after exposure to 20 ppm (82 µg/L) for 1-1.5 hours. However, the results of the only complete study available, which allowed calculation of four-hour LC_{50}s of 23.5 (96 µg/L) and 40.1 ppm (164 µg/L) for male and female rats respectively,

are clouded by the method of vapour generation, which was carried out at an elevated temperature (65°C). It was claimed that more toxic oligomers of glutaraldehyde may have led to the high acute toxicity, but this has not been substantiated.

Other LC_{50}s have been reported in the literature, ranging from 0.48 mg/L/4h-20.5 mg/L/4h, but no experimental details were available.

The method of vapour generation is critical in inhalational studies and, for glutaraldehyde, a number of different techniques have been used. Glutaraldehyde has a low volatility, and difficulty has been experienced in achieving vapour concentrations that will result in mortality. Consequently, in early studies such as the LC_{50} study above, the glutaraldehyde solution was heated to generate sufficient vapour to produce mortality. In later studies, air was bubbled through an aqueous solution at ambient temperature, but with a second bubbler in parallel to generate the higher vapour concentrations (see section 10.2.3, Respiratory irritancy in mice). These later studies have demonstrated that it is possible to generate glutaraldehyde vapours of significant concentration at ambient temperature. In light of the uncertainty generated by the studies at elevated temperatures, simultaneous LC_{50} studies at both ambient and elevated temperatures have been planned by one manufacturer.[31] Detailed vapour generation studies at various temperatures are also required to improve the correlation between solution and vapour concentrations.

In a limit test carried out under the 'maximum' glutaraldehyde vapour concentrations which could be derived statically (3 ppm v/v) and dynamically (14-16 ppm) from a 50% glutaraldehyde solution at ambient temperature, no mortality resulted. However, the vapour concentrations achieved were low and inconsistent with those in other tests, for example, 22 ppm was generated in a dynamic study using a 43.6% glutaraldehyde solution.

Many of the acute inhalational toxicity studies did not produce systemic toxicity, but the results showed that exposure of the test animals to glutaraldehyde vapours at low concentrations leads to irritant effects such as laboured and audible breathing and wetness and encrustation around the nose and eyes. In the studies resulting in mortality, congestion of the lungs, kidneys and adrenals was observed.

10.2 Irritation

10.2.1 Skin irritation

A series of skin irritation tests[32] was conducted on New Zealand White rabbits with aqueous glutaraldehyde solutions ranging in concentration between 1% and 50% w/w. The procedure was in accordance with OECD method TG 404.[33]

In each test, the shaven skins of three male and three female rabbits were treated with 0.5 mL glutaraldehyde solution, which was kept in contact with the skin for four hours with an occlusive dressing. Skin reaction was measured using the Draize scoring system at intervals from one hour to three days, with sites examined at intervals up to 21 days. The results are at Table 13.

Other earlier studies[19,20,21] in New Zealand White rabbits were carried out with 1% and 10% Sterisol (1% and 10% aqueous glutaraldehyde) in accordance with standard USA protocols. In each test, 0.5 mL solution was applied under a gauze patch to the intact skin and an abraded skin area of six animals for an exposure time of 24 hours. The results are recorded at Table 13.

Table 13

Skin irritation at various concentrations

Conc.	*Ref.*	*Result*
50%	32	Moderate to severe erythema, slight to severe oedema, many spots of necrosis.
45%	32	Moderate to severe erythema, slight to severe oedema and spots of necrosis, with minor erythema, desquamation and scabs persisting through the 21 days.
25%	32	Moderate erythema, slight oedema, scattered necrosis.
10%	32	Moderate erythema, slight oedema, necrosis on approximately half the animals. In the first test, one (of six) rabbits had erythema and three had desquamation after 21 days. In the second test, the six rabbits were sacrificed after two days, with microscopic examination revealing mild necrosis and dermatitis on all animals.
10%	21	Exposure time 24 hours — moderate to severe erythema at both sites for all animals, with erythema still well-defined after 72 hours. Moderate oedema in all animals at 24 hours, with oedema slight after 72 hours.
10%	19	Exposure time 24 hours — very slight spotted necrosis at three intact and five abraded sites.
5%	32	Slight erythema, very slight oedema, spots of necrosis on one rabbit (of six) in each of two tests. Microscopic examination of the animals in the second test revealed mild necrosis and dermatitis (on two of six).
2%	32	Very slight erythema, very slight oedema on two of 12 animals, signs of necrosis (poorly-defined) on one rabbit. Microscopic examination in one of the two tests revealed mild necrosis and dermatitis in two (of six) animals.
1%	32	No significant effects.
1%	20	Exposure time 24 hours — very slight to well-defined erythema at five intact and six abraded sites. After 72 hours, very slight erythema at four intact and abraded sites. Very slight to slight oedema at four intact and abraded sites after 24 hours, with no oedema at 72 hours.
1%	21	Exposure time 24 hours — erythema well-defined at 24 hours and very slight after 72 hours. Oedema slight at 24 hours and very slight after 72 hours.

Conc. Concentration used in test.
Ref. Reference number.

Yellow-brown staining was reported at the site of application in all the four-hour tests,[32] being severe for all concentrations except 1% and 2%, where the staining was light.

For similar exposure times, a dose-response relationship was apparent for both the severity and duration of irritation. Under the conditions of the four-hour studies, the 45% and 50% solutions were corrosive, the 25% solution severely irritant, the 2% solution slightly irritant, and 1% a no-effect concentration for skin irritation. The tests with 1% and 10% Sterisol resulted in more severe skin reactions, presumably due to the longer exposure time of 24 hours.

10.2.2 Eye irritation

A series of tests[32] was conducted on male and female New Zealand White rabbits with 5%, 2%, and 1% w/v aqueous glutaraldehyde solutions. For each concentration, 0.1 or 0.01 mL of solution was instilled into one eye of each of six rabbits, and the eyes examined at intervals up to three weeks; for 5% and 2%, an additional dose of 0.005 mL was also instilled. The procedure used and the scale for scoring ocular lesions were in accordance with OECD test method TG 405. Further tests[12] at more dilute concentrations were later carried out by the same authors. The results are shown at Table 14.

Other earlier studies[19,20] in New Zealand White rabbits were carried out with 1% and 10% Sterisol (1% and 10% aqueous glutaraldehyde) in accordance with standard US protocols. In both tests, 0.1 mL of solution was applied to one eye of each of six rabbits, with the other eye serving as the control. The results are in Table 14.

Table 14

Eye Irritation at Various Concentrations

Conc.	*Ref.*	*Volume*	*Result*
10%	19	0.1 mL	Mild corneal opacity and moderate conjunctivitis in all animals after 24 hours, and mild iritis in all six rabbits within 48 hours. Corneal opacity worsened up to the end of observation at 72 hours.
5%	32	0.1 mL	Severe corneal injury, moderate iritis, severe and persistent conjunctival irritation and necrosis
		0.01 mL	Slight corneal injury, moderate conjunctival irritation.
		0.005 mL	Very slight transient corneal injury, moderate conjunctival irritation.
2%	32	0.1 mL	Slight corneal injury, moderate iritis in all six rabbits, moderate to severe conjunctival irritation (persistent in half the animals for 2 weeks).
		0.01 mL	Minor iritis in one (of six), slight to moderate conjunctival irritation, no corneal injury.
		0.005 mL	Slight conjunctival irritation, no corneal injury.
1%	20	0.1 mL	Mild corneal opacity in four rabbits within 48 hours,and moderate conjunctivitis in all rabbits within 24 hours. Mild iritis in three rabbits within 48 hours, persisting for four days in two animals, with iritis not being scored after day four in the second animal due to severe corneal opacity. Irritative effects still present in 2 of the six rabbits after seven days.

Conc.	*Ref.*	*Volume*	*Result*
1%	32	0.1 mL	Slight corneal injury and iritis in two of the six animals, moderate to severe conjunctival irritation with necrosis in half the animals (persistent in half the animals for two weeks).
		0.01 mL	Slight conjunctival irritation which disappeared fromall animals within three days.
0.5%	12	0.1 mL	Slight conjunctival irritation.
		0.01 mL	Very slight conjunctival irritation.
0.2%	12	0.1 mL	Very slight conjunctival irritation.
		0.01 mL	No effects.
0.1%	12	0.1 mL	No effects.

Conc. *Concentration used in test.*
Ref. *Reference number.*

Under the conditions of the tests with concentrations 0.1-5%,[12,32] a dose-response relationship was established for conjunctival irritation and corneal injury. Glutaraldehyde at 5% was a severe eye irritant, with 1% and 2% being moderately irritating to the eye. The no-effects level for acute eye irritation of glutaraldehyde in rabbits was 0.1%.

10.2.3 Respiratory irritation

Respiratory irritancy in mice[34]

The irritancy of glutaraldehyde vapour to the upper respiratory system of male ND4 Swiss Webster mice was determined by measuring the decrease in respiratory rate at various concentrations. The study was conducted in accordance with ASTM method E981-84,[35] and it complied with the US EPA standards of Good Laboratory Practice.

Groups of four animals were exposed (head only) to concentrations of glutaraldehyde vapour ranging from 1.64-36.7 ppm for 30 minutes, with a seven-day recovery period after exposure. The respiratory rate in breaths/minute of each animal was measured every 15 seconds and compared with the pre-exposure rate. The glutaraldehyde vapour concentrations were generated dynamically at ambient temperature by passing compressed air through a bubbler containing 50% aqueous glutaraldehyde solution. As concentrations above 10-15 ppm could not be generated with the bubbler, a second bubbler was placed in parallel to generate concentrations of 20.4 and 36.7 ppm. No aerosol droplets were observed during the exposure periods for any concentration.

No mortality occurred during the study and no clinical signs of toxicity were observed. The respiratory rate decreased sharply at all concentrations within three minutes of exposure, with the depression maintained throughout the 30-minute period. The decrease in respiratory rate was due to a lengthening of the expiratory phase of breathing. After exposure, the respiratory rate increased, but not to the level of the pre-exposure rate. The results are shown at Table 15.

Table 15

Decrease in respiratory rate in mice

Glutaraldehyde (ppm)	*Respiratory decrease (%)*
1.64	26.4
3.21	30.2
4.65	41.5
5.80	39.6
7.47	41.1
20.40	57.1
36.7	59.0

The RD_{50}, the concentration which produces a 50% decrease in respiratory rate, was calculated to be 13.8 ppm glutaraldehyde.

Under the conditions of the study, respiratory irritation in mice, as measured by decrease in respiratory rate, was observed at all vapour concentrations, with respiratory rate decrease still considerable at the lowest concentration. No threshold could be determined from the study.

Other studies

The respiratory irritant effects of glutaraldehyde at low vapour concentrations were observed in test animals during acute inhalation studies (see sections 10.1.3 and 10.1.4). Signs of irritation include laboured and audible breathing and wetness and encrustation around the nose.

10.2.4 Synovial inflammation

The injection of glutaraldehyde into the synovium of rabbit knees resulted in a dose-related response between the degree of synovial inflammation and the concentration of glutaraldehyde.[36] At 100 ppm w/v glutaraldehyde, microscopic evidence of inflammation was observed, with necrosis, haemorrhage and gross diffuse synovitis observed at 100 ppm or greater. The disinfection of arthroscopic instruments with glutaraldehyde has been linked to post-operative complications.

10.2.5 Evaluation

The results of a well-conducted study were available to give a measure of the skin irritancy of glutaraldehyde at various concentrations. At 45% and 50%, the aqueous solution was corrosive to the skin of rabbits. Signs of skin irritation were still present with a 2% aqueous solution, but no effects were observed with a 1% solution. The finding is significant in terms of the general use of either 1% or 2% glutaraldehyde solutions for disinfection in the health care industry.

Other animal tests were carried out with 1% or 10% solutions, but the duration of skin contact was longer, for example, 24 hours, so the effects observed were more severe.

The results of a well-conducted study were available to give a measure of the eye irritancy of glutaraldehyde at various concentrations down to 1%, with supplementary information[12] by the same authors available for concentrations down to 0.1% glutaraldehyde. The tests indicated that the 5% solution was a severe irritant to the eye of the rabbit, and that dilute solutions such as 1% and 2% were moderately irritating to the eye. The further acute eye inflammation studies in the rabbit showed that the minimal transient eye irritation threshold was 0.2-0.5%, and that the minor transient corneal injury threshold was 1% glutaraldehyde. The findings emphasised the hazards associated with glutaraldehyde solutions greater than 0.1% in strength.

The other studies with 1% and 10% aqueous glutaraldehyde solutions confirmed the results obtained in the major study. Acute inhalation studies in test animals showed that the vapour from glutaraldehyde solutions was a severe eye irritant at low vapour concentrations, for example, at 3 ppm v/v.

One respiratory irritation animal study was available for assessment, with the study showing that the breathing rate of mice was significantly reduced at all vapour concentrations (1.64-36.7 ppm), no level of tolerance being achieved. Information available from acute inhalation studies has shown that glutaraldehyde is a respiratory irritant in test animals at the lowest vapour concentrations measured (2 ppm).

10.3 Sensitisation

10.3.1 Skin sensitisation

Guineapig maximisation test[37]

A skin sensitisation study was carried out in Dunkin Hartley albino guineapigs with aqueous 2% glutaraldehyde and alkalinised 2% glutaraldehyde. The test was conducted in accordance with the procedure for the guineapig maximisation test in OECD test guideline 406. The study met the requirements of the US EPA's Good Laboratory Practice Standards except that assays were not carried out to confirm the concentration, stability and homogeneity of the 2% glutaraldehyde solutions and their dilutions, and that some test samples were not archived.

Range-finding studies with the test material (2% glutaraldehyde) prior to the study enabled the doses for the induction and challenge phases to be set at 5% v/v (0.1% glutaraldehyde) for intradermal injection, 100% (2% glutaraldehyde) for topical induction, and 10% (0.2% glutaraldehyde) for the challenge and rechallenge phases. The challenge concentration was set below the skin irritation level.

On day 0, 0.1 mL of test substance was intradermally injected in the shoulders of 10 male and 10 female animals, both as a propylene glycol solution and as a 50/50 Freund's Complete Adjuvant (FCA)/water emulsion. At a third site on each animal, 0.1 mL of FCA/water was injected. On day 7, a patch containing approximately 0.2 mL of test substance was applied to the skin of the same 20 animals for 48 hours.

On day 21, the challenge dose was applied under patch to the animals for 24 hours, with dermal readings made at 24 and 48 hours after patch removal. On day 28, the challenge dose was repeated.

To ensure that the reactions during challenge were due to sensitisation rather than irritation, another five animals of each sex were treated with the vehicle and/or FCA/water during induction and then subjected to the normal challenge dose. In addition, another five animals per sex were treated with 0.1% 2,4-dinitrochlorobenzene (DNCB) to serve as a positive control group.

During the study, one animal died of emaciation, but no internal abnormalities were observed at necropsy. All other animals gained weight.

The results of the study are shown in Table 16.

Table 16

Skin sensitisation with 2% glutaraldehyde

	Aq 2%	*Alk 2%*	*DNCB*	*Control*
Incidence index (maximum 100%)				
	68	30	100	0
—at re-challenge	32	5		
Challenge severity index (maximum 3.0)				
24 h	0.8	0.4	1.7	0
48 h	0.4	0.2	1.5	0
Re-challenge severity index (maximum 3.0)				
24 h	0.5	0.2		0
48 h	0	0		0

Aq *Aqueous.*
Alk *Alkaline.*
DNCB *2,4-dinitrochlorobenzene.*

Under the conditions of the study, aqueous 2% glutaraldehyde was a moderate to strong skin sensitiser in guineapigs, and alkalinised 2% glutaraldehyde was a weak to moderate skin sensitiser. The tests with DNCB confirmed that the animals were sensitive to a positive skin sensitisation reaction, and the results for the irritation controls indicated that the challenge dose was below the irritation level.

Other studies

Glutaraldehyde tested positive in the mouse-ear swelling test[42], an assay proposed for the detection of skin allergens. Glutaraldehyde at 10% was used in the induction phase, with a concentration of 1% applied at challenge.

10.3.2 Respiratory hypersensitivity in guineapigs[39]

The potential of glutaraldehyde vapour to induce respiratory sensitisation in male Hartley guineapigs was investigated by comparing the respiratory response after a challenge exposure to that of a control group. There are no standard protocols for respiratory hypersensitivity, but a number of guineapig models under development have been described in the literature.[40] In this study, the criteria for a positive response were:

- a statistically significant increase in respiratory rate; and
- a change in the respiratory waveform, due to a lengthening of the expiratory phase.

The study complied with the US EPA standards of Good Laboratory Practice.

In the study, groups of eight animals were exposed (head only) to 14 ppm (the RD50 value (see 10.2.3, Respiratory irritancy in mice) for 1 hour/day for five days, followed by challenge with 4-5 ppm glutaraldehyde vapour on days 19, 26 and 40. The vapour was generated at ambient temperature by passing compressed air through a bubbler containing 50% aqueous glutaraldehyde solution. The respiratory rate of each animal

was measured every 15 seconds and compared with the pre-exposure rate.

No mortality occurred during the study and no clinical signs of toxicity were observed. No change in respiratory waveform was detected and the respiratory decrease in exposed animals was similar to that of the controls for each of the three challenge phases. However, the glutaraldehyde vapour concentration used for challenge in the study was at irritant level (see 10.2.3, Respiratory irritancy in mice), so any response due to respiratory hypersensitivity may have been masked by the response to respiratory irritation.

10.3.3 Evaluation

A well-conducted guineapig maximisation test showed that both the 2% aqueous solution and the 2% alkalinised solution of glutaraldehyde are skin sensitisers, with the former the stronger sensitiser. The results of a mouse-ear swelling test confirmed that glutaraldehyde is a skin sensitiser. The skin sensitising properties of the chemical are also demonstrated by human evidence in the scientific literature (see section 11.2.1).

In the only animal study on respiratory sensitisation, no response was observed in guineapigs. However, the study was conducted using glutaraldehyde vapour at irritant levels where any hypersensitivity response would be masked. Evidence for the respiratory sensitising potential of glutaraldehyde in humans is reviewed in section 11.2.2.

10.4 Repeated-dose toxicity

10.4.1 Oral

90-day inclusion in drinking water of rats[41]

A subchronic oral toxicity study in rats was carried out with UCARCIDE 250 Antimicrobial (an approximately 50% w/v aqueous solution of glutaraldehyde). The method was similar to that in OECD Test Guideline 408 and the study complied with Good Laboratory Practice standards.

Four groups each of 20 male and 20 female Fischer 344 rats received nominal concentrations of 0, 50, 250 or 1000 ppm w/v glutaraldehyde respectively in their drinking water over 13 weeks. The approximate daily intakes were 5, 25, or 100 mg/kg body weight for male rats, and 7, 35 or 120 mg/kg body weight for females. An additional 10 animals per sex were added to the 0 and 1000 ppm dose groups for a four week recovery phase.

A dose related reduction in water consumption was observed for males (at 250 and 1000 ppm) and females (at 1000 ppm), with the water consumption of high dose animals returning to normal within the four week recovery period. The reduction was attributed to an aversion to the taste and/or odour of glutaraldehyde rather than a toxicological effect.

Food consumption was also significantly reduced for male and female rats in the high dose group, and there were slight but inconsistent reductions in the 250 ppm groups. Body weight changes for males and females in the high dose groups parallelled food consumption reduction. It is likely that the decreases in food consumption and body weight gain were related to the reduction in water consumption and were not direct responses to glutaraldehyde toxicity.

Urine was collected for analysis from 10 rats/sex/group at six and 12 weeks, and some changes were observed. For both males and females in the 250 and 1000 ppm groups,

urine volume decreased with an increase in specific gravity, and slight increases in protein and ketone concentrations were noted. The effects were most likely related to the decrease in water consumption.

Blood was sampled from 10 rats/sex/group at six and 13 weeks, and no haematological effects were observed. The only significant effect on serum chemistry parameters was a dose-related increase in urea nitrogen in female rats in the 250 and 1000 ppm groups at six weeks. There was no accompanying change in serum creatinine, and urea nitrogen and creatinine at 13 and 17 weeks were similar to the controls.

A significant dose-related increase in kidney weight relative to final body weight occurred for males and females in the 250 and 1000 ppm groups, including an increase in absolute kidney weight for the female rats. Changes in final body weights and the weights of other organs were minor and/or sporadic and were unlikely to be related to glutaraldehyde exposure.

Histologic examination of tissues from male and female rats in all dose groups and the controls revealed no treatment-related findings. No changes to the kidney were observed, so the changes in kidney weight may have reflected a physiological adaptation in response to reduced water consumption.

Under the conditions of the study, 1000 ppm of glutaraldehyde was slightly toxic by ingestion over 90 days, and 250 ppm produced physiological changes. There were no significant effects at 50 ppm.

Two-year drinking water study in rats[42]

A two-year drinking water study was conducted in male and female Fischer 344 rats. The full report of this study was not available for assessment.

The dose range for the study was based on the findings from a 14-day drinking water study43 and the subchronic (90 day) drinking water study[41] (see 10.4.1, 90-day inclusion in drinking water of rats) conducted in Fischer 344 rats at concentrations of glutaraldehyde up to 1000 ppm w/v. Consequently, groups of 100 male and 100 female rats were treated with 0, 50, 250, or 1000 ppm w/v glutaraldehyde in drinking water. Ten animals per sex per dose were sacrificed at 52 and 78 weeks, with the remainder at 104 weeks.

The mortality rate for males was 25-30%, and for females 19-23%, with no dose-related increase. The major cause of death in all dose groups, including the controls, was large granular cell lymphatic leukaemia (LGLL), described below in more detail. During the study, a small increase in the incidence of urine stains was observed for the high and low dose males and females, and signs of emaciation and laboured breathing were noted in females at all doses, but there was no clear dose-response relationship.

Small dose-related decreases in absolute body weight and body weight gain occurred in males at 1000 and 250 ppm, and in females at 1000 ppm. Water consumption was reduced, with a dose-related decrease in males and females at 250 and 1000 ppm. The mean glutaraldehyde consumption for each of the three groups was 4, 17 and 64 mg/kg (body weight)/day for the males and 6, 25 and 86 mg/kg/day for the females. The food consumption was reduced for males and females at 1000 ppm.

Blood was collected for analysis from 20 rats per sex per dose at 13, 26, 52, 78 and 104 weeks. The total leucocyte count was significantly increased at week 104 in males at 250 and 1000 ppm, and in females at 250 ppm only. The variation in counts was large, possibly due to the large monocyte count at 250 and 1000 ppm. Changes in clinical

chemistry parameters included decreases in the activities of some enzymes at 250 and 1000 ppm, and occasional decreases in total protein, globulin, and phosphorous; these were probably due to reduced food consumption and body weight.

Urine was sampled from 10 rats per sex per group at 12, 25, 51, 77 and 103 weeks. For both males and females at 250 and 1000 ppm, there were dose-related decreases in urine volumes and associated increases in osmolality, both probably due to decreased water consumption.

At necropsy at 52, 78 and 104 weeks, the only statistically significant changes in organ weights were for the kidney. Relative kidney weights were increased for males and females at 52 and 78 weeks. At 104 weeks the relative and absolute kidney weights were increased in females at 250 and 1000 ppm, and decreased for males at all doses. In the absence of any supporting biochemical signs of kidney damage, the changes were attributed to physiological changes which compensated for the reduced water consumption.

Gross pathology showed evidence of gastric inflammation, particularly in rats sacrificed at the end of the study, with irritation observed as ulceration, a multifocal colour change, and thickening of the mucosa. Histologic examination of the tissues revealed squamous epithelial hyperplasia and keratinised cysts and oedema. Tubular pigmentation and basophilia were observed in 104-weeks male and female rats at 250 and 1000 ppm, but this was attributed to the haemolytic changes associated with LGLL.

The main finding of the study was a statistically significant increase in the number of LGLL observed in the liver and spleen of females only. The main cause of death during the study was LGLL, but there were few cases of LGLL observed in the routine sacrifice of 10 animals/sex/dose at 52 and 78 weeks (none at 52 weeks, 4 at 50 ppm after 78 weeks but none at 250 or 1000 ppm). The cumulative incidence of LGLL is shown in Table 17. No other significant oncogenic effects were observed during the study.

Table 17
Incidence of LGLL in liver and spleen (%)

		Dose (ppm)			
Tissue	*Sex*	*0*	*50*	*250*	*1000*
Spleen	male	43	51	40	46
	female	24	41	41	53
Liver	male	37	48	39	45
	female	23	40	40	52

Under the conditions of the study, glutaraldehyde in drinking water at 50 ppm and above produced a statistically significant increase in the incidence of LGLL in female rats after 104 weeks.

Factors moderating the finding were the high incidence of LGLL in the controls (43% in males, 24% in females), the susceptibility of Fischer 344 rates to LGLL, and the higher glutaraldehyde doses received by females. The incidence of LGLL in a previous study conducted by the same laboratory was reported as 22% for males and 66% for females. However, historical control data for untreated Fischer 344 rats in National Toxicology Program (NTP) studies indicates that the ranges for this tumour are 10-72% in males

and 6-31% in females.[44] Although the control data in this study fitted in with the historical control data reported from NTP studies, the control data from the earlier study by the same laboratory did not. Although the authors concluded that the increased incidence may have been due to the modifying effect of glutaraldehyde on at least one of the factors that routinely causes LGLL in Fischer 344 rats rather than a carcinogenic effect, the variability in control data for LGLL and the wide variation reported in the literature makes a definitive conclusion difficult. The inconsistency of control data within the study laboratory adds to these difficulties.

10.4.2 Inhalation

A nine-day inhalational rat study[25] was conducted at ambient temperature after earlier studies carried out with heated glutaraldehyde solution had indicated a high inhalational toxicity for glutaraldehyde, viz:

- an acute study[22] resulted in an LC_{50} of 23.5 ppm for males and 40.1 ppm for females; and
- a preliminary nine-day study[45] resulted in significant mortality at 2.1 ppm (see Table 18).

These studies had also confirmed the potent irritancy of glutaraldehyde to the upper respiratory system at low concentrations.

For similar reasons, a subchronic 14-week rat study[46] was also conducted by the same research laboratory. The procedures for the nine-day and 14-week studies were similar to OECD Test Guidelines 412 and 413 respectively, and both studies satisfied quality assurance requirements.

Later, two-week and 13-week inhalational studies14 were carried out in F344/N rats and B6C3F1 mice under the NTP.

The results of these studies are summarised in Table 18. In each case, exposure was for six hours per day.

Table 18
Repeated dose inhalational studies

Species	*Study*	*Ref.*	*Exposure concentration and results*
Rat (10m,f)	9-day	45	0, 0.2, 0.63, 2.1 ppm * Mortality: 9/10 m, 7/10 f at 2.1 ppm (days 3-9), 1/10 m at 0.63 ppm. * Respiratory irritation at all concentrations. * Body weight and organ weight decrease at 0.63 and 2.1 ppm.
Rat (12m,f)	9-day	25	0, 0.3, 1.1, 3.1 ppm * Mortality: 7/12 m, 6/12 f at 3.1 ppm (days 8, 9). * Nasal cavity lesions at 1.1 and 3.1 ppm. * Atrophy of the liver at 3.1 ppm. * Respiratory irritation at 1.1 and 3.1 ppm. * Body weight and organ weight decrease at 1.1 and 3.1 ppm; small increase in lung weight for males at 0.3 ppm. * Changes in urine and blood parameters at 1.1 and 3.1 ppm.

Species	*Study*	*Ref.*	*Exposure concentration and results*
Rat (20m,f)	14-wk	46	0, 21, 49, 194 ppb * No mortality. * Respiratory irritation at 49 and 194 ppb. * Body weight decrease for males at 49 and 194 ppb, and for females at 194 ppb. * No lesions of nasal cavity and no significant changes in urine and blood parameters.
Rat (5m,f)	2-wk	14	0, 0.16, 0.5, 1.6, 5, 16 ppm * Mortality: all at 5 and 16 ppm. * Nasal cavity and larynx lesions at 0.5 ppm and above, with nasal cavity lesions severe in the high-dose groups. * Lesions of the trachea (at 5 and 16 ppm), and the lungs and tongue (at 16 ppm). * Respiratory irritation at 0.5 ppm, severe at 1.6 ppm.
Rat (10m,f)	13-wk	14	0, 62.5, 125, 250, 500, 1000 ppb * No exposure-related mortality. * Lesions of nasal cavity, dose-related and in most animals at 1000 ppb, some at 500 ppb, and a few at 250 ppb; NOAEL 125 ppb. * Reduced body weight gain in males at 1000 ppb and females at 500 and 1000 ppb. * Breathing difficulty and ruffled fur for all at 1000 ppb, but only during the first five weeks. * No clear evidence of systemic toxicity.
mouse (5m,f)	2-wk	14	0, 0.16, 0.5, 1.6, 5, 16 ppm * Mortality: all at 1.6 ppm and above. * Lesions of the nasal cavity (at 1.6 ppm and above) and larynx (at 0.5 ppm and above), severe in the high-dose groups. * Lesions of the trachea at 16 ppm. * Respiratory irritation at 0.5 ppm.
Mouse(10m,f)	13-wk	14	0, 62.5, 125, 250, 500, 1000 ppb * Mortality: all at 1000 ppb and 2f at 500 ppb. * Lesions of the nasal cavity at all dose levels in females and at 250 ppb and above in males; therefore no NOAEL. * Lesions of the larynx at 1000 ppb. * Dose-related decrease in body weight gain at all dose levels in males and at 250 and 500 ppb in females. * Breathing difficulty observed in 7/10 m and 9/10 f at 1000 ppb before death, and also in 7/10 m and 5/10 fat 500 ppb in the first few weeks.

m	*Male.*
f	*Female.*
NOAEL	*No-observed adverse effect level.*

Similar signs of toxicity were observed in the various studies, including encrustation around the nose and eyes, and audible and mouth breathing. The stomach and intestines of some animals were dilated, due to the ingestion of air through mouth breathing.

The lesions of the nasal cavity observed in the studies were similar in description in each case, and included hyperplasia, squamous metaplasia, necrosis and acute inflammation.

In the 13-week NTP studies, a histoaudioradiographic study was conducted to characterise the respiratory tract responses, with the cell replication in the nasal epithelium being assessed using the unit length labelling index (ULLI). In rats and mice, there was a dose-related increase in cell replication for lesions in the anterior parts of the nasal cavity. However, the glutaraldehyde-induced lesions were different from those observed with formaldehyde, and there was no evidence of the preneoplastic changes observed with formaldehyde.

The results of the nine-day and two-week rat studies were similar, with mortality at 2-3 ppm and above, and respiratory irritation at 0.2-0.3 ppm and above. The effects were only slightly more severe for the study carried out with glutaraldehyde vapour generated by heat.[45]

The subchronic (13-, 14-week) rat studies indicated that lesions of the nasal cavity develop at 200-250 ppb and above, and that signs of irritation may occur at concentrations down to 49 ppb.

Results of corresponding mice studies showed that mice were more sensitive than rats to these effects of glutaraldehyde, with mortality and lesions of the nasal cavity occurring at lower concentrations, probably due to the smaller nasal passages of mice.

10.4.3 Dermal

A short term repeated dose study[12] in male C3H/HeJ mice was conducted by applying 50 mL of aqueous glutaraldehyde solution (from 0.5-50% w/w) to the clipped dorsal skin of the animals for a total of 10 applications. The results were as follows:

- 25% and 50% — all mice lost weight and died after 4-9 doses;
- 5% — decreased body weight after four to six doses, but not thereafter; and
- 2.5% and less — no signs of toxicity and no effect on body weight.

The results indicated that cumulative toxicity can occur through skin absorption of glutaraldehyde solutions of 25% or greater, but there was no evidence for cumulative toxicity for solutions of 5% or less.

A 28-day dermal study for concentrations 7% and below has recently been completed, with the report due later in 1994.

A two-year skin painting study in Fischer 344 rats and $B6C3F_1$ mice was begun under the NTP but, based on an assessment of the quality of the data, it was decided that no formal report should be prepared.

10.4.4 Evaluation

The three short term (nine-day or two-week) repeated dose toxicity studies showed that glutaraldehyde produced significant mortality in rats by inhalation at approximately 2 ppm v/v, and respiratory irritation at levels down to approximately 0.2 ppm. Lesions of the nasal cavity and larynx were observed in the studies, occurring at 0.5 ppm in one nine-day study. Atrophy of the liver was observed, at 3.1 ppm, in one of the studies. The signs of irritation observed were similar to those seen in the acute inhalational studies, that is, laboured breathing and discharge/encrustation around the eyes and nose. The results observed in the nine-day study carried out at ambient temperature[25] were similar to those observed in a preliminary nine-day study[45] conducted by heating glutaraldehyde solution to generate vapour.

In two subchronic rat studies (13 or 14 weeks), lesions of the nasal cavity and signs of irritation were observed at lower concentrations, with a no-observed adverse effect level (NOAEL) of 125 ppb v/v in one study and signs of nasal irritation at 49 ppb in the other.

The results of corresponding two-week and 13-week studies in mice demonstrated that mice were more sensitive than rats, with mortality at 1.6 ppm and 500 ppb in the two- and 13-week studies respectively. Nasal irritation was observed in the 13-week study at 62.5 ppb, the lowest dose tested.

The results highlighted the acute toxicity and irritancy of glutaraldehyde by inhalation at low vapour concentrations, and the harmful effects of repeated or prolonged exposure to the vapours.

The short term dermal study showed that cumulative toxicity and mortality may occur by repeated skin contact to 25-50% glutaraldehyde, but there was no evidence of cumulative toxicity at 5% or less.

A 90-day sub-chronic drinking water study in rats indicated some toxicity of glutaraldehyde at 1000 ppm w/v, and a physiological response at 250 ppm. Reductions in food and water consumption and a dose-related effect in kidney weight were observed, but as drinking water studies at high concentrations are generally hampered by a natural aversion of the animals to the taste/odour of glutaraldehyde, the significance of these results is uncertain.

In a two-year drinking water study, an increased incidence of LGLL was found in the liver and spleen of female rats only at all dose levels (50-1000 ppm w/v), but as the strain of rats used in the study has a high natural susceptibility to LGLL, the finding is not conclusive.

More long term studies are needed to properly define the effects of repeated or prolonged exposure to glutaraldehyde. Under NTP, a two-year inhalation study in rats and mice is expected to begin in 1994.

10.5 Reproductive toxicity/teratogenicity

10.5.1 Prenatal toxicity study in drinking water of rats[47]

Two range-finding studies were carried out in groups of pregnant Wistar rats to set the doses for a full study of the prenatal toxicity of glutaraldehyde by the oral route. The studies were conducted in accordance with OECD Test Guideline 414 and the USA EPA/FIFRA Pesticide Assessment guidelines, and in accordance with the OECD Principles of Good Laboratory Practice.

In the first range-finding study,[48] groups of 10 pregnant rats were administered 10 or 50 mg/kg body weight glutaraldehyde by gavage each day from days six to 15 post coitum. The controls were treated with distilled water.

At 50 mg/kg there were clear signs of maternal toxicity, with food consumption and body weight gain significantly reduced. Clinical observations during the study included a reduced nutritional state, laboured breathing and piloerection. At necropsy the relative kidney weights were increased, and the total protein and globulin concentrations in blood were reduced. All dams at the high dose had thickening of margo plicatus, with lesions of the glandular stomach in three of them. At 10 mg/kg, the only sign of maternal toxicity was thickening of the margo plicatus in one of the dams.

The only signs of embryo-/foetotoxicity was an increased postimplantation loss in one dam at 50 mg/kg, but as the dams were sacrificed on day 16 post coitum, only limited information could be obtained. There were no signs of teratogenicity in the study.

In the second range-finding study,[49] groups of 10 pregnant rats were treated with 11 or 51 mg/kg body weight glutaraldehyde in drinking water per day from day six to 16 post coitum. The controls drank distilled water. At 51 mg/kg (500 ppm), marginal signs of maternal toxicity included reduced food and water consumption, and foci in the glandular stomach of two dams. At 11 mg/kg (100 ppm), no substance-related effects on dams or foetuses were observed. There were no adverse effects in the group exposed to 100 ppm or 11 mg/kg body weight.

Based on the findings of the two preliminary studies, the full study,[47] was carried out by treating groups of 25 pregnant rats at 50, 250 and 750 ppm w/v glutaraldehyde in drinking water per day, measured as 5, 26 and 68 mg/kg body weight per day, from days six to 16 post coitum, with sacrifice on day 20 post coitum The controls drank distilled water.

A dose-related decrease in water consumption occurred for dams at 26 and 68 mg/kg, but there were no other dose-related signs of maternal toxicity observed during the study.

In examination of the foetuses after dissection from the uterus, no significant findings were observed in the sex distribution, placental weight or foetal weight. External examination revealed one foetus at 750 ppm without tongue, but this malformation is present in the historical control data at a low frequency. Soft tissue and skeletal examination revealed no statistically significant malformations or variations in the foetuses.

Under the conditions of the study, the maternal no observable effect level (NOEL) for glutaraldehyde is 5 mg/kg body weight/day (50 ppm), and 68 mg/kg body weight/day (750 ppm) for the foetus.

10.5.2 Prenatal toxicity study in rabbits by gavage[50]

Two range-finding studies were carried in groups of pregnant Himalayan rabbits to set the doses for a full study of the prenatal toxicity of glutaraldehyde by the oral route. The studies were conducted in accordance with OECD Test Guideline 414 and USA EPA/FIFRA Pesticide Assessment guidelines, and in accordance with the OECD Principles of Good Laboratory Practice.

In the first range-finding study,51 groups of six pregnant rabbits were administered 5 or 25 mg/kg body weight glutaraldehyde by gavage daily from days 7-20 post insemination. The controls were administered distilled water. At 25 mg/kg food consumption was significantly reduced, and the concentrations of calcium, glucose, total protein and albumin in blood from the ear vein of the animals were significantly

lower than for the controls. Microfocal gastritis in the fundus/pylorus region was observed in two does, but also in one control animal. At 5 mg/kg no significant substance related effects were observed. There was no evidence of embryotoxicity/foetotoxicity, but as the does were sacrificed on day 20 post insemination, only limited information could be obtained.

In the second range-finding study,[52] groups of six pregnant rabbits were treated with 100 or 500 ppm w/v glutaraldehyde, measured as 7 and 23 mg/kg body weight, in drinking water daily from days 7-20 *post insemination* the controls drank distilled water. Food and water consumption were reduced at both concentrations and, at 23 mg/kg, the postimplantation loss in the does was statistically higher than for the controls. Under the conditions of the study, glutaraldehyde was maternally toxic at 23 mg/kg, with some sign of toxicity at 7 mg/kg. There was no evidence of embryotoxicity/foetotoxicity, but as the does were sacrificed at day 20 post insemination, only limited information was available.

Based on the findings of the two preliminary studies, the full study[50] was carried out by treating groups of 15 pregnant rabbits by gavage at 5, 15 or 45 mg/kg body weight of glutaraldehyde daily from days 7-19 post insemination, with sacrifice on day 29 *post insemination*. The controls were administered distilled water.

At 45 g/kg, five of 15 does died on days 9-11 *post insemination*, and food consumption and body weight gain were significantly reduced. Clinical observations in 12 of 15 does included soft faeces, diarrhoea and blood in the bedding. At necropsy, irritation of the gastrointestinal tract was observed, and the uterus weight was significantly reduced. Nine of the 10 remaining does did not produce live foetuses. Examination of the only four foetuses indicated a reduced placental and foetal body weight. At 5 and 15 mg/kg, no statistically significant effects were observed for the does or the foetuses.

Under the conditions of the study, glutaraldehyde was markedly maternally toxic and embryolethal to pregnant rabbits by gavage at 45 mg/kg body weight/day. There was no maternal toxicity or embryotoxicity/foetotoxicity at the lower doses, nor any evidence of teratogenicity at all doses, although there were only four live foetuses at the high dose.

The NOEL on the maternal and foetal organism was 15 mg/kg body weight/day.

10.5.3 Reproductive effects in rats and mice by inhalation[14]

Under the NTP, 13-week inhalation studies on rats and mice were conducted (see section 10.4 for reports of these studies). In addition to the histopathological evaluation, an assessment of the sperm morphology and the oestrous cycle length was performed for rats exposed to 0, 62.5, 250 or 1000 ppb v/v glutaraldehyde vapour and mice at 0, 62.5, 250 or 500 ppb.

Sperm morphology measurements for the treated male rats and mice were similar to those for the controls. Oestrous cycle lengths for female rats were normal, but there were significant differences in the oestrous cycle for female mice at 250 and 500 ppb when compared with that of the controls. The oestrus and dioestrus times were longer and the metoestrus times were shorter than for the controls.

10.5.4 Teratogenic study with 25% glutaraldehyde in albino rats[53]

A teratogenic study in Charles River albino rats was carried out by dosing by gavage with 25% glutaraldehyde solution at 0, 25 or 50 mg (glutaraldehyde)/kg body weight. Groups of 18 or 19 pregnant rats were dosed daily during gestation days six-15 and sacrificed on day 20. The control females were treated with distilled water.

During the study, one rat dosed at 25 mg/kg died through injury. The body weight gain for the high dose animals was significantly less than for the controls, but similar to the controls at 25 mg/kg. At necropsy no significant reproductive effects were revealed, with the number of corpora lutea, implantation sites, resorption sites and foetuses similar for dosed rats and controls.

The body weights of the foetuses were similar for all groups and there were no significant findings related to the skeletal or internal development of the foetuses. Apart from one runt foetus at 25 mg/kg and two at 50 mg/kg, no significant external abnormalities resulted.

Under the conditions of the study, glutaraldehyde at 50 mg/kg body weight was not teratogenic.

10.5.5 Other studies

In a study in pregnant albino mice,[54] Sonacide (2% activated glutaraldehyde solution) was administered by gavage at 16-100 mg glutaraldehyde/kg body weight/day, with maternal toxicity at 40 mg/kg/day and foetal malformation at 100 mg/kg/day.

10.5.6 Evaluation

In gavage studies in rats, glutaraldehyde was maternally toxic at 40-50 mg/kg, with a NOEL in the range 5-25 mg/kg. The same studies indicated that the embryo-foetotoxicity of glutaraldehyde was slightly higher, in the range 50-100 mg/kg.

The drinking water studies in rats indicated that glutaraldehyde is maternally toxic at 50 mg/kg, with a NOEL of 5 mg/kg. The same studies resulted in a NOEL of 68 mg/kg for the foetus.

Equivalent gavage and drinking water studies in rabbits resulted in maternal toxicity and embryolethality at 25-45 mg/kg, with a NOEL of 15 mg/kg.

In all the above studies, there was no evidence of teratogenicity.

Inhalation tests conducted by the NTP showed that the oestrous cycle lengths of female rats were unaffected at 1000 ppb v/v, but the cycles of mice were altered at glutaraldehyde vapour concentrations of 250 ppb and above.

10.6 Genotoxicity

10.6.1 In vitro bacterial assays

Salmonella typhimurium mutagenicity — NTP studies[14]

Under the NTP, a series of reverse mutation assays was carried out with various *Salmonella typhimurium* strains, with and without metabolic activation provided by rat or hamster liver S9. The tests were conducted by Haworth et al (1983) and Zeiger et al (1992), with the results reported in the NTP report14 and presented in Table 19.

Table 19

Mutagenicity of glutaraldehyde in Salmonella typhimurium

Strain	*Dose (ug/plate)*	*Ref.*	*Result*	
			with S9	*no S9*
TA 100	0-333	H	pos	pos
TA 1535	0-333	H	neg	neg
TA 1537	0-333	H	neg	neg
TA 98	0-333	H	neg	neg
TA 100	0-3333	H	neg	neg
TA 1535	0-3333	H	neg	neg
TA 1537	0-3333	H	neg	neg
TA 98	0-3333	H	neg	neg
TA 102	0-300	Z	pos	pos
TA 104	0-300	Z	pos	pos
TA 100	0-300	Z	pos	pos

Ref. *Reference number.*
H *Tests conducted by Haworth et al.*
Z *Tests conducted by Zeiger et al.*
pos *Positive.*
neg *Negative.*

In the tests conducted by Haworth et al,[14] all results were negative except for TA 100, which indicated positive activity to glutaraldehyde in one laboratory and an equivocal result in the presence of rat liver S9 in the second laboratory. In the series of tests conducted by Zeiger et al,14 glutaraldehyde tested clearly positive with and without S9 in all three strains, particularly TA 102 and TA 104, which are both sensitive to carbonyl compounds.

Other studies

The mutagenicity of glutaraldehyde in *Salmonella typhimurium* has been investigated in a number of assays, with the results ranging from negative to strongly positive. Results of the studies have been summarised by Beauchamp et al (1992)10, Ballantyne (1992)[55] and BIBRA (1991)[17].

Testing with *Escherichia coli* has also yielded both positive and negative results.[10,17,55] DNA repair testing with *Bacillus Subtilis* gave positive results.[17,55]

10.6.2 In vitro mammalian cell assays

In vitro chromosomal aberrations assay in Chinese hamster ovary cells[56]

The genotoxic potential of glutaraldehyde was evaluated by conducting an in vitro chromosomal aberrations assay in Chinese hamster ovary (CHO) cells. The study was carried out in accordance with OECD Test Guidelines,[33] and it complied with the US EPA Good Laboratory Practice requirements.

The dose range was set in a preliminary toxicity test, where 0.003-10,000 mg/mL UCARCIDE Antimicrobial 250 (50% w/w aqueous glutaraldehyde) was tested on

cultured CHO cells with and without rat liver S9 metabolic activation. The relative survivals of treated cells without S9 activation were from 95% at 0.30 µg/mL to 25% at 10 µg/mL, whereas with S9, they were 97% at 3.0 µg/mL to 47% at 100 µg/mL.

The 50% aqueous glutaraldehyde was cytotoxic at high doses (≥ 30 µg/mL without S9, and ≥ 300 µg/mL with S9).

In the definitive chromosomal aberrations assay, five doses of 50% aqueous glutaraldehyde were used, 0.03-3.0 µg/mL without S9 metabolic activation, and 0.30-30 µg/mL with activation.

Scoring for chromosomal aberrations indicated 2-3% aberrant cells without S9 metabolic activation and 2-4% with activation. The relevant control scores were 2-3% for the solvent, and 36% for the positive control (triethylenemelamine) without activation, and 39% for the positive control (cyclophosphamide) with activation. No unusual types or distributions of chromosomal aberrations were observed.

There was no dose-related increase in the frequency of chromosomal aberrations, with and without S9 metabolic activation, so under the conditions of the study glutaraldehyde was not clastogenic.

Chromosomal aberrations in chinese hamster ovary cells — NTP studies[14]

Under the NTP, glutaraldehyde was tested in cultured CHO cells for the induction of chromosomal aberrations, with and without rat liver S9 metabolic activation.

The tests were carried out at two laboratories, with the results shown at Table 20. The vehicle controls in the two laboratories were distilled water and dimethyl sulfoxide respectively, and the common positive controls were cyclophosphamide with S9, and triethylenemelamine without S9.

Table 20

Chromosomal Aberrations in CHO Cells (NTP)

		Result	
Laboratory	*Dose (µg/mL)*	*With S9*	*No S9*
1	0.3-10	–	negative
1	1-30	negative	–
2	1.6-16	negative	weak positive

Under the conditions of the tests, glutaraldehyde induced chromosomal aberrations in CHO cells without S9 metabolic activation in one laboratory, but not the other. In the second laboratory, the dose was higher and a different data evaluation system was used. In both laboratories, glutaraldehyde did not induce chromosomal aberrations in CHO cells with S9.

Induction of sister chromatid exchanges in chinese hamster ovary cells — NTP study[14]

Under the NTP, glutaraldehyde was tested in cultured CHO cells for the induction of sister chromatid exchanges (SCE), with and without rat liver S9 metabolic activation.

The tests were carried out at two laboratories, with the results shown at Table 21. In the first laboratory, distilled water was the vehicle control, and in the second dimethyl sulfoxide. With S9, cyclophosphamide was the positive control in both laboratories, and triethylenemelamine the control for the tests without S9.

Table 21

Sister Chromatid Exchanges in CHO Cells

		Result	
Test	*Dose (mg/mL)*	*With S9*	*No S9*
1st laboratory			
1	0.36-10.8	weak positive	positive
2	10-15	positive	–
2nd laboratory			
1	0.5-16	–	negative
2	1.6-16	weak positive	–

Under the conditions of the tests, glutaraldehyde induced sister chromatid exchanges in Chinese hamster ovary cells with and without S9 metabolic activation in one laboratory, but was negative without S9 and weakly positive with S9 in the second laboratory, the difference being attributed to slight differences between the data evaluation systems used in the two laboratories.

Mouse lymphoma mutagenicity — NTP study[14]

Under the NTP, a forward mutation assay was conducted in mouse lymphoma L5178Y cells to measure mutations induced by glutaraldehyde. The assay was conducted at glutaraldehyde concentrations of 0, 0.5, 1, 2, 4, 8 and 16 µg/mL without S9 metabolic activation. Glutaraldehyde was cytotoxic at the high dose and no significant increase in mutations was observed up to 4 µg/mL, but at 8 µg/mL mutations were induced at the TK locus of the mouse lymphoma cells.

Under the conditions of the test, glutaraldehyde was mutagenic at 8 mg/mL in mouse lymphoma L5178Y cells without S9 metabolic activation.

Mouse lymphoma assay with 1% Sterisol[57]

A forward mutation assay was conducted in L5178Y Fischer mouse lymphoma cells with 1% Sterisol Formula #3 (1% glutaraldehyde) according to a method similar to that reported by Clive and Spector.[58]

Sterisol was completely cytotoxic at glutaraldehyde concentrations down to 29 mg/mL with S9 mouse liver activation and down to 7.2 mg/mL without activation. At a series of concentrations below the level of toxicity, no point mutations were induced in the cells, with and without activation. The controls gave positive results.

Under the conditions of the test, glutaraldehyde was not mutagenic.

Other studies

In other chromosomal aberration assays, glutaraldehyde generally gave negative results, but the doses tended to be lower than in those studies which produced positive results. Glutaraldehyde was mutagenic in an assay using cultured human TK6 lymphoblasts.[59]

Glutaraldehyde-induced unscheduled DNA synthesis in rat hepatocyte cultures showed a small dose-related response in one assay, but in a second assay, no induction was observed.[10,55]

10.6.3 In vivo assays

In vivo peripheral blood micronucleus test[60]

UCARCIDE Antimicrobial 250 (50% w/w aqueous glutaraldehyde) was administered by gavage to male and female Swiss-Webster mice as a single dose in a micronucleus assay to measure the incidence of micronucleated polychromatic erythrocytes in peripheral blood cells. The study complied with the generally accepted standards of Good Laboratory Practice.

On the basis of an LD_{50} of 317 mg/kg body weight from a previous study in mice, the doses were set at 80, 160 and 250 mg/kg (as UCARCIDE Antimicrobial 250, i.e., 40, 80 and 125 mg glutaraldehyde/kg). Five male and five female mice were dosed at 80 and 160 mg/kg, and eight per sex at 250 mg/kg. The vehicle control was water, and the positive control triethylenemelamine.

During the study no female mice died and there were no clinical signs of toxicity. However, four male mice died (2 at 250 mg/kg and one each at 80 and 160 mg/kg), three of them within an hour of dosing.

Micronucleus observations were carried out for each dose on up to five mice per sex by sampling blood from the tail vein at 30, 48 and 72 hours after treatment, and staining the micronuclei in peripheral blood polychromatic erythrocytes (PCE). The polychromatic erythrocyte/normoerythrocyte (NCE) ratios, that is, PCE/NCE, for 1000 cells per animal were calculated to give an estimate of the cytotoxicity of glutaraldehyde. No significant changes in PCE/NCE were observed between the dosed animals and those dosed with water.

The number of micronucleated PCEs per 1000 PCEs was then calculated for each animal per dose, and no significant increases in micronuclei were observed for the dosed animals or the water controls. The positive control showed increased micronuclei for both males and females.

Under the conditions of the study, glutaraldehyde did not induce micronuclei in the PCEs in the peripheral blood of mice.

Rat bone marrow chromosomal aberration assay[61]

A summary only of this assay was available for assessment. UCARCIDE Antimicrobial 250 (50% w/w aqueous glutaraldehyde) was administered by gavage to Sprague-Dawley rats at 25, 60 and 120 mg/kg body weight for the males and at 15, 40 and 80 mg/kg for the females. The dose was set from an earlier acute oral toxicity study[16] which resulted in an LD_{50} of 246 mg Antimicrobial 250/kg body weight for male Sprague-Dawley rats and 154 mg/kg for the females (see section 10.1.1, Acute oral toxicity in the rat).

Five animals per sex per dose were sacrificed at 12, 24 and 48 hours after treatment, and bone marrow removed and examined for induced chromosomal aberrations. For each time period, five rats per sex were treated with distilled water at 10 mg/kg by gavage as the vehicle controls and five rats per sex were dosed with cyclophosphamide at 30 mg/kg by intraperitoneal injection as the positive controls. During the study one male rat at 120 mg/kg died.

Scoring for the number of aberrant cells in bone marrow resulted in similar readings for both males and females at each dose, with no evidence of any dose-response relationship. The readings for each time period (12, 24 and 48 hours) were similar to the counts for the vehicle control. The positive control mean counts (at 24 hours only) were 17 and 18 respectively for the males and females compared with mean counts of 0.4-3.6 for the rats treated with glutaraldehyde.

Under the conditions of the study, glutaraldehyde was not clastogenic in the rat bone marrow chromosomal aberrations assay.

Drosophila melanogaster sex-linked recessive lethal test — NTP studies[14]

Under the NTP, the ability of glutaraldehyde to induce sex-linked recessive lethal (SLRL) mutations in the germ cells of *Drosophila melanogaster* was evaluated.

Two series of tests were carried out. In the first, male adult Canton-S wild-type flies were fed for 72 hours on a glutaraldehyde-in-sucrose solution at a dose to induce 30% mortality. No response was obtained, so insects were injected with glutaraldehyde solution. In the tests, the number of lethal mutations from the mating of newly-emerged flies was determined. The results were negative

In the second series of tests, the eggs of mated Canton-S flies were exposed to cornmeal containing glutaraldehyde. The results of this larval feeding experiment were also negative.

Under the conditions of the tests, glutaraldehyde did not induce SLRL mutations in the germ cells of *Drosophila melanogaster* treated as adults by feeding or injection, or treated as larvae by feeding.

Other studies

In a mouse dominant lethal assay[10], glutaraldehyde at oral doses of 30 and 60 mg/kg (body weight) was negative. In an assay[17] for unscheduled DNA synthesis, the oral administration of up to 600 mg (glutaraldehyde)/kg (body weight) in groups of male rats did not induce DNA damage.

10.6.4 Evaluation

The results of in vitro bacterial assays, especially the more recent ones, have shown glutaraldehyde to be mutagenic, with and without S9 metabolic activation. Glutaraldehyde has also been shown to produce mutations, sister chromatid exchanges and chromosomal aberrations in mammalian cells in vitro, with and without any metabolic activation system.

The results of *in vivo* assays to date have been negative.

10.7 Summary

Animal studies indicate that the oral LD_{50} of glutaraldehyde in rats, mice and guineapigs, is approximately 50-250 mg/kg, and that the acute dermal toxicity in rabbits, rats and mice is approximately 1000-4500 mg/kg, with skin absorption at high concentrations. Glutaraldehyde has a high acute inhalational toxicity in rats and mice and lung damage has been reported. Four-hour LC_{50} values of 23.5 and 40.1 ppm have been obtained for the male and female rat respectively, but the glutaraldehyde solution had to be heated in order to generate glutaraldehyde vapour at high enough concentrations. Repeat acute inhalational toxicity studies at both ambient and elevated temperatures are being carried out.

Glutaraldehyde is corrosive to the skin and eyes of rabbits at high concentrations, with signs of skin irritation evident at 2%, and eye irritation at 0.2%. Exposure to glutaraldehyde vapours in acute inhalational studies resulted in nasal irritation and respiratory difficulties. Joint irritation was seen in rabbits after intra-articular administration. The skin sensitisation effect of glutaraldehyde was demonstrated in tests with guineapigs.

Short term (nine day or two-week) repeated dose inhalational rat studies resulted in significant mortality at approximately 2 ppm v/v, and nasal irritation at levels down to approximately 0.2 ppm. Lesions of the nasal cavity and larynx were observed at 0.5 ppm and, in a nine-day study, atrophy of the liver was observed at 3.1 ppm. Signs of irritation included laboured breathing and discharge and encrustation around the eyes and nose.

In two subchronic (13-14 weeks) rat studies, signs of irritation were observed at lower concentrations, with a NOAEL of 125 ppb in one study and signs of nasal irritation at 49 ppb in the other. In corresponding two-week and 13-week studies in mice, mortality resulted at 1.6 ppm and 500 ppb respectively, with signs of nasal irritation observed at the lowest dose (62.5 ppb) in the 13-week study. The results highlighted the toxicity and irritancy of glutaraldehyde by inhalation at low vapour concentrations, and the harmful effects of repeated or prolonged exposure to the vapours.

A short term dermal study in mice showed that severe cumulative toxicity and mortality may occur by repeated skin contact to 25-50% glutaraldehyde, but there was no evidence of cumulative toxicity at 5% or less.

A subchronic drinking water study in rats indicated some toxicity at 1000 ppm w/w, and a physiological response at 250 ppm. Reductions in food and water consumption and a dose-related effect in kidney weight were observed, but as drinking water studies at high concentrations are generally hampered by a natural aversion of the animals to the taste/odour of glutaraldehyde, the significance of these results is low.

A two-year drinking water study in rats resulted in an increased incidence of LGLL in the liver and spleen of females only at all dose levels (50-1000 ppm), but the finding was not conclusive as the strain of rats used in the study has a high natural susceptibility to LGLL and variation in control data existed within the study laboratory.

Repeated oral doses given during pregnancy to rabbits, rats and mice caused embryotoxicity and foetotoxicity, but only at maternally toxic doses. No teratogenic effects were observed.

Early mutagenicity studies were negative, but more recent studies have indicated that glutaraldehyde is mutagenic *in vitro* in bacterial assays and tests in mammalian cells. *In vivo* genotoxicity tests to date have proven negative.

In view of the information gaps in the toxicity profile for glutaraldehyde, additional information is required in:

- two-year inhalation effects; and
- LC_{50} at ambient temperature.

11. Human health effects

11.1 Irritation

11.1.1 Skin irritation

Skin irritation has been experienced in workers exposed to glutaraldehyde solutions and vapours, with numerous cases of contact dermatitis cited in the scientific literature. In some of these cases, a local skin irritant effect has been accompanied by eye and/or respiratory irritation. Cases in the literature include:

- Swedish hospital workers using aqueous glutaraldehyde solution experienced an increased incidence of skin disorders compared with workers at the same hospital not exposed to glutaraldehyde, for example, 18 of 39 workers (46%) exposed to glutaraldehyde experienced dermatitis of the hands compared with 11 of 68 workers (16%) for a control group;[62]
- a cleaner and a nurse in a hospital experienced dermatitis on the hands and arms;[63]
- a study of 541 cleaners in a hospital indicated an increased incidence of skin disease compared with 157 controls;[64]
- of nine staff employed in an endoscopy unit, three experienced facial dermatitis;[65]
- fourteen of 44 hospital workers using a 2% solution experienced skin irritation;[66] and
- an endoscopy technician employed in making up 2% glutaraldehyde solution from a 50% stock solution experienced dermatitis on the forearms.[67]

In the USA, the NIOSH Hazard Evaluations and Technical Assistance (HETA) branch has issued a number of Health Evaluation Reports on skin irritation in hospital workers exposed to glutaraldehyde solutions.[66,68,69,70]

In Australia, dermatitis has been observed in a number of different types of workers who are exposed to glutaraldehyde, including endoscopy nurses, hospital cleaners, radiographers and dental assistants.[71] In a South Australian study,[72] hand dermatitis was reported in dental assistants, and facial irritation was reported in egg collectors spraying eggs with a glutaraldehyde sanitising solution.

In a survey carried out in 1993 by the South Australian Occupational Health and Safety Commission, dermatitis of the hands, arms and/or face was diagnosed in a number of health care workers (see Appendix 4).

In several cases of dermatitis, sensitisation to glutaraldehyde has been demonstrated by patch testing (see section 11.2.1, Observed effects in workers).

11.1.2 Eye irritation

Eye irritation has resulted from exposure to glutaraldehyde in a number of cases cited in the scientific literature, including endoscopy nurses and other hospital workers. In NIOSH HETA reports, eye irritation occurred in hospital workers exposed to atmospheric glutaraldehyde concentrations up to 0.5 ppm v/v,[66,68,69,73] for example, in a survey conducted at Montgomery Hospital, Pennsylvania, 28 of 44 workers (64%) who

used a 2% glutaraldehyde solution at least once per week reported eye irritation while using the solution.

In a case where 2% aqueous glutaraldehyde was accidentally splashed in the eye, irritation, pain and an increased sensitivity to light resulted.[74]

In the survey carried out by the South Australian Occupational Health and Safety Commission in 1993, eye irritation was reported in workers at seven different hospitals (see Appendix 4).

- **Respiratory irritation**

Irritation of the nose and throat and general tightness of the chest have been experienced by workers exposed to glutaraldehyde vapours. Cases cited in the scientific literature include:

- Swedish hospital workers exposed to concentrations less than 0.2 ppm experienced irritation of the nose and throat;[62]
- hospital staff experienced irritation of the nose and throat after working with 2% glutaraldehyde solution;[75]
- four endoscopy nurses experienced asthma and rhinitis after working with 2% aqueous glutaraldehyde;[76] and
- an endoscopy technician employed in preparing 2% aqueous glutaraldehyde from a 50% stock solution experienced nose bleeding in addition to irritation of the nose and throat.[67]

Symptoms reported in the NIOSH HETA reports on hospital workers exposed to glutaraldehyde at atmospheric concentrations up to 0.5 ppm v/v included nose and throat irritation, chest tightness and coughing.[66,68,69,70,73]

In the survey carried out by the South Australian Occupational Health and Safety Commission in 1993, nine cases of nose and/or throat irritation and two cases of lower respiratory tract irritation were reported in hospital workers (see Appendix 4).

In the documentation of threshold limit values (TLVs) by the American Conference of Governmental Industrial Hygienists (ACGIH),[77] glutaraldehyde is reported to have a strong irritant effect on the nasal passages and the upper respiratory tract, this being the basis of their TLV and the National Occupational Health and Safety Commission (the National Commission) national exposure standard.[8]

11.2 Sensitisation

11.2.1 Skin sensitisation

Observed effects in workers

The skin sensitising effect of glutaraldehyde in workers exposed to the chemical is well-documented, with numerous cases of allergic skin reactions reported in the scientific literature. Some of the cases are listed below:

- a hospital cleaner without any personal or family history of atopy or dermatitis developed dermatitis of the hands and fingers and around the mouth and eyes after exposure to a 2% glutaraldehyde solution. Patch testing with 0.5% and 1% glutaraldehyde gave positive results at 48 and 72 hours;[78]

- a surgical instruments nurse and an endoscopy nurse, each with dermatitis on the hands, tested positive to patch testing with glutaraldehyde;[79]
- a hospital maintenance employee with no history of atopy or skin disease developed allergic contact dermatitis of the hands, arms, face and neck. A positive reaction was obtained by patch testing with 1% glutaraldehyde in accordance with standard guidelines;[80]
- allergic contact dermatitis of the hands was found in 13 health care workers, comprising five dental assistants, three endoscopy nurses, two supply nurses, a veterinarian, a respiratory technician and an embalmer, who were exposed regularly to glutaraldehyde. At least seven of the workers had no history of atopy. The patients were patch tested to standard procedures on the upper back with 1% glutaraldehyde, the patch being in place for 48 hours and readings taken soon after removal (30-60 minutes) and at 96 hours. Nine of the workers showed a positive response at the first reading and all 13 showed positive at 96 hours;[81]
- in a patch testing study of 84 funeral service workers exposed to glutaraldehyde and 38 control workers, six of the exposed workers and none of the controls tested positive to glutaraldehyde at 48 hours after patch removal. The family history of allergic response was similar for both groups;[82]
- three hospital cleaners, an endoscope cleaner and a nursing aid who developed contact dermatitis on the hands and forearms all tested positive to patch testing with 1% glutaraldehyde solution, with three of the workers testing positive to 0.1% glutaraldehyde (the other two were not tested at 0.1%);[83]
- a radiologist and an x-ray technician with dermatitis of the fingers tested strongly positive to patch testing with 1% glutaraldehyde;[84]
- three dental assistants suffering dermatitis of the hands and fingers and two patients being treated with glutaraldehyde therapeutically (one for excess sweating of the feet, and one for fingernail infection) tested positive to patch testing with 1.0% and 0.25% glutaraldehyde solution and tanned leather containing glutaraldehyde. All tested negative to 2.5% formaldehyde solution;[85]
- twenty persons were confirmed as being contact sensitive to glutaraldehyde by patch testing with a 1% aqueous glutaraldehyde solution on the back. There was no cross-sensitivity to formaldehyde;[86] and
- a person with hair loss and dermatitis of the scalp was patch-tested with 1.0%, 0.5%, 0.1% and 0.05% aqueous glutaraldehyde. The person, an atopic, tested positive to 1.0%, 0.5% and 0.1% at 72 hours, but negative to 0.05%. The person did not work with glutaraldehyde solutions, but she used a hair conditioner containing glutaraldehyde at less than 1%. Her condition improved after discontinuing use of the conditioner.[87]

Repeated insult patch test — test 188 (IBL4099)

Aqueous glutaraldehyde solution was applied to the skin of two groups of volunteers in a series of 15 primary applications, with a challenge dose applied two weeks after the final primary dose.

In the first group of 20 persons, aged between 20 months and 55 years, the first two applications of 5% glutaraldehyde solution each remained in contact with the skin under an occluded patch for 24 hours. Severe erythema and oedema resulted, so the further 13 primary applications with 5% solution were left uncovered. On challenge with 5% solution (uncovered), no reaction was detected. The application of 1% and then 2% solution under occluded patches on the same group, followed by challenge with 2% (occluded), produced six cases of slight erythema.

The second group of 40 persons, aged from approximately 30-70 years, was exposed to 5% glutaraldehyde under a occluded patch for 24 hours, and then a second patch (occluded) for five days, resulting in moderate to severe erythema and oedema. A third patch (1% occluded) was applied for five days, a fourth (5% open) for 24 hours, and then a fifth (2% occluded) for five days. Challenge at two sites, with 2% (occluded) and 5% (uncovered) resulted in no reaction for either dose.

Despite the positive skin reactions, the authors of the study atttributed the reactions to the dressing adhesive rather than the chemical, concluding that 5% glutaraldehyde was neither a primary irritant nor a sensitiser, a finding inconsistent with those of other studies and the human experience. There were no controls of occluded dressing without glutaraldehyde.

Repeated insult patch test — test 2[89] (Testkit 80-39)

Dilute solutions of glutaraldehyde (0.1%, 0.2% and 0.5%) were applied under an occluded patch for 48 hours to the backs of 109 male and female persons, all 12 years of age or more. Ten patches were sequentially applied, followed by challenge at a fresh site on the back.

With 0.5% solution, there were seven cases of erythema and nine of slight irritation. On challenge, one case of erythema and oedema and one case of slight irritation resulted. With both the 0.1% and 0.2% solutions, one case of erythema of two of slight irritation resulted, but there was no reaction on challenge.

Under the conditions of the study, 0.5% glutaraldehyde was a skin irritant in humans, and a skin sensitiser in 1-2% of the test population. The more dilute solutions (0.1% and 0.2%) indicated signs of skin irritation but no sensitisation.

11.2.2 Respiratory sensitisation

Occupational asthma is a respiratory disease characterised by variable bronchial obstruction and variable hyperactivity caused by specific agents inhaled at work,[40] and rhinitis is a disease that invokes inflammation of the nasal mucous membrane, characterised by periods of nasal discharge, sneezing and congestion.[40] Respiratory sensitisation is an immune status resulting from an immune response to an antigen,[40] which may be a finding in the diagnosis of occupational asthma and/or rhinitis.

The definition of occupational asthma is subject to some debate in the literature, depending on its purpose, for example, for epidemiological or medical-legal purposes. Balmes[90] proposed the broadening of the definition to include the exacerbation of airways obstruction by workplace exposure.

When considering individual cases of occupational asthma and rhinitis, the diagnosis is based on the following information:[40]

- a clinical history — with emphasis on occupational and family history;
- a physical examination;
- lung function tests — such as the peak expiratory flow rate (PEFR), forced expiratory volume in one second (FEV_1), forced vital capacity (FVC) and maximum midexpiratory flow rate (MMEF);
- bronchial provocation tests — to confirm, if necessary, the diagnosis of allergic asthma; and
- immunological tests — to detect the presence of specific IgE antibody.

Respiratory allergy reactions from exposure to antigens are generally but not always effected by a specific antibody. Allergic asthma and rhinitis are usually immediate-onset reactions, resulting from the the local release of inflammatory mediators and usually effected by the IgE antibody. However, asthma may also be late-onset or persistent, due to a different type of immune reaction.

Specific antibodies against occupational sensitisers have been mainly detected for high molecular weight agents. However, for glutaraldehyde, as with other low molecular weight chemicals, immunological tests may be limited as specific IgE antibodies have not been demonstrated in affected workers,[91] and the type of allergic mechanism is not yet known.

A number of cases of respiratory disease such as occupational asthma and rhinitis have been linked with exposure to glutaraldehyde in the workplace, with some cases concerning workers with no past history of allergic response. Difficulties have arisen in determining whether the response in each case is due to an irritant effect or to an allergic hypersensitivity. The type of allergic mechanism that causes asthma after exposure to glutaraldehyde is not yet known, and no specific antibody has been identified.[91]

Cases of occupational asthma and rhinitis in workers exposed to glutaraldehyde that have been reported in the scientific literature include the following:

Case 1 An endoscopy unit sister suffered asthma-like symptoms on exposure to a 2% glutaraldehyde solution. The sister was routinely exposed to glutaraldehyde from Mondays to Fridays, and measurements with a peak-flow meter confirmed an improvement in flow levels during the weekend and on removal from direct exposure to glutaraldehyde.[92]

Case 2 Four endoscopy nurses reported respiratory symptoms after exposure to 2% glutaraldehyde. Three of the nurses had a past history of asthma and rhinitis, with their condition deteriorating on exposure to glutaraldehyde. The fourth nurse experienced chest tightness on exposure. The results of lung function testing (FEV1 and FVC) were within normal limits for the four nurses. On provocation testing with 2% glutaraldehyde, delayed wheezing resulted in one of the atopic cases, and an immediate and delayed increase in nasal discharge and sneezing resulted in one other.[76]

Case 3 In an endoscopy unit, six of the nine workers experienced rhinitis on exposure to 2% glutaraldehyde, with one of the workers, an endoscopy nurse, also suffering asthma-like symptoms, watering of the eyes and facial dermatitis. None of the workers had any history of atopy.[65]

Case 4 A dentist using 2% glutaraldehyde for the disinfection of instruments reported hay fever-type symptoms which disappeared after discontinuing use of glutaraldehyde.[93]

Case 5 A study of 554 cases of occupational asthma in the United Kingdom in 1989 revealed two cases attributable to glutaraldehyde exposure. The clinical details of the cases were not available.[94]

Case 6 A respiratory technologist with a history of asthma in childhood suffered severe acute exacerbation of her asthma after beginning employment in a bronchoscopy unit where a 3.6% glutaraldehyde solution was used for disinfection. After peak-flow measurements indicated an improvement in her condition away from the workplace, a hypersensitivity to glutaraldehyde was confirmed by workplace challenge testing. As her lung function parameters (FEV1 and PEFR) did not return to normal after 24 hours, a late asthmatic reaction was also indicated.[91]

Case 7 A radiographer with a history of hay fever but not asthma experienced breathing difficulties over a 12-month period. On provocation testing for five minutes with the 11% glutaraldehyde solution used in the workplace, a late asthmatic response was confirmed by FEV1 measurements. A second radiographer with a history of hay fever also experienced wheezing at work, but challenge testing with 1% and 2% glutaraldehyde did not affect her lung function parameters.[95]

Case 8 An endoscopy nurse without any previous history of respiratory disease experienced recurrent episodes of chest tightness, wheeziness and shortness of breath on exposure to glutaraldehyde. The symptoms disappeared on holidays and on weekends, and then finally after relocating to another work area.[96]

Case 9 A female technician without any previous history of respiratory disease developed occupational asthma after exposure to 2% glutaraldehyde solution, which was used to clean and disinfect respiratory therapy equipment. Initially she experienced eye irritation only after exposure, but after approximately one year, she sufferred asthma, nasal congestion and watering of the eyes approximately two hours after returning home after work. The frequency and severity of attacks gradually increased, with the latter apparently related to the duration of exposure. A glutaraldehyde inhalational challenge test resulted in a delayed response only, as measured by PEFR. However, an immunological mechanism did not appear to be responsible, as the serum IgG and IgE levels were normal, and a skin scratch test with 2% glutaraldehyde was negative. The worker subsequently moved to another department and the severity and frequency of attacks decreased markedly. However, on one day she experienced a severe asthmatic attack after making repeated visits to the glutaraldehyde storage area.[97]

Case 10 In the survey carried out by the South Australian Occupational Health and Safety Commission in 1993, occupational asthma was diagnosed in a nurse exposed to glutaraldehyde. (see Appendix 4)

In the United Kingdom, glutaraldehyde has been added to the indicative list of respiratory sensitisers on the recommendation of the Industrial Injuries Advisory Committee that glutaraldehyde may cause occupational asthma.[98] Under the Surveillance of Work-related and Occupational Respiratory Disease (SWORD) reporting scheme, run by the Epidemiological Research Unit of the London Chest Hospital, in collaboration with the Society of Occupational Medicine and the British Thoracic Society, 20 cases of occupational asthma resulting from glutaraldehyde exposure were reported during 1989-90.[99]

From the case studies cited above, there is sufficient evidence to conclude that occupational asthma and rhinitis can result from exposure to glutaraldehyde in the workplace. Whether the responses have been due to an irritant effect or to allergic hypersensitivity is less clear.

In most of the cases cited, no atmospheric monitoring of glutaraldehyde was conducted, so it is not known whether the vapour concentrations were above or below the irritant level. Similarly the vapour concentrations during provocation testing with glutaraldehyde solutions were not measured.

Lung function measurements were carried out after provocation testing in several of the cases, with a delayed onset of asthma in four cases (2, 6, 7, 9). Delayed nasal discharge and sneezing occurred in one case (Case 2). As asthmatic reactions caused by irritation generally occur immediately after exposure and are transient,[91] these cases provide

some evidence for respiratory sensitisation and are therefore of concern.

In several, but not all, of the cases, the affected workers were atopic. Atopy appears to be a significant risk factor in the onset of asthma after exposure to antigens that cause asthma by IgE-mediated mechanisms, for example, high molecular weight antigens, but there is no evidence that it is a risk factor in asthma caused by antigens which do not induce an IgE-mediated response, for example, low molecular weight antigens such as glutaraldehyde.[90]

The summary of cases and discussion above highlight the difficulty in determining whether the occupational asthma seen is a result of respiratory sensitisation. Improvements in the reporting of cases of respiratory disease caused by exposure to glutaraldehyde, both in the literature and to occupational physicians, would help reviews of this subject in future.

11.2.3 Photosensitisation

Phototoxicity[100] (TKL 906001)

The ability of glutaraldehyde to induce a phototoxic reaction in the skin of humans was determined by using a controlled photopatch test, where a combination of ultra-violet (UV) light and the chemical/skin tissue complex causes a clinical sunburn-type reaction.

Glutaraldehyde at concentrations of 0.05%, 0.02%, 0.01% and 0.005% w/v was applied to two sites on the backs of 49 female and three male healthy volunteers (aged 22-73) for 24 hours. Atopics and individuals with skin disorders were not considered for the tests.

One site was irradiated with 24 J/cm^2 UV-A (320-400nm) and the second site remained unexposed to UV light. A third site, without glutaraldehyde, was irradiated to serve as a control. All sites were scored for erythema and oedema 24 and 48 hours after irradiation.

Approximately 20 subjects experienced slight to minor erythema at all concentrations with the irradiated product and the irradiated control, but not with glutaraldehyde only. Eight others experienced slight to moderate erythema at the chemical/UV site only, with six of these at 0.05% glutaraldehyde only. Faulty equipment was suspected of allowing UV-B and excess UV-A to the sites, so the eight subjects were retested with one of the negative subjects. Two subjects experienced very slight erythema at 24 and 48 hours with 0.05% irradiated product, but not with glutaraldehyde or UV only.

The authors of the study concluded that there was no evidence of phototoxicity to any of the concentrations of glutaraldehyde tested, but in view of the need for retesting, and the very slight reaction in two subjects on retest, the study did not conclusively show that glutaraldehyde is not phototoxic.

Photoallergy[101] (TKL 907001)

The ability of glutaraldehyde to induce a photoallergic skin reaction in humans was determined by use of a controlled photopatch test. This procedure was for the detection of photoallergic contact dermatitis only.

Glutaraldehyde was applied to two sites on the backs of 91 female and eight male volunteers (aged 18-77 years) at concentrations of 0.05%, 0.02%, 0.01% and 0.005% w/v at a frequency of twice per week for a total of six inductions. Atopics and individuals with skin disorders were not considered for the tests.

Twenty-four hours after each application, one of the sites was irradiated with UV-A (320-400nm) at twice each subject's minimal erythemal dose. After a 10-13 day rest

period, challenge was effected by applying glutaraldehyde to two new sites, and irradiating one set with 6 J/cm^2 of UV-A. A third site was irradiated as a control.

All sites were scored for erythema and oedema 24 hours after application of the test material and 24, 48, and 72 hours after irradiation for both the induction and challenge phases of the test. No significant erythema or oedema was observed.

Under the conditions of the test, glutaraldehyde did not induce photoallergic contact dermatitis at concentrations 0.05-0.005%.

11.3 Other effects

Other symptoms reported in workers after exposure to glutaraldehyde have included headache, nausea and light-headedness.[17]

In Western Australia, palpitations and tachycardia were reported in seven health care workers after regular exposure to glutaraldehyde,[102] but the reports have not been confirmed by scientific and toxicological evidence.

A study in hospital staff engaged in the chemical disinfection of instruments found that an increased frequency of spontaneous abortions did not correlate with exposure to glutaraldehyde.[103] A later study comparing 164 nurses who had suffered miscarriage with 464 who had normal births indicated that glutaraldehyde exposure was similar in both groups.[104] The same study gave similar results when comparing nurses who have borne malformed children with those producing normal children.

11.4 Mortality studies

11.4.1 Mortality study of glutaraldehyde production workers[105]

In a mortality study of 186 males employed during the period 1959-78 at a glutaraldehyde production unit (GPU) in West Virginia USA, the number of cancer deaths and the total number of deaths were compared to those of US white males and to that of 29,000 other chemical workers during the period 1959-78.

All subjects were observed for at least 10 years, with an average time since their first exposure to glutaraldehyde of 20.6 years, and an average duration of employment at the GPU of 3-7 years. Standardised mortality ratio analyses were conducted, using US mortality rates for white males up to 1988 for the calculation of the number of expected deaths.

The number of deaths was 14 (25.4 expected) and the total number of cancer deaths four (6.1 expected). There was no evidence of glutaraldehyde being carcinogenic, but the study was hampered by the relatively short observation period and the number of subjects still relatively young.

The average glutaraldehyde exposure during the period 1977-88 was 0.05 ppm (range 0.01-0.17 ppm), but unfortunately little or no monitoring was conducted prior to 1977.

11.5 Medical record reviews

11.5.1 Review of workers assigned to glutaraldehyde production or drumming[106]

A study of the medical records of 218 workers employed at a GPU from 1959-92 was carried out for a chemical plant in West Virginia, USA. At the plant, workers were exposed to an extensive range of other chemicals, some of them being skin and respiratory sensitisers.

A mortality study[105] was previously carried out on the 186 workers employed during 1959-78 (see section 11.4.1). The study population therefore comprised:

- all workers employed in the GPU during 1959-78;
- 25 shift workers at the unit during 1992; and
- seven drummers in the distribution section during 1992.

Of the 218 workers, 210 had medical records, and 193 of these were complete. The records were screened to identify any specific or non-specific symptoms of sensitisation, and a more detailed inspection was conducted by the plant physician to determine whether the symptoms correlated with the possible effects of glutaraldehyde exposure.

Glutaraldehyde monitoring at the plant began in 1977, with the mean time weighted average (TWA) concentration for 1977 being 0.08 ppm, and the mean for the years 1977-88 being 0.05 ppm. Exposure levels prior to 1977 were probably higher.

Short term (15 minutes) exposure limit (STEL) testing began in 1989, with a STEL mean of 0.06 ppm since that year and a range of 0.01-0.34 ppm. The mean exposure time of all subjects was 3.8 years, although the average for drummers was 6.4 years.

Of the 210 workers with medical records, 89 were identified with symptoms, but only 11 of these were identified as being possibly related to glutaraldehyde exposure. In five of these cases, the sensitisation symptoms were attributed to another chemical, four due to toluene di-isocyanate and one to bis (2,3-epoxycyclopentyl) ether. The remaining six cases were classified as 'unsure', with their diagnoses as follows:

Case 1 At GPU from 1987 — sinusitis.

Case 2 Drummer from 1984 — eye irritation, with earlier history of conjunctivitis (from 1976).

Case 3 At GPU 1977-85 — contact dermatitis.

Case 4 At GPU 1961-80s — dermatitis, conjunctivitis, and nasal irritation, inflammation and bleeding.

Case 5 At GPU 1965-78 — eye irritation, contact dermatitis.

Case 6 At GPU 1966-68 — contact dermatitis, sinusitis.

None of the above six workers was removed from possible exposure to glutaraldehyde.

On the evidence in the review, it cannot be determined whether the six cases classified as 'unsure' were in response to a sensitisation effect by glutaraldehyde. The diagnoses reported were consistent with the known irritant effects of glutaraldehyde, but the workers were exposed to a number of other chemicals in the workplace.

11.6 Summary

Human evidence has shown that glutaraldehyde is an irritant to the skin, eyes and respiratory system, with the effects consistent with those revealed in animal testing.

Many cases of dermatitis have been reported for workers exposed to glutaraldehyde solutions, usually 2% or higher. Facial dermatitis has resulted from the use of glutaraldehyde in spray form.

Irritation of the nose and throat and general tightness of the chest have been experienced by workers exposed to glutaraldehyde vapours. In a study of Swedish hospital workers, nose and throat irritation was experienced at concentrations below 0.2 ppm.

Human evidence indicates that skin and respiratory irritant effects are exacerbated on repeated exposure to glutaraldehyde.

Human evidence and patch testing have shown that glutaraldehyde is a skin sensitiser. Photosensitisation testing on volunteers did not produce a positive phototoxic or photoallergic response.

A number of reports of occupational asthma and/or rhinitis in workers exposed to glutaraldehyde have produced concern that glutaraldehyde may be a respiratory sensitiser. In the absence of adequate case reporting or an identified immune mechanism, it is difficult to say definitively that glutaraldehyde is a respiratory sensitiser, so there is debate on whether the symptoms are due to an irritant or allergic respiratory response. However, in the United Kingdom, glutaraldehyde has been added to the indicative list of respiratory sensitisers. Further studies are required into the mechanism and cause of occupational asthma in workers exposed to glutaraldehyde.

Limited epidemiological data is available on the long term effects of glutaraldehyde, and only the irritant and skin sensitising effects of glutaraldehyde have been confirmed. There was no evidence of adverse reproductive health effects on exposure to glutaraldehyde, consistent with the results of animal testing. A mortality study did not reveal any increased incidence of cancer deaths.

12. Hazard classification

12.1 Classification of hazardous substances

12.1.1 General

The classification of chemical substances is the process where the toxicological, physicochemical and ecotoxicological properties of the substances are evaluated against defined criteria for the purposes of regulatory action.

Under the National Commission's *National Model Regulations for the Control of Workplace Hazardous Substances*,[107] and the imminent Commonwealth, State and Territory government regulations to be introduced in accordance with these national model regulations, manufacturers and importers of substances supplied for use at work will be required to determine whether they are hazardous to health before supply.

In determining whether a substance is hazardous to health or not, manufacturers and importers will firstly refer to the *List of Designated Hazardous Substances*[108] (the List) published by Worksafe Australia. If the substance is not on the List,[108] then it must be classified by the supplier in accordance with *the Approved Criteria for Classifying Hazardous Substances*[109] (the Approved Criteria).

The health effects criteria in the Approved Criteria[109] are the same as those used by the Commission of the European Community in its Dangerous Substances and Preparations Directives 67/548/EEC and 88/379/EEC, except for corrosivity, which is determined in accordance with the criteria for corrosive substances in the *Australian Code for the Transport of Dangerous Goods by Road and Rail*[110] (ADG Code).

In Australia, glutaraldehyde is on the List[108] because it has a national exposure standard. At present, no risk and safety phrases appear with the listing as none have been assigned for glutaraldehyde in the Commission of European Communities' corresponding list of dangerous substances.[111] Risk and safety phrases are needed for the appropriate labelling of glutaraldehyde.

For labelling, suppliers also need to consider the physicochemical hazards of the substance, as defined in the ADG Code[110] and addressed under the relevant dangerous goods legislation of the Commonwealth, State and Territory governments, and any other applicable legislation.

Glutaraldehyde is not listed separately in the ADG Code[110], but it falls within the scope of Toxic Aldehydes, NOS.

Glutaraldehyde is listed on the National Health and Medical Research Council's *Standard for the Uniform Scheduling of Drugs and Poisons*[112] (SUSDP).

Both the health and physicochemical hazards of glutaraldehyde must be considered when producing labels and Material Safety Data Sheets (MSDS).

12.1.2 Health effects criteria

The Approved Criteria[109] for classifying a substance hazardous to health are in three parts:

- fundamental criteria for the different types of health effect, for example, acute lethal effects, irritant effects and carcinogenicity;
- concentration cut-off limits for the substance in a mixture; and
- formulae which may need to be used for a mixture where the concentrations are below the concentration cut-off limits.

For each of the different types of health effect, a risk phrase can be assigned to the substance, for example, R35 (causes severe burns for a Very Corrosive substance). The risk phrases used in Australia are consistent with those used by the Commission of the European Communities. A substance may have more than one health effect, and therefore more than one risk phrase assigned. For the purposes of labelling, the risk phrases used should identify the hazards present with the normal, or reasonably foreseeable, handling or use of the substance.[113]

12.2 Classification of glutaraldehyde

In classifying glutaraldehyde, each of its different health effects needs to be considered. In the classification of mixtures containing glutaraldehyde, for example, a 2% aqueous solution of the chemical, the following information is used:

the results of testing of the mixture as a whole substance, for example, the acute oral toxicity of a 2% glutaraldehyde solution, or

where insufficient data is available on the mixture, the appropriate concentration cut-off limits listed in the Approved Criteria,[109] together with information on a higher concentration of glutaraldehyde.

12.2.1 Acute lethal effects

Oral

Acute oral toxicity studies in the rat have resulted in LD_{50} values for glutaraldehyde in the range 77-820 mg/kg body weight. In accordance with the Approved Criteria,[109] glutaraldehyde as a pure chemical is classified as Toxic in terms of its acute lethal effects by the oral route (risk phrase R25).

From the results of acute oral toxicity studies in the rat conducted with glutaraldehyde solutions from 0.5-50% (see section 10.1.1), glutaraldehyde solutions at concentrations $\geq$ 50% are classified as Toxic (risk phrase R25) on the basis of their acute oral toxicity and at concentrations $\geq$ 5% and < 50%, they are classified as Harmful (risk phrase R22).

Dermal

Data for acute dermal toxicity studies in the rabbit have resulted in LD_{50} values in the range 640-2000 mg/kg body weight, and in the rat > 2500 mg/kg, so glutaraldehyde as a pure chemical is classified as Harmful in terms of its acute lethal effects by the dermal route (risk phrase R21).

From the results of acute dermal toxicity studies in the rabbit conducted with glutaraldehyde solutions from 5-50% (see section 10.1.2), glutaraldehyde solutions at concentrations above 25% are classified as Harmful on the basis of their acute dermal toxicity (R21).

Inhalation

The criterion for classification of substances on the basis of their acute inhalational toxicity is the LC_{50} in the rat, with the limits for classification as Very Toxic, Toxic and Harmful being 0.25, 1 and 5 mg/L/4hr respectively.[109]

For glutaraldehyde, the results of acute inhalational toxicity testing are described in sections 10.1.3 and 10.1.4, with the LC_{50} values listed in section 10.1.3. In the only complete LC_{50} study available for assessment, a four-hour value of 23.0 ppm (96 mg/L) was obtained for the male rat and 40.1 ppm (164 mg/L) for the female.[22] The high toxicity in this study has been attributed to the presence of more toxic higher molecular weight species of glutaraldehyde formed during the generation of vapours from solution at 65°C, but no supporting evidence for this view is available. Moreover, a study[18] in rats exposed to 20 ppm glutaraldehyde (82 mg/L) resulted in 50% of the animals dying within 90 minutes, and a four-hour rat LC_{50} of 480 mg/L has been reported.[26] These findings, together with the results of nine-day studies in the rat, where significant mortality occurred at 2.1 and 3.1 ppm, tend to support the LC_{50} values of 23.0 and 40.1 ppm for male and female rats respectively.

The literal application of these results would indicate that glutaraldehyde as a pure chemical should be classified as Very Toxic in terms of its actual lethal effects by inhalation, that is, an LC_{50} in the rat of < 0.25 mg/L/4hr.

However, due to the limited data available, a moderated approach could be adopted in this instance to give a provisional classification because the low vapour pressure and its occurrence in aqueous solutions should generally limit its availability. Vapour generation studies with various strengths of solution (see section 10.1.3) have confirmed that glutaraldehyde, by virtue of its low vapour pressure (see Chapter 5 and Table 23 in Chapter 14), is liberated from aqueous solutions at vapour concentrations significantly below toxic levels. For example, a maximum of 6.6 ppm was obtained above a 50% solution.

Consequently, on the basis of limited available data and vapour pressure data for various concentrations of aqueous solution, solutions above 25% could be classified as Toxic (risk phrase R23), and solutions from 1% to 25% should be classified as Harmful (risk phrase R20).

Due to concerns regarding the method of vapour generation in the only available LC_{50} study, comparative LC_{50} tests are currently being carried out at ambient and elevated temperatures. When data from these studies are available, together with any other relevant data such as aerosol test results, this classification should be reviewed.

12.2.2 Corrosivity/irritancy

Testing with 45% and 50% w/w aqueous glutaraldehyde solutions on the skin of rabbits resulted in visible necrosis at the site of application. According to the Approved Criteria,[109] 45% and 50% glutaraldehyde is Corrosive (risk phrase R34).

The results of skin irritation testing at various concentrations (see section 10.2.1) indicate that solutions above 25% are Corrosive, and that solutions at 1% and up to 25% are Skin Irritants (risk phrase R38).

The results of eye irritation testing at various concentrations (see section 10.2.2) indicate that solutions greater than 5% may cause Serious Eye Damage (risk phrase R41), and that solutions greater than 0.1% and up to 5% are Eye Irritants (risk phrase R36).

Glutaraldehyde is a Respiratory Irritant on the basis of observed effects in humans and the results of animal inhalation studies (risk phrase R37). As respiratory irritation has been observed in workers using dilute solutions, and as 1% and 2% solutions have similar vapour pressures and health effects, solutions of 1% and above should be classified as Respiratory Irritants.

12.2.3 Sensitisation

From the results of animal testing and the human evidence in the scientific literature, glutaraldehyde is a Skin Sensitiser (risk phrase R43). By applying the concentration cut-off limit from the Approved Criteria,[109] solutions ≥ 1% should be classified as Skin Sensitisers.

The classification of glutaraldehyde in terms of its respiratory sensitising effect is less clear cut. From the Approved Criteria,[109] a substance is classified as a sensitiser by inhalation…

> 'If practical evidence is available which shows that the substance is capable of causing a sensitisation reaction in humans by inhalation, at a greater frequency than would be expected from the response of a general population.'

The criteria for sensitisation are currently being reviewed in the EEC to provide more guidance in their application; the existing criteria describe sensitisation by a particular route of exposure rather than describing the disease that may be caused by the substance, that is, respiratory hypersensitivity and/or skin sensitisation.

There is some evidence for the possible respiratory sensitising effect of glutaraldehyde in humans, with cases of exposure-related occupational asthma and rhinitis summarised in section 11.2.2. In addition, glutaraldehyde has been added to the indicative list of respiratory sensitisers in the United Kingdom after 20 cases of occupational asthma were reported after exposure to glutaraldehyde during 1989-90.

However, in light of the history of atopy in many of the patients, the limited exposure data for the cases listed, and the difficulty in determining whether a particular case of occupational asthma or rhinitis is due to an irritant effect or an allergic hypersensitivity, the classification of glutaraldehyde as a sensitiser by inhalation in terms of the Approved Criteria109 is not conclusive. However, to reflect the evidence that is available, the following statement is recommended for inclusion in MSDS of substances containing ≥ 1% glutaraldehyde:

> 'Occupational asthma and/or rhinitis have been indicated in a number of workers exposed to glutaraldehyde.'

Further information and better reporting from case studies, together with the study of possible mechanisms of action, are expected to clarify this situation, as may future changes in the classification criteria.

12.2.4 Severe effects after repeated or prolonged exposure

A two-year drinking water study[42] in Fischer 344 rats revealed an increased incidence of LGLL in females only at all dose levels (50-1000 ppm w/v), but the findings were not conclusive, so no classification is recommended for glutaraldehyde in terms of its repeated exposure effects by the oral route.

A number of repeated dose inhalation studies on rats and mice have shown that glutaraldehyde at approximately 50-60 ppb v/v (0.21-0.24 mg/L) may result in an exacerbation of the irritant effects observed in acute inhalational studies.

Therefore glutaraldehyde should not be classified in terms of any repeated exposure

effects by inhalation.

12.2.5 Mutagenicity

Glutaraldehyde has been shown to be mutagenic in some bacterial assays and evidence of DNA damage and chromosome damage has been found in some tests in mammalian cells. However, all in vivo tests reported to date have yielded negative results.

According to the criteria for mutagenicity, glutaraldehyde should not be classified as a mutagen. However, in view of the number and variety of positive in vitro tests, the following statement is recommended for inclusion in MSDS for products containing glutaraldehyde:

> 'The results of more recent assays have generally shown that glutaraldehyde is mutagenic in vitro. In vivo tests to date have been negative. Consequently glutaraldehyde does not meet the criteria for classification as a mutagen.'

12.2.6 Carcinogenicity

The only evidence of tumour formation to date is the increased incidence of LGLL in female Fischer 344 rats in the two-year drinking water study. However, the finding is inconclusive so, in accordance with the Approved Criteria,[109] glutaraldehyde does not meet the criteria for classification as a carcinogen.

12.2.7 Reproductive toxicity/teratogenicity

Studies on the incidence of miscarriage in pregnant women have shown no difference between those exposed to glutaraldehyde and those not exposed to the chemical.

Studies in female rats and mice have resulted in embryotoxicity/foetotoxicity for glutaraldehyde, but only at doses which are maternally toxic.

A number of studies have found no evidence of teratogenicity.

12.2.8 Non-lethal irreversible effects after a single exposure

There is no evidence of any irreversible effects by glutaraldehyde after a single exposure.

12.2.9 Summary

The main concentrations of aqueous glutaraldehyde imported and produced in Australia are 50%, 45%, 25%, 10%, 5%, 2% and 1% and, based on the above conclusions, these can be classified as listed at Table 22.

Table 22

Risk phrase classification for concentrations of glutaraldehyde

Concentration	*Risk phrase(s) to be used*
50%	R21, R23, R25, R34, R37, R41, R43
45%	R21, R22, R23, R34, R37, R41, R43
25%	R20, R22, R37, R38, R41, R43
10%	R20, R22, R37, R38, R41, R43
5%	R20, R22, R36, R37, R38, R43
2%	R20, R36, R37, R38, R43
1%	R20, R36, R37, R38, R43
> 0.1-< 1%	R36
≤ 0.1% no classification	

For the purposes of labelling, the risk phrase for Serious Eye Damage (R41) may be covered by R34.

In the classification of glutaraldehyde solutions which contain other hazardous substances, for example, x-ray film processing solutions which may sodium bisulfite and hydroquinone, consideration of all the hazardous substances in the mixture must be taken into account.

The choice of risk phrases by suppliers in the labelling of their products is discussed in section 13.2.

12.3 Dangerous goods classification

Glutaraldehyde is not listed in the ADG Code.[110] However, it comes within the scope of Aldehydes, Toxic, NOS. At concentrations where the aqueous glutaraldehyde solution is Corrosive, for example, 45% and 50%, it should be classified as a Class 8 substance. More dilute solutions should be classified as a Class 6.1(b) substance.

A Hazchem code of 2ZE is appropriate for concentrated glutaraldehyde.

12.4 Poisons schedule

Glutaraldehyde for human therapeutic use is listed on Schedule 2 of the SUSDP.[112]

Glutaraldehyde for preparations containing < 5%, except when on Schedule 2, is listed on Schedule 5.

Glutaraldehyde, except when on Schedule 2 or Schedule 5, is listed on Schedule 6.

For domestic end-use products, the warning statements and safety directions listed in Appendix F part 3 of the SUSDP[112] must be assigned to the label. For glutaraldehyde, for example, in sanitisers for aircraft toilets, these are as follows:

- warning statement 5 (Irritant) for all strengths; and
- safety directions:
  - 1 (avoid contact with eyes) and 4 (avoid contact with skin) for all strengths, or
  - 1, 4 and 8 (avoid breathing vapour or spray mist) for > 25%.

For agricultural and veterinary products, the safety directions listed in Appendix H part 2 of the SUSDP[112] must be assigned to the label. For glutaraldehyde, for example, in animal health products, these are as follows:

- safety directions for all strengths:
  - harmful (or poisonous for Schedule 6) if absorbed by skin contact or inhaled,
  - will irritate the eyes and skin,
  - avoid contact with eyes and skin,
  - do not inhale vapour when using the product,
  - wear elbow-length PVC gloves and faceshield or goggles,
  - after use and before eating, drinking or smoking, wash hands, arms and face thoroughly with soap and water, and
  - after each day's use, wash gloves, faceshield or goggles and contaminated clothing.

As importers and manufacturers need to comply with requirements under the SUSDP,[112] ADG Code[110] and hazardous substances regulations in various circumstances, any differences in requirements between jurisdictions may be confusing.

For glutaraldehyde, this is particularly so for corrosivity/irritancy, where under the SUSDP[112] there is a warning of irritancy rather than corrosivity for concentrations above 25%. Also, no warning is required for skin sensitisation under the SUSDP.[112]

It is recommended that the warning statements in the SUSDP[112] for glutaraldehyde are reviewed to take into account this assessment.

13. Hazard communication

13.1 Material Safety Data Sheets

MSDS are the primary sources of information for workers employed in the handling, use, storage and disposal of industrial chemicals, especially those which are classified as hazardous substances. Glutaraldehyde is a hazardous substance and mixtures containing > 0.1% of the chemical are hazardous substances.

Glutaraldehyde is used in approximately 40 different products in Australia. In the information submitted for assessment, 30 MSDS of mixed quality were submitted, with only approximately 10 of the MSDS written in accordance with the National Commission's *National Code of Practice for the Preparation of Material Safety Data Sheets*,[114] or the National Commission's *Guidance Note for Completion of a Material Safety Data Sheet* (1991). The MSDS submitted are listed in Appendix 2.

A good MSDS should contain:

- identifying information about the product;
- complete health hazard information;
- precautions for use; and
- safe handling instructions.

A number of the MSDS were written outside Australia, and did not contain information specific for the use of the product in this country. These MSDS quoted ACGIH TLV's and overseas regulations instead of the National Commission Exposure Standard[8] and other Australian regulatory requirements.

In most MSDS, the concentrations of the individual ingredients were given as a range, as required by the National Commission's Code of Practice or Guidance Note, rather than as an exact concentration. However, the exact concentration of glutaraldehyde is provided on labels, so a similar approach for MSDS would assist workers and their supervisors in determining the hazards of the product.

There was considerable variation in the health effects information on glutaraldehyde provided on the MSDS, with many containing insufficient data on known human health effects, and many containing little or no animal toxicity data.

In the precautions for use in the MSDS, most suppliers used standard phrases when outlining the engineering controls to be used. Guidance could be more specific in some cases, for example, the use of enclosed systems for formulation using concentrated glutaraldehyde solutions, and the use of local exhaust ventilation in disinfection. Most MSDS specified the appropriate personal protective equipment to wear during the routine use of glutaraldehyde solutions and in case of spills.

For most MSDS, the sections on first aid and safe handling, including firefighting and disposal procedures, were satisfactory.

To satisfy the regulatory requirement that an MSDS be included in the assessment report, two examples submitted during the assessment have been appended to this report:

- the Union Carbide Chemicals Australia MSDS for 50% glutaraldehyde; and
- the ICI Australia MSDS for Aldecyde 28, which contains approximately 2% glutaraldehyde.

13.2 Labels

Preparing a label for glutaraldehyde highlights the difficulties experienced by suppliers in satisfying the labelling requirements of the various regulatory codes and schedules.

In general, industrial chemicals are labelled in accordance with the National Commission's *National Code of Practice for the Labelling of Workplace Substances*[113] (the Labelling Code). There are exceptions, including:

- agricultural chemical products, as defined under *the Agricultural and Veterinary Chemicals Act* and when labelled in accordance with *the Code of Practice for Labelling Agricultural Chemical Products*; and
- hazardous substances imported from overseas, provided that the labels fulfil Australian requirements.

Domestic end-use products covered by the SUSDP[112] need to be labelled in accordance with SUSDP[112] requirements, but for such products used in the workplace, additional information in accordance with National Commission requirements may be needed on the label.

For glutaraldehyde-containing products, the following requirements should be noted:

- glutaraldehyde products used in the animal housing industry must be registered and labelled according to the Agricultural Chemicals Labelling Code;[113]
- glutaraldehyde is on Schedules 2, 5 and 6 of the SUSDP,[112] so products in Australia designed for domestic use, for example, sanitisers for portable and aircraft toilets, must fulfil the labelling requirements of the SUSDP;[112] and
- imported products containing glutaraldehyde, for example, some x-ray film processing solutions, are regarded as hazardous substances if they contain > 0.1% of the chemical.

In addition, for some concentrations of glutaraldehyde the labelling requirements of the ADG Code[110] also apply. Aqueous solutions containing > 25% glutaraldehyde fall into Class 8 (Corrosive), with more dilute solutions falling into Class 6.1(b) (Harmful [Toxic]) substances of packaging group III.

When labelling industrial chemicals in accordance with the Labelling Code,[113] risk phrases dependent on the hazard classification of the substance in accordance with the Approved Criteria[109] are selected to describe the risks associated with the normal, or reasonably foreseeable, handling or use of the substance. The risk phrases appropriate for glutaraldehyde are specified in chapter 12, Hazard Classification (all the risk phrases from the Approved Criteria[109] are listed in Appendix 1). Safety phrases appropriate to the proposed use of the product are then assigned in accordance with the Labelling Code,[113] with suitable phrases for glutaraldehyde listed at Table 23.

Table 23

Safety phrases suitable for use with glutaraldehyde

Phrase number	Phrase
S23	Do not breathe vapour
S24	Avoid contact with skin
S25	Avoid contact with eyes
S26	In case of contact with eyes, rinse immediately with plenty of water and contact a doctor or Poisons Information Centre
S29	After contact with skin, wash immediately with plenty of water
S36	Wear protective clothing
S37	Wear suitable gloves
S38	In case of insufficient ventilation, wear suitable respiratory equipment
S39	Wear eye/face protection
S51	Use only in well-ventilated areas

Under the SUSDP[112] labelling provisions, the labels of domestic end-use products containing < 5% glutaraldehyde should contain the following signal word and phrase:

WARNING

KEEP OUT OF REACH OF CHILDREN

Other glutaraldehyde preparations for domestic end-use should contain the following signal word and phrases on the label:

POISON

NOT TO BE TAKEN

KEEP OUT OF REACH OF CHILDREN.

The warning statement required by the SUSDP[112] for glutaraldehyde is Irritant (for all concentrations). The safety directions required on the label are listed at section 12.4.

In the information submitted for assessment, 21 labels of variable standard were submitted. They are listed in Appendix 3 with their risk and safety phrases. As required, all labels specified the concentration of glutaraldehyde in the product and most contained good first aid and emergency response information. However, there was a lack of consistency in the risk and safety phrases applied. Some products were labelled with a fairly complete set of risk phrases in accordance with the hazard classification of the product (see chapter 12). Some other labels had only one or no risk phrase, but most labels contained some safety phrases. Deficiencies in hazard identification noted on labels listed in Appendix 3 included the following:

- only 11 of the 21 labels included a risk phrase for skin sensitisation (such as R43);
- only eight of the 21 labels included a risk phrase for eye irritation or damage (such as R36 or R41), with another five including a safety phrase for avoidance of contact with the eyes (S25); and

- only 11 of the 21 labels included a risk phrase for respiratory irritation (such as R37) or a safety phrase for avoidance of vapour/mist respiration (S23).

Furthermore, there was a lack of consistency in the labelling of similar products within an industry, for example, 2% disinfectant solutions.

The labels on the four domestic end-use products fulfilled the SUSDP[112] and National Commission requirements and conveyed risk information about the hazards identified in the classification of glutaraldehyde according to the Approved Criteria.[109]

Some of the labels contained excellent information about the use of the product, whereas others contained little or no directions for use.

In the animal health industry, glutaraldehyde is sometimes used in spray form, leading to an increased risk of exposure to workers unless control measures are implemented. To alert workers to this hazard, it is recommended that products which may be used in spray form carry the following warning on the label:

CAUTION: AVOID BREATHING SPRAY.

13.3 Other information

In most cases, the importers of glutaraldehyde in Australia are not end-users. Also, many of the manufacturers of glutaraldehyde-containing products in Australia are not end-users, so in many instances in this country, there is a potential information gap between supplier and end-user. While glutaraldehyde solutions are repackaged and sold "downstream" to end-users, information on glutaraldehyde often does not accompany the product.

Some suppliers have provided specific information about the hazards of glutaraldehyde and safe handling guidance to end-users, but in other cases the information has been limited. Employees need to be informed of the specific hazards related to their use and handling of the product, and of any new information about the product, for example, results of atmospheric monitoring in their workplace, or new health effects data.

In the health care industry, guidelines have been produced in New South Wales, Victoria and Western Australia to convey information to workers and management on the safe use of glutaraldehyde, for example, the NSW Health Department has produced *Guidelines for the Safe Use of Glutaraldehyde in Health Care Establishments*,[115] which provides guidance on the use of 1% and 2% disinfectant solutions and x-ray film processing solutions.

Similar safe use guidelines are needed for the other industries in which glutaraldehyde

- the use of glutaraldehyde in spray from, e.g., in animal housing

is used, for example:

the use of glutaraldehyde in tanning; and

A number of industry members have been involved in the provision of health and environmental use information through Responsible Care programs but, in view of information obtained during the assessment period, some importers and suppliers of glutaraldehyde need to be more active.

14. Occupational exposure

14.1 Routes of exposure

Workers are exposed to glutaraldehyde by inhalation and skin contact. In general, exposure is at room temperature to simple aqueous glutaraldehyde solutions which contain glutaraldehyde and only low concentrations of other chemicals, for example, disinfectant solutions may be made alkaline with 0.3% of sodium bicarbonate. In some instances aerosol exposure may occur, for example, during the use of a spray or fog in animal housing and air duct disinfection. In other cases more complex glutaraldehyde solutions may be used, for example, x-ray film processing solutions generally contain a number of other chemicals, for example, sodium bisulfite, hydroquinone and acetic acid.

The risk of adverse health effects from exposure will increase with strength of glutaraldehyde solution handled, as the atmospheric concentration of glutaraldehyde vapour will increase. Table 24 illustrates the increase in glutaraldehyde vapour pressure with the concentration of glutaraldehyde in aqueous solution.

Table 24
Glutaraldehyde Vapour Pressure over Aqueous Solutions

%w/w in solution	*Vapour pressure (Pa)*	
	20°C	*35°C*
1	0.13	0.77
2	0.16	0.95
5	0.23	1.27
10	0.32	1.76
25	0.67	3.60
50	2.03	10.67

14.2 Formulation

Glutaraldehyde is imported into Australia mainly as a 45% or 50% concentrated aqueous solution and diluted with water to give the end-use product, which in most cases contains 1% or 2% glutaraldehyde. Occupational exposure during production can therefore be to aqueous glutaraldehyde ranging from 1-50% w/w.

Dilution is carried out at approximately 15 sites, with up to 20 workers employed in the operation at each site. Dilution is a batch process and at most sites is scheduled on an intermittent basis, for example, the dilution of glutaraldehyde may be scheduled for two days each month.

At some sites, the glutaraldehyde-containing product is simply repacked, with only one or two workers employed in the repacking process.

The types of worker potentially exposed to glutaraldehyde during production are:

- mixing and blending operators;
- filling line operators;
- maintenance workers;
- storage workers;
- analysts and quality control workers; and
- supervisors.

The most concentrated glutaraldehyde solutions will be handled by those workers involved in the mixing process, and in some cases storepersons and analysts. Most of the blending operations in Australia are conducted in a closed system, with exposure limited to the initial opening of the drum of raw material for transfer to the mixing vessel.

Filling line operators may be exposed to glutaraldehyde vapours, especially if ventilation and fume extraction is inadequate. Exposure by both inhalation and skin contact may occur in the case of spills during the filling operation.

Atmospheric monitoring during a well-ventilated operation resulted in 15-minute glutaraldehyde concentrations in the range 0.02-0.10 ppm v/v (the National Commission's exposure standard is 0.2 ppm, with a peak limitation).[8]

14.3 Cold disinfectant

The widest exposure to glutaraldehyde is during its use as a disinfectant in the health care industry. All large hospitals and many of the smaller ones throughout Australia use 1% or 2% aqueous glutaraldehyde solutions for the disinfection of medical and surgical instruments, for example, endoscopes, bronchoscopes and small tools such as those used in dentistry, ultrasound testing, and ear, nose and throat examinations.

In a questionnaire sent to 276 hospitals in Australia in 1987, 123 of the 145 hospitals which responded used endoscopes regularly.[116] Glutaraldehyde was the most common disinfectant used.

In a questionnaire circulated to health care establishments in Tasmania in 1993 by the Department of State Development and Resources, 19 of 47 establishments replied that they were using glutaraldehyde (see Appendix 4).

In a survey of health care establishments conducted by the South Australian Occupational Health and Safety Commission in 1993, 25 of 33 establishments replied that they were using 1% and/or 2% glutaraldehyde (see Appendix 4).
Workers potentially exposed to glutaraldehyde disinfectant solution on a regular basis include:

- endoscopy nurses;
- operating theatre nurses;
- physicians and surgeons;
- technical assistants in hospitals;
- dentists and dental nurses;
- cleaners in hospitals and clinics;
- podiatrists;

- acupuncturists
  ;
- tattooists; and
- medical research workers.

Workers such as endoscopy nurses may be exposed to glutaraldehyde solutions daily and, in some cases, exposure may occur throughout a working day.

Sources of exposure identified in the use of glutaraldehyde as a disinfectant include:

- preparation and dilution of solutions;
- transfer of solution into soaking baths and tanks;
- emission of vapours from open baths;
- placing of instruments in baths;
- transfer of soaking baths from one location to another;
- removal of instruments from baths for rinsing;
- emptying of baths; and
- disposal of waste glutaraldehyde.

As the use of glutaraldehyde in dentistry has been reduced in recent times, occupational exposure is low. Most dental instruments are now autoclaved, although in some cases the more fragile instruments are still disinfected by soaking in solutions of 0.33%, 1% and 2% glutaraldehyde. The use of glutaraldehyde varies considerably from one State or Territory to another.

A number of reports containing atmospheric monitoring results for glutaraldehyde during its use in cold disinfection are available, with glutaraldehyde concentrations generally less than 0.1 ppm in well-ventilated workplaces.

Some results of monitoring carried out in Australia are included in Table 25.

Table 25
Glutaraldehyde Concentrations in Cold Disinfection

Workplace	*Worker*	*Conc (%)*	*Sample type*	*Ppm*	*Ref.*
Hospital	endoscopy nurse	1	P	0.005-0.105	72
Hospital	endoscopy nurse	1	A	0-0.05	72
Dentist	dental assistant	2	P	0.007-0.022	72
Endoscopy		1	A	0.01-0.20	9
Operating		1	A	0-0.9	9
theatre		2	A	0.01-0.16	9
Hospital		1	A	0-0.05	SA
Hospital	endoscopy nurse	1,2	A	0.04-0.38	Q
Hospital	endoscopy nurse	2	A	0.2	WA1
Endoscopy			A	0-0.49	WA2
Dentist			A	0.01-0.02	WA3

P Personal monitoring.
A Area monitoring.
S Royal Adelaide Hospital (see Appendix 4).
Q Queensland hospitals.
WA1 Fremantle Hospital.
WA2 Results of survey of 13 hospitals conducted by Health Dept of WA — 52 measurements for a mean of 0.06 ppm.
WA3 Results of survey of 2 large dental clinics conducted by Health Dept of WA — 14 measurements for a mean of 0.01 ppm.

In the USA, NIOSH has issued several reports[66,68,69,73] on the atmospheric monitoring of glutaraldehyde in hospitals, with personal monitoring results of up to 0.6 ppm and area monitoring results of up to 0.3 ppm being obtained in a number of hospitals where workers had experienced adverse health effects on exposure to glutaraldehyde.

14.4 X-ray film processing

In the handling of glutaraldehyde-containing solutions used in x-ray film processing, workers may be exposed to other hazardous substances, for example, sodium bisulfite, hydroquinone and acetic acid.

- Workers potentially exposed to these solutions include:
- radiographers in hospitals, clinics and radiology practices;
- dark room technicians;
- printers; and
- engineers.

The total number of workers potentially exposed is considerable, as most large hospitals have x-ray departments and there is a large number of radiology clinics. Some workers such as radiographers at a large hospital may be exposed to glutaraldehyde daily whereas others, for example, an engineer conducting a welding inspection, may be exposed irregularly for brief periods.

X-ray developers are supplied to end-users in kit form as concentrates for subsequent mixing and dilution. Glutaraldehyde is included in one of the solutions in the kit at a concentration up to 50% w/w, depending on the manufacturer and supplier. It is present as free glutaraldehyde or as a glutaraldehyde-sodium bisulfite complex. After mixing and dilution, the concentration of glutaraldehyde is generally less than 1% in the working solution. Automatic mixers are generally used for the preparation and dispensation of working solutions to the processor, so the risk of exposure by both inhalation and skin contact is reduced. Smaller radiology units still use manual procedures.

The automatic machines generally used for the film processing stage normally operate at high temperature, so faults with the equipment, for example, faulty seals, poor vapour extraction, or leaking hoses, may lead to a release of glutaraldehyde vapours into the work area and therefore increased exposure. The loading of the machines with solution and the cleaning of the rollers within the machines may also lead to exposure by inhalation and skin contact.

Sources of exposure identified in the use of glutaraldehyde in x-ray film processing include:

- manual preparation of processing chemicals;
- transfer of chemicals in and out of chemical tanks and processors;
- emission of vapours from open tanks and leaking mixers, processors and piping;
- exhaust from automatic processors;
- drying of x-ray films;
- emptying of tanks; and
- cleaning of processor rollers and tanks.

Atmospheric monitoring in x-ray film processing work areas has been conducted, with glutaraldehyde concentrations generally below the exposure standard of 0.2 ppm, especially in areas using automatic mixing and processing equipment.

Some results of monitoring carried out in Australia are included in Table 26.

Table 26
Glutaraldehyde concentrations in x-ray film processing

Workplace	*Worker*	*Conc. (%)*	*Sample type*	*Ppm*	*Ref*
Hospital	radiographer	0.4	P,A	0.001	72
Hospital		<0.5	A	0-0.1	9
Hospital		8	A	0	9
Hospital	radiographer		A	0.03-0.06	Q
Hospital			A	0.02-0.4	WA

Conc Concentration in processing solution.
Ref Reference number.
P Personal monitoring.
A Area monitoring.
Q Queensland hospitals.
WA Results of survey of five workplaces conducted by Health Dept of WA — 14 measurements for mean of 0.12 ppm.

In the monitoring conducted with 8% glutaraldehyde solution,[9] an automatic mixer was used to dilute the processing chemicals on some occasions, with the manual method used on others.

A series of air monitoring studies was conducted in x-ray processing areas during the operation of the processors and during the preparation of the working strength solutions, with the study parameters designed to simulate poor ventilation conditions. The results are in Table 27.

Table 27
Air monitoring results in x-ray film processing

Processor (Kodak)	*Acetic acid*	*Ammonia*	*Glutaraldehyde*	*SO_2*
ML-300	0.4-0.5	0.07-0.1	<0.005	0.38-1.1
M6RA	0.2-0.6	0.09	<0.005	0.08
M6RA	0.2-1.3	0.14	<0.001	0.15-0.30
Mixing	0.9-2	0.14	<0.02	0.2

Measurements in ppm.

14.5 Tanning

Workers are exposed to glutaraldehyde in the tanning industry at about 10 different sites in Australia. Workers are employed in the mixing of tanning solutions, the soaking of leather and pelts in the solutions, and the discharge and cleaning of tanks after treatment. The total number of workers exposed to glutaraldehyde in tanning in Australia is comparatively low, as only two or three workers are employed at some sites.

In the treatment of leather and pelts, glutaraldehyde is generally pumped from the drum to the mixing vessel, the operation taking about 5-10 minutes. Depending on the type of tanning, other ingredients are added at different times throughout the treatment period, which may be up to several hours. During the tanning process, the temperature in the mixer may be elevated up to 50°C, increasing the risk of exposure by inhalation. Exposure to glutaraldehyde may occur during these periods of addition and also at the completion of treatment, when unused reactants, including glutaraldehyde, are discharged from the mixing vessel.

Depending on the type and volume of tanning at each site, glutaraldehyde may be used in one batch per week, one batch per several months, or on a continuous basis. Occupational exposure to glutaraldehyde is therefore variable from one site to another, depending on tanning conditions and the ventilation and handling facilities in place at each site.

No records of any atmospheric monitoring for glutaraldehyde at tanning worksites in Australia were available.

14.6 Water treatment

Workers are potentially exposed to glutaraldehyde during the addition of glutaraldehyde-containing products to the water treatment system or during the mixing of the solutions. The types of workers potentially exposed include:

- water treatment operators;
- maintenance fitters and engineers;
- technical representatives; and
- storepersons.

Exposure may be to the concentrated biocide (up to 50% w/w aqueous glutaraldehyde solution), diluted biocide (0.5-10%) or to the dosed water (50-200 ppm v/v glutaraldehyde), with the risk of exposure, by inhalation or skin contact, increasing with concentration.

Exposure by workers is intermittent, for example, during dosing or maintenance, but the number of workers potentially exposed to glutaraldehyde is considerable, as glutaraldehyde-containing biocides are used widely in water treatment systems throughout Australia.

Exposure to glutaraldehyde concentrate may occur during the following circumstances:

- addition of biocide to water treatment system;
- maintenance and cleaning of the dosing system;
- during spills and leaks; and
- sampling for analysis.

Glutaraldehyde may be added manually or by the replacement of an empty feed container with a full one. The trend towards the use of automatic feed systems has reduced the risk of exposure, as less direct handling of the glutaraldehyde solutions is required.

No records of any atmospheric monitoring for glutaraldehyde in water treatment were available.

14.7 Animal housing

Workers are exposed by inhalation and skin contact to glutaraldehyde in the animal housing industry during the preparation and application of the solutions for disinfection. The types of workers potentially exposed include the following:

- production workers;
- cleaners;
- professional contractors;
- farmers;
- veterinarians;
- egg collectors; and
- managers and supervisors of establishments such as piggeries, poultry sheds and catteries.

In the dilution of glutaraldehyde concentrate, workers may by exposed to solutions containing up to 50% w/w glutaraldehyde. In the application of the dilute solution for disinfection, generally by washing but occasionally by spraying or foaming, the concentration of glutaraldehyde solution is usually less than 0.3% w/w. Spraying will increase the risk of exposure.

Disinfection is carried out intermittently, for example, monthly, with groups of two to three people generally employed in the process of dilution and application.

Some atmospheric monitoring has been carried out in Australia, with the results in Table 28.

Table 28
Glutaraldehyde concentrations in animal housing

Workplace	*Worker*	*Conc (%)*	*Sample type*	*Ppm*	*Ref*
Chicken farm	Egg collector*	0.1-0.3	A	0.007	72

* The glutaraldehyde solution was sprayed, and the worker experienced face and respiratory irritation.

14.8 Preservative/general biocide

In the use of glutaraldehyde as a biocidal additive in conveyor chain lubricants, workers are potentially exposed by inhalation and skin contact to glutaraldehyde during the addition of biocide to the lubricant and at various points along the conveyor. Glutaraldehyde solution is usually added to the lubricant via an automatic dosing system, so exposure is limited to the brief connection of biocide supply to the line. Atmospheric monitoring for glutaraldehyde along a conveyor system has been carried out, with results up to 0.03 ppm recorded, well below the National Commission's exposure standard of 0.2 ppm.

In the use of glutaraldehyde in sanitary fluids, workers may be exposed by inhalation and skin contact in the preparation and addition of glutaraldehyde solution to the toilet system.

In the disinfection of air ducts, workers may be exposed by inhalation and skin contact to glutaraldehyde mists or vapours in the application of the solution as a spray or fog. They may also be exposed to more concentrated glutaraldehyde in the preparation of solutions prior to application.

14.9 Microscopy

Workers may be exposed to solutions containing up to 50% glutaraldehyde during the preparation of fixative solutions for use in electron and light microscopy and histology, and to the working strength solutions (3-5%) during tissue fixation.

14.10 Summary

Exposure to glutaraldehyde occurs by skin contact with the solutions or by inhalation of the vapours liberated from solution.

The number of workers potentially exposed to glutaraldehyde is considerable, with the chemical used in a number of different industries.

Exposure is most likely in the health care industry, where approximately 75% of glutaraldehyde is used. Due to the frequency and method of use, health care workers may experience frequent skin contact with solutions, and the results of atmospheric monitoring have shown that workers may be exposed to vapour concentrations exceeding the national exposure standard. In x-ray film processing, workers may also be exposed to other hazardous substances.

In tanning, the number of workers and the volume of use are low, but high glutaraldehyde concentrations and elevated temperatures are used, so the risk of exposure may be significant.

In animal housing, the concentrations used are very low, but sometimes the solutions are used in spray form, when the risk of exposure may be significant.

In the other industries, the number of workers potentially exposed is low and/or the use of glutaraldehyde is well-controlled, so the risk of exposure is low compared to those industries mentioned above. In formulation, the concentration of glutaraldehyde is high and the quantities are often large but the number of workers is low and, in general, the process is well-controlled, so the risk of exposure is low.

15. Examples of current practices involving glutaraldehyde — photographs

Section 16.12 and the recommendations in section 21.3 should be consulted when referring to the photographs in this chapter.

15.1 Glutaraldehyde as a raw material

Photograph 1

Glutaraldehyde is not manufactured in Australia. It is usually imported in large drums as a concentrate in drums of varying sizes or as a dilute solution for end-use purposes (right).

Photo: Union Carbide (Australia) Pty Ltd.

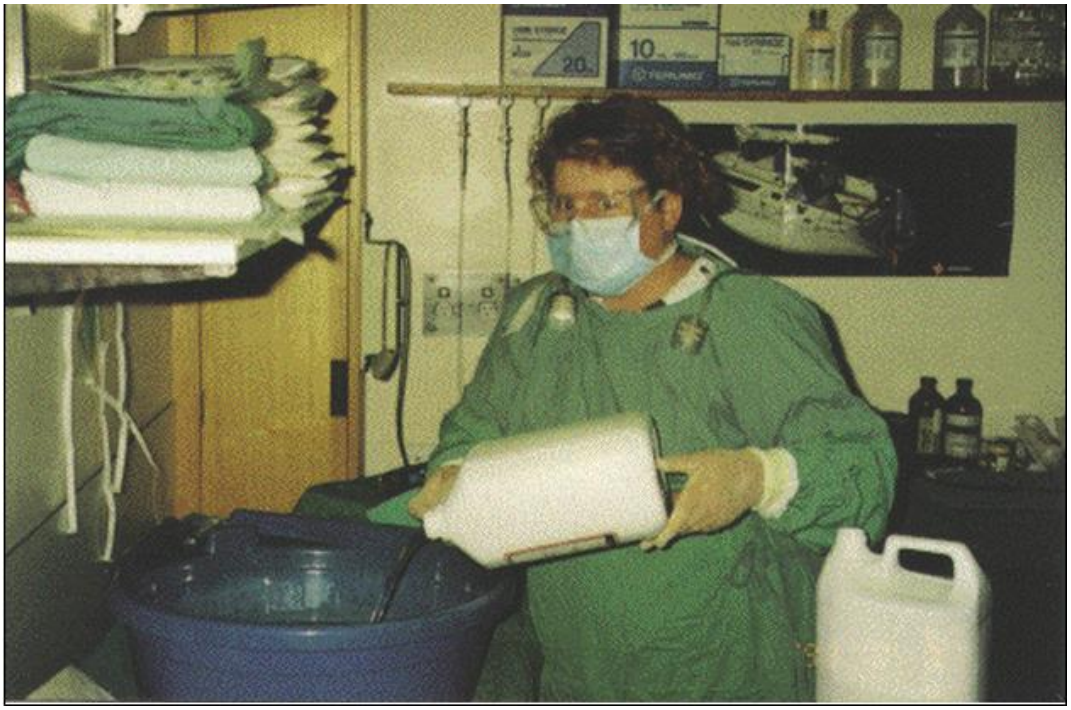
Photograph 2

Transferring glutaraldehyde from an open drum to its end-use purpose, in this case, as a biocide in coolant.

Photo: WorkCover Authority of NSW.

15.2 Current practice in disinfection of endoscopes

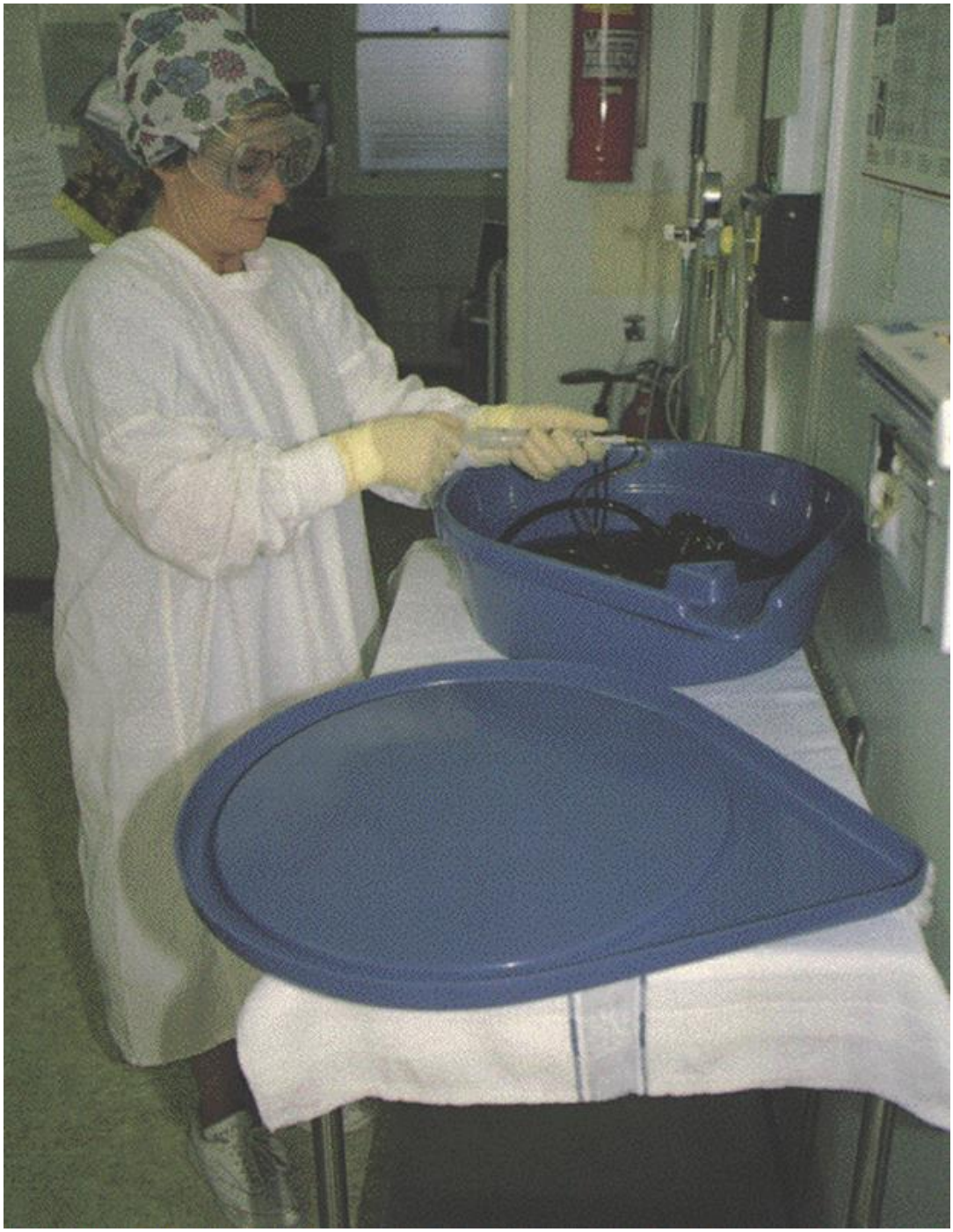
Photograph 3



Addition of glutaraldehyde to soaking bath in a hospital disinfection unit.

Photo: WorkCover Authority of NSW.

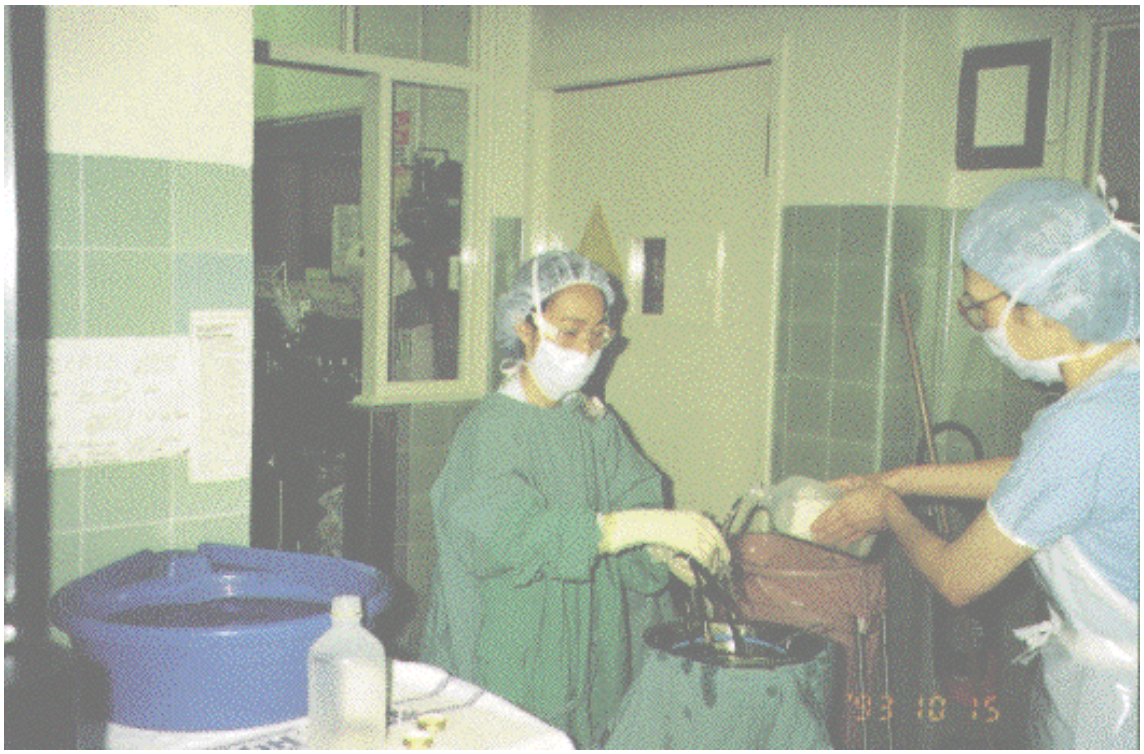
Photograph 4



Disinfection of endoscopes in open bath.

Photo: WorkCover Authority of NSW.

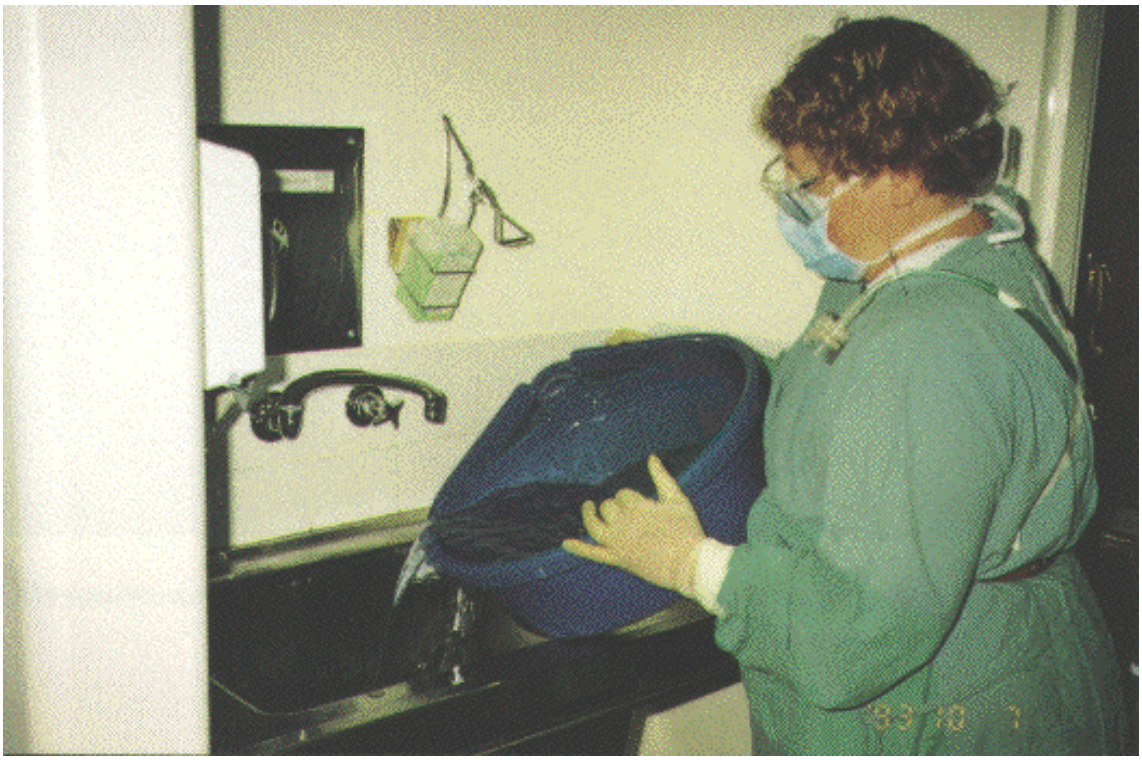
Photograph 5



Rinsing of endoscope in open bath.

Photo: WorkCover Authority of NSW.

Photograph 6



Disposal of spent glutaraldehyde solution after disinfection.

Photo: WorkCover Authority of NSW.

Photograph 7

A soaking disinfection bath on a mobile trolley.

Photo: WorkCover Authority of NSW.

Photograph 8

Disinfection of endoscopes using automatic equipment inside a fume cabinet.

Photo: WorkCover Authority of NSW.

15.3 Current practice in x-ray photography

Photograph 9

Addition of solution to automatic processor.

Photo: WorkCover Authority of NSW.

Photograph 10

Mixing of chemicals for x-ray photography.

Photo: WorkCover Authority of NSW.

15.4 Current practices in animal housing

Photograph 11

Addition of chemicals to a chemical feed system.

Photo: WorkCover Authority of NSW.

Photograph 12

The use of personal protective equipment in the application of glutaraldehyde by spraying

Photo: WorkCover Authority of NSW.

Photograph 13

The operator is wearing and holding the personal protective equipment required for animal housing disinfection.

Photo: WorkCover Authority of NSW.

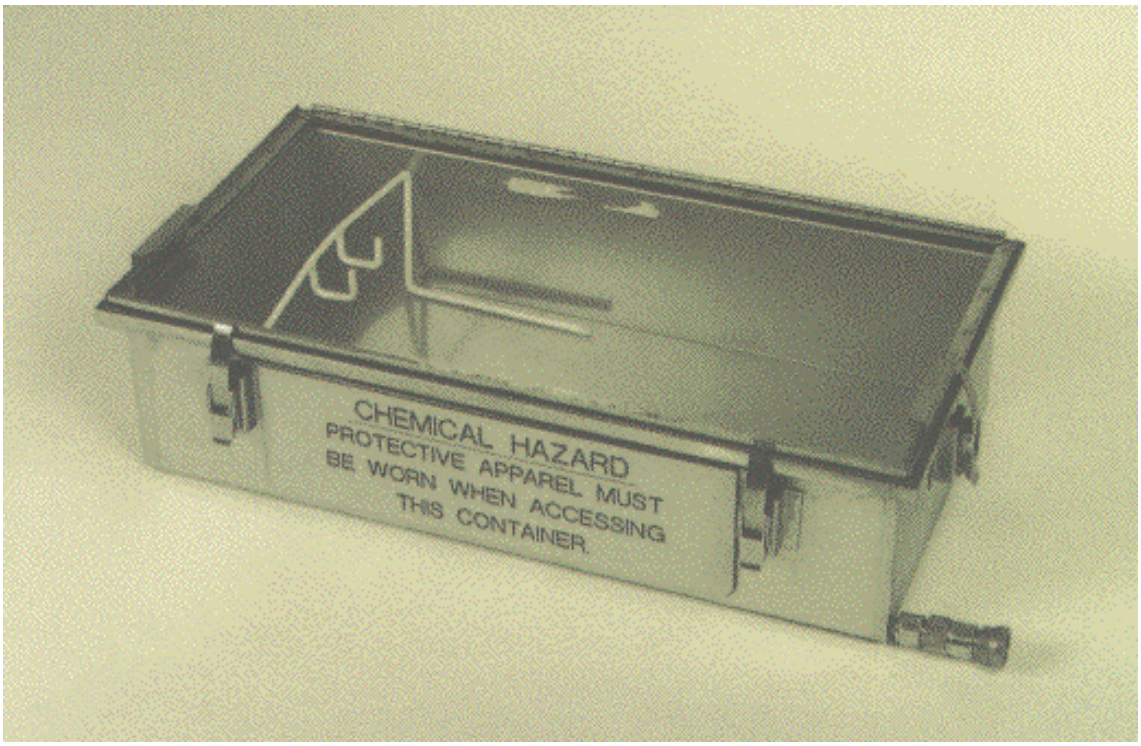
15.5 Specially-designed equipment recommended for disinfection

Photograph 14

A washing machine with lid developed by Royal Adelaide Hospital for washing and rinsing of scopes. Specially designed to minimise splashing and personal handling.

Photo: Royal Adelaide Hospital.

Photograph 15



Soaking container developed by Royal Adelaide Hospital for the disinfection of scopes. The container has a transparent cover to minimise splashing and personal exposure.

Photo: Royal Adelaide Hospital.

Photograph 16

A laminar flow (fume) cabinet designed and built by Saint Luke's Private Hospital, Launceston, for their day surgery unit. All procedures are enclosed with well-designed local exhaust ventilation. Note the stainless steel construction, covered edges and corners, full-width perspex access door (opening limited to elbow height), two stainless steel lids on the sinks, and external controls (the electrical exhaust fan control is located on the opposite wall).

Photo: Saint Luke's Private Hospital, Launceston.

Photograph 17

Frontal view of a laminar flow cabinet. Note the full width raised perspex door. The only movable parts are the water spout between the sinks and the waste plugs (operated by remote control).

Photo:Saint Luke's Private Hospital, Launceston.

16. Occupational health and safety assessment

16.1 Health and safety hazards

The results of animal testing have shown that glutaraldehyde is a potent irritant to the skin, eyes and upper respiratory system. At high liquid concentrations, it is corrosive and studies have shown that skin absorption may be significant on repeated exposure. Animal studies showed that glutaraldehyde has a high acute inhalational toxicity. The results of 13- or 14-week rat studies demonstrated that the respiratory irritant effects of glutaraldehyde are exacerbated on repeated or prolonged exposure.

The human experience has confirmed the irritant properties of glutaraldehyde, with a number of papers and case studies reporting adverse health effects such as dermatitis, rhinitis, sore throat and eye irritation after exposure to glutaraldehyde. Glutaraldehyde has been shown to be a skin sensitiser, with many confirmed cases cited in the literature. A number of cases of occupational asthma and/or rhinitis have been reported in workers exposed to glutaraldehyde.

In industry, glutaraldehyde is used almost exclusively as an aqueous solution in concentrations from 50% w/w to less than 1%, so glutaraldehyde solutions are not flammable hazards. The vapour pressure of glutaraldehyde is lower than for many other chemical disinfectants, for example, formaldehyde, so the vapour concentrations generated from solutions are low, especially at ambient temperatures.

Like most aldehydes, glutaraldehyde is reactive and may undergo reaction with numerous other industrial chemicals.

16.2 Assessment of use in formulation

In the occupational health and safety (OHS) assessment of the use of glutaraldehyde in the formulation of glutaraldehyde-containing products, for example, in the manufacture of disinfectants, x-ray developers and water treatment solutions, the most significant factors are:

- exposure to large quantities of glutaraldehyde;
- exposure to high and low concentrations of aqueous glutaraldehyde solutions;
- small numbers of workers potentially exposed;
- periodic exposure rather than daily exposure, for example, the dilution product may be manufactured on only one day per month; and
- enclosure of the mixing process to prevent worker exposure.

In formulation, the greatest risks to workers are:

- during the transfer of the raw material, generally 50% w/w glutaraldehyde, to the mixing vessel;
- during mixing; and
- during handling of the diluted product.

Glutaraldehyde concentrate is generally supplied in 200 litre drums, so the greatest risk to workers is usually in the transference of raw material to the mixer, as concentrated glutaraldehyde solutions are corrosive and high vapour concentrations may be generated during transfer. However, in most manufacturing plants in Australia, production is not continuous, so the frequency and duration of activity is significantly reduced. Regular production of glutaraldehyde products from concentrate may significantly increase the risk of exposure, leading to possible skin absorption and inhalation of harmful vapours.

In Australia, most mixing operations are carried out in a sealed system to minimise worker exposure. However, if formulation is conducted in an open mixing vessel, then the risk of adverse health effects is greater, as the vapour concentrations will be higher, especially if the mixing temperature is elevated above ambient conditions.

During the handling of diluted product, generally more workers are potentially exposed, although the glutaraldehyde concentration is much lower. The likelihood of spillage is greater at this stage of production, and adverse health effects may be experienced in workplaces without the proper procedures to handle spills.

In summary, the risk of adverse health effects in the manufacture of glutaraldehyde products in Australia is generally low, due to:

- enclosure of the process;
- low numbers of workers potentially exposed to glutaraldehyde; and
- low frequency of production.

16.3 Assessment of use as cold disinfectant

Glutaraldehyde is generally used as a 1% or 2% w/v aqueous solution at ambient temperature for the disinfection of medical instruments such as endoscopes, bronchoscopes and dental instruments. The key elements in the assessment of glutaraldehyde in this use are:

- large numbers of workers potentially exposed, for example, all large hospitals and most other hospitals in Australia use glutaraldehyde as the chemical disinfectant of choice;
- regular exposure to glutaraldehyde by many workers, for example, some nurses may disinfectant endoscopes daily and a number of times each day;
- the high degree of exposure during the disinfection process;
- exposure to low concentrations of aqueous glutaraldehyde; and
- poor control measures in many workplaces.

As glutaraldehyde is often used on a regular basis as a disinfectant, the risk of adverse health effects will be high if effective control measures are not in place. In the scientific literature, most incidences of adverse health effects such as dermatitis and rhinitis have occurred in health care workers, for example, endoscopy nurses, a trend confirmed in Australia, where there have been reports of health care workers experiencing skin irritation and, to a lesser extent, respiratory irritation.

Instruments such as endoscopes and bronchoscopes are firstly cleaned to remove organic matter, and then disinfected in a 1% or 2% activated solution of glutaraldehyde for a period of 5-30 minutes, depending on the concentration and the equipment to be disinfected. After soaking, the instruments are removed from the bath and rinsed with clean water; washing of the intricate parts of scopes with a syringe is often necessary. In many hospitals the risk of exposure is considerable as proper control measures such as

local exhaust ventilation and good safe handling facilities have not been provided, the emphasis being on personal protective equipment to reduce the risk of exposure.

In general, the standard of skin protection is good, although the use of unsuitable, short or old gloves and unsuitable clothing have been reported. Short-sleeve nurses' uniforms do not provide adequate protection against glutaraldehyde solutions. Respiratory protection is not used in routine tasks.

Although there has been a trend towards automation of the disinfection process, much of the disinfection of instruments and equipment is still carried out manually. Also, glutaraldehyde solutions and soaking baths containing the solutions are often transported from one work location to another. Splashing and spills are more likely to occur, increasing the risk of exposure by both inhalation and skin contact.

On the evidence from hospitals and State and Territory authorities that many current control measures in Australia are still inadequate, the risk of adverse health effects is still high, as most hospitals use glutaraldehyde on a daily basis and the total number of workers potentially exposed to glutaraldehyde solutions and their vapours is high. A survey of four hospitals in Sydney carried out by the Sydney Hospital Occupational Health and Safety Service for the NSW Health Department concluded that, in many instances, cold disinfection was not carried out in a proper manner.[117] In the survey, only one of the disinfection units was equipped with local exhaust ventilation, with a majority set up in rooms with poor general ventilation.

However, a number of workplaces have already demonstrated that the risk of exposure can be significantly lowered by the implementation of effective control measures to reduce worker exposure (see section 16.12).

Glutaraldehyde disinfectants are supplied in 5 litre plastic containers and must be stored away from heat and sunlight. The Sydney Hospital survey[117] found that glutaraldehyde solutions were not stored properly.

Glutaraldehyde has also been used for the general surface disinfection of beds, work benches and trays. However, the risk of exposure was unacceptably high, so this use has been largely discontinued as safer procedures are available for general surface disinfection.

16.4 Assessment of use in x-ray film processing

Adverse health effects experienced after the use of glutaraldehyde-containing x-ray film products may be complicated by exposure to other hazardous substances in the processing solutions, for example, hydroquinone, potassium hydroxide and acetic acid. Key elements in the OHS assessment of glutaraldehyde in this application are:

- the large number of workers potentially exposed, as most hospitals have x-ray departments, and there are many private radiology clinics;
- the high frequency of exposure by most workers;
- the high concentration of glutaraldehyde in stock solutions, for example, 30-50% w/w;
- the handling required in preparing working strength solutions; and
- the variable level of exposure control.

Apart from the use of glutaraldehyde as a disinfectant, there have been more reports of adverse health effects in workers handling x-ray film processing solutions than for any other use of glutaraldehyde. Radiographers and dark room technicians have experienced dermatitis and/or respiratory disorders after exposure.

The risk of adverse health effects is highest in the preparation of working strength solutions, as the strength of glutaraldehyde concentrate is 30-50% w/w, a concentration at which significant skin absorption may occur on repeated exposure. The higher strength solutions will also generate higher vapour concentrations, particularly in confined workspaces such as dark rooms. The risk of exposure to glutaraldehyde in the preparation of working strength solutions has been overcome in some workplaces by the installation of automatic mixers, notably in the larger institutions.

In handling working strength solutions, the risk is still significant, as glutaraldehyde is an irritant at low concentrations, and harmful vapour concentrations can still be generated, particularly in a small enclosed work area. The risk of adverse health effects has been reduced to some extent by the introduction of automatic film processors, but the benefit is moderated if their exhaust gases are not completely removed from the work area. Also, automatic processors must be maintained properly; in the survey of four Sydney hospitals by the Sydney Hospital Occupational Health and Safety Service,[117] corrosion was observed on some of the processors. The large number of tubes and connections on automatic processors necessitates regular inspection to prevent leakage.

In summary, the risk of adverse health effects from the use of glutaraldehyde in x-ray film processing is significant for those involved in the mixing of solutions, due to high glutaraldehyde concentrations and the poor level of control in many workplaces. The risk to workers handling the dilute working-strength solutions is significantly lower.

16.5 Assessment of use in tanning

In assessing the OHS risks associated with the use of glutaraldehyde in tanning in Australia, the key elements are:

- small number of tanneries using the chemical;
- few workers potentially exposed at each tannery;
- usually a low frequency of use at each tannery;
- high concentrations of glutaraldehyde solution (25-50% w/w) used;
- large quantities used;
- tanning conditions, for example, soaking at elevated temperature; and
- poor control measures.

Although glutaraldehyde is often used at a low frequency in tanning, and the number of workers potentially exposed is small, there is a significant risk of adverse health effects in the use of glutaraldehyde in tanning. The strength of glutaraldehyde solution is high and elevated temperatures are used in the soaking process, so potentially significant skin absorption and inhalational exposure may occur, for example:

- during the addition of glutaraldehyde to the mixing vessel;
- during mixing if the vessel is not sealed; and
- after treatment, when the pelts are dried and the contents of the mixing vessel are discharged.

Even though the number of workers in Australia is low, adverse health effects such as dermatitis have been reported after exposure to glutaraldehyde.

In general, the poor level of control of glutaraldehyde use in some tanneries has resulted in a significant risk of adverse health effects.

16.6 Assessment of use in water treatment

In the assessment of glutaraldehyde as a biocide in water treatment, the key elements are:

- large number of sites which use glutaraldehyde;
- reasonably small number of workers potentially exposed;
- low frequency of exposure;
- small quantities usually used;
- exposure to high and low strengths of solution; and
- general use of effective controls to minimise exposure.

No reports of adverse health effects experienced after the use of glutaraldehyde in water treatment were found in the literature, and no case reports were received during the assessment period.

The most significant risk of adverse health effects occurs at the dilution stage, when more concentrated solutions and large quantities are handled. However, this process is generally carried out under good control at the formulation site rather than at the water treatment site.

At dosing, smaller quantities of glutaraldehyde solution are handled intermittently, so the OHS risk is less significant.

The trend towards the use of automatic feed systems has decreased the risk due to less handling of solutions and subsequent reduced exposure.

16.7 Assessment of use in animal housing

In the assessment of glutaraldehyde use in the animal housing industry, the key elements are:

- large number of sites;
- small number of workers potentially exposed at each site;
- low frequency of use at each site;
- low concentration of glutaraldehyde solution;
- method of application, for example, spray, foam or wash; and
- variable level of exposure control.

The use of glutaraldehyde as a disinfectant in the animal housing industry has led to sporadic reports of adverse health effects, for example, an egg collector in South Australia experienced facial and respiratory irritation after spraying eggs with 0.1-0.3% glutaraldehyde solution.[72] From information received during the assessment period, the level of control during preparation and application of the solutions varies from one worksite to another.

The risk of adverse health effects is significant during the dilution of glutaraldehyde concentrate to working strength solution, as larger quantities may be handled and higher vapour concentrations may be generated unless good control measures are in place. The risk is increased if dilution is carried out in the field without sufficient control.

When applied as a liquid solution in disinfection, the risk of adverse health effects is low as the strength of solution is low (generally less than 0.3%) and the number and frequency of workers potentially exposed to glutaraldehyde is also low. However, the

use of glutaraldehyde solutions in spray form increases the risk of exposure and so increases the risk of adverse health effects.

16.8 Assessment of use as preservative/biocide

The OHS risks associated with the use of glutaraldehyde as a preservative and a general biocide are low due to the low volume of use and the small number of workers involved.

In the use of glutaraldehyde in conveyor chain lubricants, the glutaraldehyde solution is added via an automatic feed system, so exposure is restricted to the periodic addition of new 5% solution to the feed system and to low vapour concentrations along the conveyor.

The risks associated with the application of sanitary fluids containing glutaraldehyde in aircraft and portable toilets are low as few workers are involved, the concentration is low and the duration of exposure is short.

In the use of glutaraldehyde as a disinfectant for air ducts, the duration of exposure is brief and infrequent.

16.9 Microscopy

Glutaraldehyde solutions at approximately 3-5% are used in very small quantities for fixation, but if the use is regular and the controls are poor, for example, lack of effective ventilation, then the risk of adverse health effects may be significant. Eye, skin and respiratory irritation have been reported for workers engaged in tissue fixing.[68]

16.10 Other uses

The use of glutaraldehyde in other areas, for example, embalming, is small, so the risks to health and safety are expected to be low.

16.11 Education and training

Guidelines for the induction and training of workers who may be potentially exposed to hazardous substances are provided in the *National Model Regulations and Code of Practice to Control Workplace Hazardous Substances*,[107] which lists the key elements of a good induction and training program.

In some workplaces, there is a lack of the proper technical expertise to conduct high quality training about the hazards of glutaraldehyde and how it should be handled. This has led to the incorporation of glutaraldehyde-related training into special training courses, for example, Fairfield Hospital in Melbourne conducts Disinfection: A Course for Dental Practice as part of its HIV dental programs. This includes education in the hazards of glutaraldehyde and training in proper handling procedures.

The Western Australia Health Department has conducted a seminar on the safe use of glutaraldehyde and implemented extensive workplace training programs.

16.11.1 Formulation

From the information obtained for assessment, workers employed in the formulation of glutaraldehyde-containing products are informed of the hazards of glutaraldehyde, and trained in the proper handling procedures. The use of videos, safety manuals and specific use information was reported by producers.

16.11.2 Health care industry

The training and education of workers is variable between hospitals and between other health care establishments such as radiology and dental clinics. In some hospitals and other health care workplaces, a formal program is in place to properly train workers in the safe handling of glutaraldehyde, but in other workplaces there is little training in the hazards of glutaraldehyde and the proper safe handling procedures. Guidelines such as those prepared by the NSW Health Department[115] are an excellent aid in training programs; the guidelines cover the use of glutaraldehyde both as a cold disinfectant and as an ingredient in x-ray film developers. In some health care regions, OHS coordinators have provided training programs for workers who are potentially exposed to glutaraldehyde.

16.11.3 Other industries

From the information submitted for the assessment of glutaraldehyde, there was little evidence of formal training programs in industries outside formulation and the health care industry for workers potentially exposed to glutaraldehyde. In particular, end-users of glutaraldehyde products may be unaware of the health effects of the chemical and therefore unaware that control measures need to be implemented to reduce exposure. Safe use guidelines specific to the industry and similar in style to those available in the health care industry would be an aid to effective training in the other industries.

16.12 Control measures

16.12.1 Control of hazardous substances

Glutaraldehyde is a hazardous substance and solutions of glutaraldehyde above 0.1% concentration should be also classified as hazardous substances. Under *the National Model Regulations and Code of Practice to Control Workplace Hazardous Substances,*[107] control measures to reduce exposure must be in place to minimise the risks to health and safety. In particular, controls should be in place:

- to minimise inhalational exposure by maintaining atmospheric concentrations as low as possible; and
- to minimise skin contact with glutaraldehyde solutions.

The control of glutaraldehyde should be achieved through the following hierarchy of control measures to reduce exposure:

- elimination;
- substitution;
- isolation;
- engineering controls;
- administrative controls;
- safe work practices; and
- personal protective equipment.

A holistic approach to effective control is required, for example, a combination of good workplace design and effective engineering controls and safe work practices have been proposed to overcome the potential occupational health problems in x-ray film processing,[118] and control strategies have been proposed for disinfection units.[119]

16.12.2 Elimination and substitution

For most applications of glutaraldehyde, elimination is not an option. However, where glutaraldehyde solutions have been used as simple surface disinfectants, a more thorough cleaning process may be sufficient.

Glutaraldehyde is a very effective disinfectant and, due to its efficacy, no equivalent substitute is available in many of its uses in the health care industry. However, in some instances it has been successfully replaced, for example, tonometers (for measuring eyeball pressure) have been disinfected with sodium hypochlorite solution as residual glutaraldehyde may damage the eye. In the use of glutaraldehyde as a general surface disinfectant, a non-hazardous substance could be substituted.

In general, any proposed alternative to glutaraldehyde should be carefully considered to ensure that the risks to health and safety are not increased. In animal housing, glutaraldehyde has been substituted in some cases with formaldehyde, a more hazardous substance.

16.12.3 Isolation

In terms of the current use and application of glutaraldehyde solutions, isolation of the chemical by the adoption of a remote control process may not be practical in many situations. In x-ray film processing, commercially available mixers and processors are used to enclose the mixing and processing operations, but the equipment generally requires manual filling with glutaraldehyde solutions. Automatic washers are used in some hospitals for instrument disinfection (see section 16.12.4).

In the formulation of glutaraldehyde-containing products by mixing and dilution, large quantities of concentrated glutaraldehyde (up to 50% w/w) are handled, so enclosed mixing vessels are generally used to isolate the worker from the process and reduce the risk of spillage. Enclosure of the mixing process is essential when glutaraldehyde may be heated, as vapour concentrations are increased at elevated temperatures.

16.12.4 Engineering controls

If elimination, substitution and isolation are not feasible options in the reduction of exposure, then engineering controls should be considered. In the case of glutaraldehyde, controls need to focus on reducing exposure by inhalation and skin contact so that any reliance on personal protective equipment only is minimal. A survey by Leinster et al[120] demonstrated the effectiveness of good ventilation and automatic equipment in reducing exposure to glutaraldehyde.

Through observation and information received during the assessment period, the standard of engineering controls in workplaces in Australia where glutaraldehyde is used is extremely variable, with controls ranging from opening a window to a sophisticated downflow booth. In some workplaces little or no mechanical ventilation has been introduced. The level of control introduced should be proportional to the quantity and concentration of glutaraldehyde solution used and the risk of exposure to the worker. Ideally, engineering controls should be introduced at the design stage so that the proper materials, dimensions and safety facilities are built into the work area. The Environmental Health Branch of the Health Department of Western Australia has issued criteria for the design of dark rooms where glutaraldehyde may be used.

In the formulation of glutaraldehyde products and in the dilution of stock solutions, drums of glutaraldehyde concentrate can be opened in a well ventilated area and the contents transferred to the mixing vessel or dilution matrix via a sealed pump system.

The filling of containers with diluted glutaraldehyde product should be carried out in a well-ventilated area.

In the handling of glutaraldehyde products, both at formulation sites and at end-use, mechanical ventilation is required to minimise exposure to glutaraldehyde by inhalation. This may consist of one or more of the following types:

- local exhaust ventilation;
- dilution ventilation; and
- in-built exhaust ventilation, for example, in x-ray film processors.

In the handling of glutaraldehyde outdoors, engineering controls such as closed feed tanks and automatic dosing systems have been used to reduce exposure.

Ventilation should be provided in accordance with the relevant Australian Standards, in particular AS 1668.2-1991[121]. The following matters need to considered:

- type and size of fan;
- air cleaning device, for example, carbon filter to absorb glutaraldehyde;
- ductwork, including consideration of duct velocity;
- maintenance of the ventilation system; and
- final discharge to atmosphere.

Guidance in the design and maintenance of effective local exhaust ventilation is available in the United Kingdom Health and Safety Executive literature.[122,123]

Engineering controls introduced to overcome the hazards associated with glutaraldehyde use include:

- specially designed fume cupboards and soaking baths;
- soaking baths fitted with clear perspex tops and snap-down clasps to completely seal the contents;
- gravity-feed dispensers for filling and emptying the soaking baths;
- disposable tubes for soaking scopes — the Scope Guard disinfectant system;[124]
- *the Safelab Endoscopy Work Station*, which comprises three sinks, four taps, two pumps and two glutaraldehyde containers (under the bench-top) within a fume cupboard;[125] and
- the Labworks Portable Recirculating Fume Cabinet,* a self-contained unit which contains disposable carbon filters to adsorb vapours.

At Royal Adelaide Hospital, a prototype mobile washing machine for scopes has been designed and built by the engineering staff at the hospital (see photographs). An improved version is expected to be available in early 1994.

Mobile units are available for situations where fixed locations for disinfection may be impractical, although in general their use is discouraged, due to possible splashing and potential problems with disposal of spent solution and monitoring of the carbon filters for chemical breakthrough. Commercial mobile units such as the KC10 Mobile Disinfection Station* and the Keymed 'Auto-Disinfection' system*, a later fully automatic unit, have been used in hospitals for cleaning and disinfecting instruments such as endoscopes. The EW10 Automatic* is a further improvement on the KC10.

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* Comments in this report on commercial equipment do not constitute an endorsement by Worksafe Australaia

Local exhaust ventilation

A number of different types of local exhaust ventilation (LEV) have been used in Australia to cope with the health hazards of glutaraldehyde.

The two main types of LEV are the:

- partial enclosure, for example, a booth or a fume cupboard; and
- hood, for example, a fume hood or an extraction fan.

Hoods and fans tend to give poorer control than enclosures as the air flow can be influenced by operator movement and local air current fluctuations. A simple extraction fan in the wall or ceiling is not appropriate for glutaraldehyde vapours.

Features of an effective fume cupboard[125] for glutaraldehyde include:

- air directed from the front access of the cupboard, across the work area, and extracted through a baffle at the rear of the cupboard;
- a fan above the work area, with air extracted via ducting to a safe location outside the building; and
- a face velocity of 0.5-1.0 m/sec at the front of the cupboard.

The ventilation system exhaust must be sited away from air intakes so that extracted air does not re-enter the building.

In a number of hospitals around the country, fume cupboards have been constructed to reduce exposure to glutaraldehyde vapours, for example, at St. Luke's Private Hospital in Launceston, an effective custom-made laminar flow unit with specially designed soaking basins (see photographs) has been installed. In glutaraldehyde production at one factory, the filling station has been enclosed, and the vapours exhausted into the main extraction system.

At King Edward Memorial Hospital in Perth, a downdraught system around the rim of the soaking trays has been utilised.

At Fremantle Hospital, fixed fume cupboards and mobile units with extractors are provided for the handling of glutaraldehyde solutions.

In some hospitals, mobile disinfection units have been fitted with LEV to reduce exposure to vapours, for example, at the Mater Misericordiae Children's Hospital in South Brisbane, a modified Nederman Extractor unit* has been fitted.

LEV units in use for the reduction of glutaraldehyde exposure are often fitted with carbon adsorption filters to prevent the escape of glutaraldehyde to either the work environment or to the air outside the building. Activated carbon is most effective in adsorbing glutaraldehyde, but the adsorption units (filters) need to be changed regularly to ensure that breakthrough (of glutaraldehyde vapours) does not occur. Canisters are available for large-scale use, for example, for the ventilati*on of storage tanks and mixing vessels. Carbon filters in use for volatile organics often have flame arresters attached. Some agencies have chosen not to use mobile units fitted with carbon filters because of the risk of chemical breakthrough.

LEV units need to be maintained, examined and tested at regular intervals.

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Dilution Ventilation

Most indoor workplaces in Australia that use glutaraldehyde are equipped with some form of mechanical dilution ventilation, with fresh air being introduced into the work environment. The capacity and capability of the ventilation should be proportionate to the size of the room/work area and the quantity/concentration of glutaraldehyde used. A ventilation system based on recirculated air only is not appropriate for the control of glutaraldehyde vapours in the workplace.

In one production area, the ventilation rate is 18 changes per hour, with a make-up of 10% outside air. In the corresponding filling area, the rate is the same, but with the capacity to be increased to 33 changes per hour if a spillage occurs.

In-built ventilation

Much of the x-ray film processing work in Australia is carried out using automatic processors, which have built-in fans that operate continuously. Problems often arise in the connection of the exhaust to an existing ventilation system. The exhaust system must be independent of indoor air supply and any air conditioning system, so additional ductwork may be required. Exhaust air can be treated, for example, by carbon adsorption, before discharge to the environment.

16.12.5 Administrative controls

In some work areas, individual exposure has been reduced by the introduction of administrative controls such as job rotation, where a worker may spend only part of the working week in the area where glutaraldehyde is handled, and the remainder of the week in another area. Other administrative controls which may be introduced include the rescheduling of operations involving glutaraldehyde so that potential exposure in any work period is minimised.

16.12.6 Safe work practices

Occupational exposure to glutaraldehyde can be reduced by the adoption of safer work methods.

Safe work practices applicable to the handling of glutaraldehyde solutions include:

- use of the minimum amount of glutaraldehyde solution for the task;
- the proper labelling of glutaraldehyde solutions in the workplace, including trays, drums and other containers;
- prompt clean-up of spills — a written procedure for spill clean-up is advisable;
- the handling of solutions and equipment in such a way as to prevent splashing or the creation of a mist;
- the proper emptying, cleaning and rinsing of containers and equipment after use;
- the proper disposal of all contaminated containers and equipment;
- good housekeeping in the work area; and
- high standard of personal hygiene.

16.12.7 Personal protective equipment

Personal protective equipment (PPE) is used to support other control measures in preventing worker exposure to glutaraldehyde, both by inhalation and skin contact. Guidance is provided in the Standards Australia handbook HB9.[126] From the information submitted for this assessment, there was evidence of a reliance on PPE rather than engineering and administrative controls. PPE should always be used in conjunction with other control strategies. If PPE is to be used, then it should be appropriate for the concentration of glutaraldehyde to be used, and the type of task to be carried out, for example, proper eye, respiratory and skin protection is required when glutaraldehyde solutions are used in spray form.

Eye protection

The selection and use of eye protection should be in accordance with Australian Standards AS 1336[127] and AS 1337[128].

For the handling of concentrated glutaraldehyde solutions, or in situations where splashing may occur, chemical safety goggles should be used. For the handling of small quantities of dilute glutaraldehyde solutions, chemical safety spectacles with side-shields may suffice.

Gloves

The permeability of 2%, 25% and 50% w/w aqueous glutaraldehyde solution through different types of gloves has been assessed using ASTM Permeation Test Procedure F739-81.[35] The test results[129] indicated that polyethylene, butyl rubber, surgical latex rubber and nitrile rubber would provide adequate protection from contact with aqueous glutaraldehyde solutions. PVC and neoprene gloves were also tested but were found to retain or absorb glutaraldehyde on extended exposure.

In hospitals in Australia, the tendency is towards the use of nitrile rubber, butyl rubber or surgical latex gloves for the handling of 1% or 2% solutions. In some jurisdictions, surgical latex gloves are not regarded as suitable as permeation by glutaraldehyde has been observed. In recent years, an increasing number of severe allergic responses to latex have been reported,[130] especially in the health care industry. When latex gloves are used, two pairs are generally worn, with the outer pair discarded after use in the disinfection process.

In general, gloves should be discarded after use, especially latex gloves. If gloves are to be re-used, then they must be thoroughly cleaned. Old or poor quality gloves should not be used.

The relevant Australian Standard for the design of industrial safety gloves and mittens is AS 2161.[131]

Respirators

The selection and use of respiratory protection should be in accordance with Australian Standards AS 1715[132] and AS 1716.[133]

In the proper handling of glutaraldehyde solutions, workers in most work situations should not need respiratory protection. However, if it is used, then careful consideration of the quantity and concentration of glutaraldehyde solution is required — the more concentrated the solution, the higher the vapour concentration. In general, respiratory protection, for example, the half-face or full-face cartridge respirator, should be used

only for short periods, for example, during the clean-up of spills, and in the application of glutaraldehyde solution as a spray.

Clothing

Proper protective clothing, for example, overalls and impervious aprons, should be worn when handling glutaraldehyde solutions, particularly concentrated solutions, which are corrosive.

The type of clothing will depend on the particular use of glutaraldehyde in the workplace, but full skin protection, including protection of arms and legs, is recommended as glutaraldehyde can be skin sensitising in some workers. Aprons to be used during disinfection in hospitals should be made of proven impervious materials (as for gloves). Special clothing may be required during maintenance or during the clean-up of spills.

The appropriate Australian Standard for choice and use of clothing is AS 3765.[134]

16.13 Emergency procedures;

As for any hazardous substance an emergency response plan is essential for those workplaces handling glutaraldehyde, especially production sites and work areas where glutaraldehyde is handled in large quantities and/or as a concentrated solution. In the event of a substantial leak, spill or other release of glutaraldehyde, a written procedure is necessary for workers in the area and for emergency services who may be required to deal with the release.

In the submission for assessment, a suitable emergency response plan for 50% glutaraldehyde contained the following items:[6]

- emergency contact numbers;
- health effects and physicochemical properties of glutaraldehyde;
- first aid procedures;
- immediate action required in case of a spill or leak;
- immediate follow-up action, including decontamination;
- evacuation plan;
- protective equipment and supplies that may be required in the emergency;
- clean-up procedures and waste disposal;
- MSDS and label.

16.14 Atmospheric monitoring;

From information obtained during the assessment period, monitoring for glutaraldehyde is carried out in some but not all worksites in Australia. As adverse health effects have been experienced after exposure to low concentrations of glutaraldehyde, an assessment of the workplace under the *National Model Regulations and Code of Practice for the Control of Workplace Hazardous Substances*,[107] may indicate that monitoring for glutaraldehyde is required to measure occupational exposure to glutaraldehyde and/or to ensure that the control measures are effective. Where the level of exposure is not known, a small number of analyses is required initially to establish a baseline for assessment of the workplace and to determine whether improved control measures and/or regular monitoring are necessary.

Monitoring for glutaraldehyde in hospitals has been carried out in all States and Territories by the respective Health Departments, with glutaraldehyde levels generally

below the exposure standard. The exposure standard is a peak limitation, so monitoring is usually conducted over 15 or 30 minute periods. For most workplaces, a mix of personal and fixed-point monitoring is generally carried out.

Except for some production sites, there is little evidence of regular monitoring for glutaraldehyde outside the health care industry, even though exposure is potentially significant during some operations, for example, in tanning and in dilution work.

Some results of atmospheric monitoring for glutaraldehyde are listed in Chapter 14.

A number of analytical methods are available for the determination of glutaraldehyde in air. Some of these are listed in Chapter 6. A number of government departments and consulting laboratories have technical experience in measuring atmospheric glutaraldehyde in the workplace environment.

17. Regulatory controls

17.1 Exposure standard;

The National Exposure Standard for glutaraldehyde is 0.2 ppm (peak limitation), or 0.82 mg/m^3, with a sensitiser notation.[8]

The ACGIH TLV for glutaraldehyde is also 0.2 ppm (ceiling value), set in 1979.77 The value is for both unactivated glutaraldehyde and glutaraldehyde activated with sodium bicarbonate, and is based on the irritation threshold of glutaraldehyde in humans. Glutaraldehyde is currently under review by the ACGIH TLV committee. Also in the USA, both OSHA and NIOSH have established exposure limits of 0.2 ppm (ceiling value) for glutaraldehyde, based on irritation of the eyes, nose and throat in humans.

Exposure standards for glutaraldehyde in other parts of the world include:

- **Germany**
  0.2 ppm, with short term level (5 min./8 times per shift) 0.4 ppm and sensitiser notation.
- **Sweden**
  0.2 ppm (ceiling), sensitiser.
- **United Kingdom**
  10 min. STEL 0.2 ppm (reviewed 1987)[135].
-

The evaluation of the health effects of glutaraldehyde in this assessment supports the need for a revision of the current exposure standard, with the following values recommended for consideration by the National Commission's Exposure Standards Expert Working Group:

- STEL (15 min)
  0.15 ppm (0.62 mg/m^3).
- TWA (8 hr)
  0.1 ppm (0.41 mg/m^3).
-

Supporting evidence for the recommendations include:

- irritation of the nose and throat has been observed in workers exposed to glutaraldehyde concentrations less than 0.2 ppm;[62]
- a 13-week NTP inhalation study in rats[14] resulted in nasal irritation at 250 ppb, with a NOAEL of 125 ppb;
- in the corresponding NTP study in mice,[14] no NOAEL was reached as signs of nasal irritation were observed at the lowest dose (62.5 ppb); and
- a 14-week inhalation study in rats resulted in some signs of nasal irritation at 49 and 194 ppb.

Repeated-dose animal studies have shown that the irritant effects of glutaraldehyde are exacerbated on repeated exposure.

Experience in Australia has shown that, provided the proper control measures are in place, atmospheric concentrations of glutaraldehyde can generally be maintained below

the proposed exposure standard. In a number of instances, the introduction of control measures has led to lower exposure levels and a reduction in the incidence of adverse health effects. Problems may still arise during spills or maintenance or, in some instances, in the application of glutaraldehyde in spray form. In such instances, respiratory protection is needed to prevent inhalation of vapours.

17.2 Health surveillance

In line with the National Model Regulations for the Control of Workplace Hazardous Substances,[107] employers have a responsibility to provide health surveillance in those workplaces where the workplace assessment has shown that exposure to a hazardous substance may lead to an identifiable substance-related disease or health effect.

A number of adverse health effects have been identified in workers exposed to low concentrations of aqueous glutaraldehyde, especially skin, eye and respiratory irritation. Skin sensitisation, occupational asthma and rhinitis have also been diagnosed in some workers exposed to glutaraldehyde (see Chapter 11).

Some work areas such as hospitals have in place a health surveillance program which is able to detect at an early stage any adverse health effects, for example, contact dermatitis and occupational asthma. Where there are indications of the failure of control mechanisms, such a program enables an immediate examination of the worksite and the early implementation or reinforcement of control measures to reduce exposure.

However, many workplaces where exposure to glutaraldehyde may be significant do not have formal health surveillance programs in place.

A number of workplaces have shown that the implementation of effective control measures, for example, the introduction of automatic equipment or local exhaust ventilation, has led to minimal exposure to glutaraldehyde and a negligible incidence of associated adverse health effects. Atmospheric monitoring procedures are available to ensure that the effectiveness of control measures is maintained. Consequently, the listing of glutaraldehyde on the National Commission schedule of substances requiring health surveillance is not considered necessary.

In those workplaces where a health surveillance program may be required, careful planning, implementation and evaluation of the program are essential. Medical practitioners involved in health surveillance programs for glutaraldehyde need experience and an understanding of the relationship between pre-existing skin and respiratory disease and glutaraldehyde-induced health effects, as well as an understanding of the difficulty in assessing individuals for glutaraldehyde-associated illnesses such as occupational asthma and irritant or allergic contact dermatitis.

Early diagnosis of glutaraldehyde-induced health effects is important. A baseline medical check of workers prior to employment serves to assist in identifying future signs of skin or respiratory disease, for example, identifying atopics and individuals with pre-existing skin or respiratory problems who may be at greater risk. Information available suggests that atopics are at a greater risk of sensitisation than non-atopics to naturally-occurring agents, but for synthetic agents such as glutaraldehyde, atopy is a much less significant risk factor.[136]

The incidence of skin disease in workers exposed to glutaraldehyde is detailed in sections 11.1.1 and 11.2.1. Most occupational skin disease from exposure to glutaraldehyde involves dermatitis of the hands and/or arms. Medical practitioners should note that it is often impossible on appearance alone to to distinguish hand eczema in atopics from dermatitis in non-atopics. The clinical presentation may be

affected by the duration of exposure and the concentration of chemical used. Persons with previous hand eczema, a strong risk factor, are most at risk of aggravating their skin disease with exposure to skin irritants such as glutaraldehyde. People with weak risk factors, for example, those with a respiratory allergy, do not seem to develop hand eczema more commonly than non-atopics. In cases of contact dermatitis, patch testing using standard procedures has been utilised successfully in the diagnosis of allergic contact dermatitis.[80,81]

The incidence of respiratory disease in workers exposed to glutaraldehyde is detailed in sections 11.1.3 and 11.2.2, together with definitions of the relevant terms, for example, respiratory sensitisation and occupational asthma. In the diagnosis of respiratory disease, early referral of of suspected cases is important. Guidelines for the diagnosis of occupational asthma have been proposed,[40,137] based on the following criteria (see section 11.2.2):

- clinical history;
- physical examination;
- lung function tests;
- bronchial challenge; and
- immunological tests.

However, immunological tests may not be appropriate for glutaraldehyde as the allergic mechanism is not yet known.

Suitable tests which have been used in health surveillance programs for occupational asthma include:

- spirometry for the measurement of FVC and FEV_1;
- the PEFR, which can be measured by the workers themselves if appropriate; and
- inhalation challenge testing.

Some of the techniques used may be insensitive, for example, spirometry and peak flow measurements, but new techniques to increase the sensitivity of early diagnosis of occupational asthma have been recently reported.[138] The standardisation of procedures for spirometry is important,[139-141] and recent work has been carried out internationally to update them.[142-144,145,146]

18. Public health assessment

18.1 Public exposure

The public is unlikely to be exposed to glutaraldehyde during importation and transportation. Public exposure to glutaraldehyde during industrial use, disposal and use of treated products depends on the particular use pattern and will be discussed under the relevant heading below.

18.1.1 Cold disinfectant

Aqueous glutaraldehyde solutions (1% or 2%) are used in medical, veterinary and dental clinics for the disinfection of heat sensitive equipment, including fibre optic and lensed instruments, anaesthetic, respiratory and other equipment which cannot be autoclaved. Public exposure can occur due to inadequate cleaning and rinsing, which can leave a maximum residual volume of 3 mL, equal to the normal maximum working volume of any individual channel in a fibre optiscope. This could result in localised irritation or hypersensitivity.

Exposure from spillage or vapours from open containers is unlikely as the disinfection procedure is normally conducted in non-patient areas. Disposal (to sewer diluted with water) is unlikely to produce significant public exposure.

18.1.2 X-ray film processing

Glutaraldehyde is used in black and white, high temperature, rapid process developers as a hardening (cross-linking) agent, mainly in automated processing. Photographic developers containing glutaraldehyde are not used by the general public. Spent developer is either collected for removal by a licensed agent or discharged to sewer. Glutaraldehyde will form chemical complexes with sulfite in the fixers. No public exposure is envisaged with this use pattern.

18.1.3 Tanning

Glutaraldehyde is used as a tanning agent in the leather industry with total quantity used below 10 tonnes per year. Potential public exposure would be from contact with processed hides and discharged waste. Due to its cross-linking activity, glutaraldehyde is fixed into the leather during processing, thus minimising any public exposure. The final concentration of glutaraldehyde in total tannery effluent is expected to be less than 1 ppm, with the majority being fixed by dissolved proteins in the effluent. Public exposure to glutaraldehyde in tannery effluent is therefore likely to be minimal.

18.1.4 Water treatment

Glutaraldehyde is used as a water treatment microbiocide in cooling towers, air washers, pasteurisers and other recirculating water systems. It is not for use in potable waters. Effluents are discharged to sewerage, with a large industrial tower discharging 20,000 L of glutaraldehyde in 1,000,000 L of combined sewerage per day.

The public is also potentially exposed to glutaraldehyde in drift escaping to the atmosphere from cooling towers. This drift would contain 45-90 ppm glutaraldehyde.

The potential for public exposure to this drift is considered moderate but would be on an occasional basis.

18.1.5 Animal housing

Intensive animal production industries use aqueous glutaraldehyde solutions containing glutaraldehyde at a final concentration at approximately 0.1-0.3% w/v. The uses include the disinfection of farrowing crates in piggeries and the sanitation of poultry sheds after the animals have been removed from the area. The products are not recommended for direct application to animals. No public exposure is expected with this use pattern.

Glutaraldehyde is also used in specialised disinfectants in veterinary hospitals, but public exposure is minimal.

18.1.6 Preservative/general biocide

Fogging of air ducts is carried out using 2% glutaraldehyde products. The process is carried out once personnel have left the area, with reoccupation only after ventilation with maximum fresh air for 20 complete air changes. Thus public exposure is expected to be minimal.

Glutaraldehyde (2%) is also used at 20-40 mL per 1 L water in the initial charge of portable toilet systems. The products are used by the general public and hence potential exposure is high.

Glutaraldehyde is also used as an oil well and metal working antimicrobial and as a biocidal additive for conveyor chain lubricants. No public exposure is expected.

18.1.7 Electron and light microscopy

Glutaraldehyde is used in scientific establishments as a fixative in electron and light microscopy and as a tissue preservative. No public exposure is expected.

18.2 Assessment of public health effects

18.2.1 Assessment of toxicological hazards

In humans, the main health effects reported for glutaraldehyde are described in Chapter 11.

The results of animal studies and tests in *in vitro* systems are discussed in Chapter 10.

18.2.2 Assessment of public exposure;

The public is unlikely to be exposed to glutaraldehyde during its routine importation, transportation and formulation. Domestic use of glutaraldehyde is expected to be minimal, at present there being only 2% formulations for use in portable toilets available to the general public. This is unlikely to result in widespread public exposure. Appropriate safety directions, as listed in Appendix F of the SUSDP,[112] have been set for products used in this manner.

The cross-linking activity and ready reactivity of glutaraldehyde would decrease the available glutaraldehyde for public exposure. Some specific uses, for example, the cold disinfection of fibre optic equipment and the disinfection of air ducts, can result in direct or significant exposure if proper cleaning and ventilation procedures are not followed.

Moderate but infrequent exposure from drift emanating from water cooling towers can occur. However, the majority of uses of glutaraldehyde do not result in direct public exposure.

Therefore, for the uses of glutaraldehyde described in this report, it is unlikely that glutaraldehyde will pose a significant health and safety hazard to the public.

Improper cleaning of medical and dental equipment or inadequate ventilation of premises following duct biocide treatment may increase public exposure and appropriate measures to minimise glutaraldehyde residue should be employed.

Domestic products containing glutaraldehyde should be labelled with appropriate first aid and safety directions.

The majority of effluents are discharged to sewerage in a diluted form. Discharge is not recommended to storm water drains.

Glutaraldehyde is not recommended for use in animals or potable water.

19. Environmental assessment

19.1 Environmental exposure

19.1.1 Formulation

Local dilution of glutaraldehyde is carried out at sites in Melbourne and Sydney, where concentrated glutaraldehyde (45-50%) is pumped into blending vessels where it is mixed with water before being drummed-off and transported via road or rail to the users.

From information provided on one formulation process, it is estimated that approximately 0.3-0.5% of the final product is lost to wastewater treatment systems. This amounts to between 12 and 20 L per batch (approximately 3.2 and 5.3 kg of glutaraldehyde) being discharged to effluent treatment every one to two months.

Cold chemical disinfectants containing 1-2% glutaraldehyde are formulated by pumping glutaraldehyde concentrate via closed systems to a suitable liquids processing vessel containing water. Other materials are pumped into the vessel and blended. The solution is made up to volume with water and filled directly into 5 L containers for packing and distribution. Any vapours emitted are discharged via local extraction systems to the atmosphere.

Concentrations of glutaraldehyde discharged to sewer from one cold chemical disinfectant formulation site have been monitored. An initial concentration of 25 mg/L was reduced to less than 2 mg/L.

X-ray film processing chemicals are formulated by adding glutaraldehyde concentrate via an air pump to water in a mixing tank followed by blending with other chemicals.

The release of 25% glutaraldehyde solution to the sewers from one x-ray development formulation process has been estimated as between 10-12 L (2.5-3 kg glutaraldehyde) per month.

Water treatment chemicals are formulated by repacking concentrated glutaraldehyde solution into 25 L pails and 800 L returnable containers, or by pumping glutaraldehyde solution into stainless steel blending vessels in an air conditioned isolated production area. The turbine agitated vessel is equipped with an air extraction scrubbed emission system.

Glutaraldehyde discharges from one formulation site are said to be negligible as tank washings are collected and reused and the site is bunded.

The formulation of animal housing biocides involves transferring the required quantity of glutaraldehyde to a mixing tank, adding remaining formula ingredients, mixing for the specified time, and adjusting batch volume with purified water.

One formulator reported that minute amounts of vapour escape to the atmosphere during manufacturing operations. Also, minute amounts of liquid are released to drain following clean up of manufacturing equipment.

19.1.2 Use and disposal

The major releases of glutaraldehyde are expected to occur from the users rather the formulators. Most of this will enter aqueous waste streams, with a minor proportion discharged to the atmosphere.

Solutions of glutaraldehyde will be disposed of to sewer when they have lost the desired level of activity. Requirements vary from State to State, but in general they restrict discharges of spent glutaraldehyde solutions to 10 L batches and specify that they must be flushed with copious amounts of water (typically 100-fold dilution). Concentrated wastes should be disposed of by incineration.

The exception appears to be South Australia where inactivation is required prior to disposal. Inactivation can be achieved by dilution to subcidal concentrations (10 mg/L active), treatment with dibasic ammonium phosphate, or caustic hydrolysis. Reaction with bisulfite is another option.

Cold disinfectant

Exhausted cold chemical disinfectant solutions appear to represent the major source of glutaraldehyde in wastewaters. A MSDS recommends that such solutions should routinely be discarded after 28 days. Sewer discharge should involve dilution with copious quantities of water. Where septic systems are involved, the active glutaraldehyde should be neutralised before disposal.

Health care establishments are major users and dischargers of cold disinfectant solutions. The glutaraldehyde solutions are discarded when the concentration of glutaraldehyde falls by about 25% (to approximately 0.7-1.5%). Typically, this entails discharge of 10-14 L of 1% solution from each treatment tank every four weeks.

Health care establishments range in size from major hospitals, with large wastewater flows available for dilution, to small clinics with negligible flow at any particular time.

X-ray film processing

X-ray film developers containing glutaraldehyde are used in high temperature, rapid process, automated developers, predominantly for medical x-ray processing but also in radiology departments of public and private hospitals, radiology practices and clinics. Smaller quantities are used in industrial x-ray and general purpose black and white film processors. Concentrations of glutaraldehyde in the developers are 40-45%. When diluted to form a working solution, the glutaraldehyde concentration should be less than 0.5%. Automated processors drain to sewer and generally vent to the atmosphere.

Spent solutions from x-ray processors are discharged via an overflow weir to a collection system that drains the processor. Spent developer, fixer and wash water are either collected for removal by a licensed agent or discharged to sewer after appropriate treatment for silver removal. Free glutaraldehyde will not be present in the effluent flow because of reaction with sulfite from the fixer.

Tanning

Glutaraldehyde is used as a tanning agent in the leather and fur industries for its softening and filling effects, which add value to hides and skins. The tanning agents contain 25-50% glutaraldehyde and are used at tanneries in Ballarat and South Geelong, Victoria, Narangba, Queensland and Thebarton, South Australia. On completion of all tanning operations the contents would be discharged for effluent treatment.

Unused glutaraldehyde from leather tanning operations amounts to between 1% and 3% of the original charge. For example, at a usage rate of 5 kg per day, unused material would amount to 0.05-0.15 kg of product daily. Tanneries have an effluent discharge rate of 240-290 kL per day. Therefore, the maximum concentration of glutaraldehyde in tannery effluent would be in the order of 0.6 mg/L. The actual concentration would be lower as tannery effluent contains large quantities of dissolved proteins as well as amino

acids with which glutaraldehyde will largely react before reaching effluent treatment works.

Water treatment

Glutaraldehyde is used as a water treatment microbiocide for use in cooling towers, air washers, pasteurisers and other recirculating water systems. The products are effective in controlling slime-forming bacteria, sulfate-reducing bacteria, and algae. One supplier recommends that cooling towers be given an initial dosage of 68-90 mg/L glutaraldehyde with a maintenance dosage of 45 mg/L glutaraldehyde. The product is fed by a feed pump system.

Product strengths vary from a maximum of 40% to 0.5% depending on the application. Chemicals are applied via metering pumps, usually on timer or auto control systems, to maintain a regular controlled biocide level.

The half-life of glutaraldehyde in cooling tower water is approximately 24 hours. Glutaraldehyde may enter the environment from such applications in drift from the cooling towers. Typically, drift represents less than 0.01% of cooling tower recirculated water volume. Such drift would contain a concentration of glutaraldehyde of 45-90 mg/L.

Cooling towers discharge glutaraldehyde to sewer at a maximum concentration of 250 mg/L. Typically a large industrial tower would discharge 20 kL per day into a flow of 1 ML per day. Therefore, approximately 5 kg glutaraldehyde would be discharged daily from a large industrial cooling tower at a concentration of 5 mg/L.

Animal housing

Glutaraldehyde based products are used to disinfect animal and poultry housing. Commercial products contain 12-15% glutaraldehyde. The recommended dilution factor of 50-400 provides working concentrations between 0.30 and 0.03%. Animals are removed prior to use and the shed cleaned of refuse and droppings before disinfection. In the poultry industries, disinfection takes place at 6-8 week intervals.

Releases to sewer from use in animal housing are likely to be minimal as the glutaraldehyde solution is generally applied to surfaces and allowed to dry before the animals are rehoused. In some instances, glutaraldehyde residues may be discharged to effluent ponding systems. Cleaning of application equipment may entail some disposal to sewer.

Aquaculture

For the use of glutaraldehyde in aquaculture, it has proved difficult to obtain information on the quantity used per annum, the application methods, and the release of glutaraldehyde to the environment.

While no details are available at this time for glutaraldehyde, antiprotozoal use of formalin in aquaria entails application at 150-250 mg/L for 30-60 minutes, while in ponds a concentration of 25 mg/L is applied and allowed to dissipate.

19.2 Environmental fate

Glutaraldehyde will predominantly enter aqueous waste streams when waste solutions are disposed of to sewer. Limited atmospheric exposure will also occur from vapour emissions and from water-cooling tower drift.

19.2.1 Hydrolysis

The hydrolysis of [1,5-^{14}C]-glutaraldehyde has been examined in sterile aqueous solutions at pH 5, 7 and 9.[3] The study was conducted at 25°C in the dark at a nominal concentration of 10 mg/L. The parent compound degraded slowly in pH 5 and 7 buffer solutions during the 31 day study, with extrapolated half-lives of 508 and 102 days respectively. At pH 9, degradation proceeded more rapidly (half-life 46 days) with the formation of a cyclic dimer of glutaraldehyde.

19.2.2 Photodegradation

Photochemical processes will be important in removing glutaraldehyde from the atmosphere. Formaldehyde vapours are reported[147] to undergo direct photochemical transformation in the troposphere, as well as photo-oxidative degradation (reaction with hydroxyl radicals). Half-life in the sunlit troposphere is a few hours.

Hydrophilicity of glutaraldehyde will ensure removal of unreacted residues from the atmosphere by dissolution in rain.

19.2.3 Biodegradation by sewage microorganisms

Ready biodegradability of glutaraldehyde was investigated[148] at a concentration of 100 mg/L in a 15 day modified MITI-Test (OECD Guideline 301C[33]). The test article proved to be 22.8% degradable after six days. After 15 days the test article was only degraded by 35.2%. The concentration of the test article was 100 mg/L, which is known to be biocidal.

The OECD guidelines for this test state that a result of less than 60% of biochemical oxygen demand (BOD) does not necessarily mean that the test compound is not biodegradable under environmental conditions, but indicates that more work will be necessary to establish biodegradability. It should be noted that the concentration of glutaraldehyde used may have been inhibitory to the bacteria used in the study.

Results from a five day BOD test[149] are more favourable. The test involved exposure of glutaraldehyde (0.9 and 1.7 mg/L) to unacclimated sewage sludge. At these subcidal concentrations, the mean five day BODs were 71% and 55% of the theoretical value respectively. Based on loss of glutaraldehyde, the degree of degradation approached 90% at both concentrations.

19.2.4 Metabolism in soils and aquatic systems

The behaviour of glutaraldehyde in soil adsorption tests[5] indicates ready metabolism in soils, with half-lives of a few days.

Aerobic studies in aquatic systems[150] confirm the limited persistence. Radiolabelled glutaraldehyde (10 ppm) was incubated in Sacramento River water/sediment (ratio 5) for 30 days. The sediment was the same as that used in the adsorption test.

Radiocarbon was mainly found in the aqueous phase (at least 90%) in the first four hours of the study, but declined to below 20% by 14 days, when about 20% of applied radiocarbon was in the sediment and 48% had been liberated as carbon dioxide. At termination, about 10% remained substantially bound to sediment and 80% could be accounted for as carbon dioxide in headspace and water.

Analysis by HPLC indicated that glutaraldehyde was oxidised rapidly to glutaric acid, which mineralises. The pseudo first-order half-life was 10.6 hours.

An anaerobic metabolism study is in progress. Preliminary results indicate that anaerobic metabolism follows a completely different pathway, mainly involving reduction to 1,5-pentanediol (half-life is appoximately one day).

19.2.5 Bioaccumulation

Bioaccumulation of glutaraldehyde in aquatic organisms is precluded by its hydrophilicity and limited persistence.

19.2.6 Summary

Glutaraldehyde is a hydrophilic substance that will be mainly associated with the aquatic compartment, with minor amounts partitioning to the atmosphere, following release to the environment. Hydrolysis is slow, but glutaraldehyde, like other aldehydes, undergoes aerial oxidation in solution. It biodegrades rapidly in aerobic and anaerobic aquatic environments at subcidal concentrations (below 10 mg/L) and will not bioaccumulate. Tropospheric degradation is also rapid.

19.3 Environmental effects

19.3.1 Avian toxicity

Table 29
Avian Toxicity of Glutaraldehyde

Test	*Species*	*Result*	*Reference number*
Acute oral	Mallard duck	LD_{50} = 408 mg/kg	151
Acute oral	Mallard duck	LD_{50} = 466 mg/kg	152
8 d dietary	Mallard duck	LC_{50} > 5000 ppm	153
8 d dietary	Bobwhite quail	LC_{50} > 2500 ppm	154
8 d dietary	Bobwhite quail	LC_{50} > 5000 ppm	155

The above results indicate that single doses of glutaraldehyde in corn oil are moderately toxic to the species tested, but that the substance is practically non-toxic in the diet. This may reflect reaction of glutaraldehyde with proteinaceous constituents of the feed.

19.3.2 Aquatic toxicity

Glutaraldehyde solutions of 25 and 50% concentration were tested. Results tabulated below refer to the nominal concentration of glutaraldehyde itself.

Table 30

Aquatic toxicity of glutaraldehyde

Test	*Species*	*Result*	*Reference number*
96 h acute	Bluegill sunfish	LC_{50} = 11.2 mg/L	156
48 h acute	Oyster larvae	$LC5_{50}$ = 2.1 mg/L	157
96 h acute	Green crabs	LC_{50} = 465 mg/L	157
96 h acute	Grass shrimp	LC_{50} = 41 mg/L	157
48 acute	Daphnia magna	LC_{50} = 0.35 mg/L	158
48 acute	Daphnia magna	LC_{50} = 16.3 mg/L	159
21 d reproduct'n	Daphnia magna	LOEC = 4.3 mg/L	160
96 h algal growth inhibition	Selenastrum capricornutum	ILm = 3.9 mg/L (median inhibitory limit)	161
96 h algal growth	Scenedesmus	EC_{50} = 1.0 mg/L	162
inhibition	subspicatus		
Bacterial inhibition	Sewage microbes	IC_{50} = 25-34 mg/L	—

Static conditions and nominal concentrations were used in the bluegill sunfish test, which followed US EPA bioassay practices with the exception that replicate concentrations were not used. Glutaraldehyde would be expected to degrade under the test conditions, and this is reflected in similar end-points at 48 and 96 hours. The no effect level was 5 mg/L. A 96 hour end-point of 10 mg/L for rainbow trout is listed on a MSDS but no data was available during the assessment period to substantiate this value. Results indicate that glutaraldehyde is slightly to moderately toxic to fish.

The end-point in the oyster larvae test was based on nominal concentrations and indicates moderate toxicity to these organisms. Concentrations were measured in the crab and shrimp bioassays, and found to remain reasonably constant at concentrations above 50 mg/L. Glutaraldehyde is practically nontoxic to the crab and slightly toxic to the shrimp.

The more sensitive of the two acute daphnid studies was carried out under static conditions with end-points expressed as nominal concentrations. No deaths were observed at 0.28 mg/L, but complete mortality occurred at the next highest concentration (0.5 mg/L). The reasons for the anomalous sensitivity are unclear but would appear to reflect experimental error. Mortalities observed at 0.18 and 0.10 mg/L cast further doubt on this study.

The second acute daphnid study was carried out under the same conditions but provided results more consistent with the reproduction test. The no-effect level (based on mortality) was 8 mg/L. Glutaraldehyde has slight acute toxicity to Daphnia magna.

The reproduction test was conducted under semi-static conditions, initially with two duplicates containing ten daphnids at each concentration, but changing to ten duplicates

containing single organisms after four days. This falls short of requirements contained in the OECD Test Guideline 202.[33] Test solutions were renewed three times per week, with concentrations measured for the initial and final renewal. Results should be treated with caution as measured concentrations were extremely erratic, ranging from 99.3% of nominal to below the limit of detection, and not correlated with nominal concentration or exposure period.

In terms of the number of young produced, the lowest effect concentration (>50% reduction) was 4.3 mg/L, with a no effect concentration of 2.1 mg/L (nominal concentrations). Reductions of about 25% at concentrations of 0.2 and 1.1 mg/L were also evident. The former was said in the report to be an artifact of two rather infertile water fleas, while the latter was ignored. These results allow a tentative conclusion that glutaraldehyde has a moderately toxic effect on *Daphnia* reproduction.

The algal end-points are nominal concentrations. Concentrations measured in the *Scenedesmus* test were about an order of magnitude lower than nominal. Glutaraldehyde is moderately to highly toxic to algae based on these results.

No test report was provided for the bacterial inhibition test as it was a preliminary study only. The test is said to be conservative as it used low densities of unacclimated microorganisms. Rather than the usual indicator of respiration, effects were detected by measurement of turbidity (an indicator of population density) as described elsewhere.[163,164] No effect levels were 5-10 mg/L. This is consistent with observations from the aerobic aquatic metabolism test,[150] where a decline in bacterial colony forming units in the water column was detected during the first 4 hours, while glutaraldehyde concentrations in the water would have been in the order of 10 ppm. No such inhibitory effects were detected in the sediment. Results suggest slight toxicity of glutaraldehyde to sewage microorganisms. The full test report for the definitive study that is said to be currently underway should be provided when available.

In summary, the test results indicate that glutaraldehyde is slightly to moderately toxic to aquatic fauna and moderately to highly toxic to algae. In some instances, glutaraldehyde appeared to be rapidly lost from test waters in the laboratory. Such behaviour in aquatic toxicity tests generally means that their results will underestimate the inherent toxicity of a substance. However, the toxicity that will prevail under environmental conditions is likely to be lower than that recorded in the laboratory in view of the rapid degradation that would be expected to occur in natural surface waters.

19.4 Environmental hazard

Waste glutaraldehyde from cold disinfectant solutions would appear to represent both the largest and most concentrated source (up to 15000 mg/L leaving the sterilisation vessel) of glutaraldehyde entering wastewater streams. Accordingly, hazard evaluations will focus on this application as the worst case.

Based on import and production volumes provided during the assessment, a large urban centre such as Melbourne, where about one-sixth of Australia's population resides, may consume up to 7 tonnes of glutaraldehyde annually, or an average 20 kg per day. Assuming that 75% is discarded as spent disinfectant solutions, and that all passes through Werribee Sewage Treatment Works (daily flow 500 ML), glutaraldehyde at the treatment works would be diluted to 50 mg/L simply by dilution.

For country areas, daily sewage flows of 5 ML are typical. Assuming as a worst case that health care establishments in such areas service a population of 100,000 — or roughly 0.5% — of Australia's population, daily use of glutaraldehyde sterilants may slightly exceed 0.5 kg, or a worst case daily discharge of about 0.4 kg. Dilution in sewage flow would lead to a concentration in treatment works of 160 µg/L.

The above estimates indicate that safety factors for sewage microorganisms, based on a no effect level of 5 mg/L, will be in the order of 30-100. These factors are very conservative as they are based on a no effect level to low population densities of unacclimated microbes, and make no allowance for the considerable losses of glutaraldehyde that occur through reaction with proteinaceous components of sewage effluent. Accordingly, adverse effects on sewage microbes are not anticipated. Advice from the Sydney Water Board, which has no evidence that glutaraldehyde has ever adversely affected sewage treatment at even its smallest treatment plant, confirms this prediction.

As the maximum concentration expected to prevail in sewage treatment works is 160 µg/L, concentrations discharged would not be expected to impact on receiving waters even if no degradation occurred prior to release. Given the expected degradation, the predicted aquatic hazard is low.

Atmospheric emissions of glutaraldehyde do not represent a hazard to the environment in view of the small amounts involved and limited atmospheric persistence.

19.5 Conclusions

Glutaraldehyde is widely used in Australia, with the main dissipative use being cold chemical sterilisation in medical establishments. As much as 75% of the glutaraldehyde used for this purpose is flushed to sewer with water.

Glutaraldehyde is a hydrophilic substance that will mainly partition to water upon release to the environment. Like other aldehydes, the environmental persistence of glutaraldehyde is extremely limited. It reacts with proteins and is rapidly biodegraded at aqueous concentrations below about 10 mg/L.

Glutaraldehyde is moderately toxic to aquatic fauna and moderately to highly toxic to algae. However, its lack of persistence confers adequate aquatic safety margins, and it has not been associated with any incidents of environmental damage in the years in which it has been used in Australia.

20. Conclusions

From the assessment of information about the health and environmental effects of glutaraldehyde, hazards during its use, exposure data and control measures currently available, it is concluded that glutaraldehyde can be used safely in Australia if the proper control measures are in place.

The main health hazards of glutaraldehyde are irritation of the skin, eyes and respiratory system. The main symptoms seen in workers in Australia are contact dermatitis and eye, nose and throat irritation, with occupational asthma and rhinitis also observed. Adverse health effects have been observed principally in the health care industry, due to the high number of workers in this industry and the poor controls in many workplaces.

Based on information about its human health effects and the results of animal and in vitro testing, glutaraldehyde is a hazardous substance at concentrations > 0.1% w/w according to the Approved Criteria.[109]

For the uses of glutaraldehyde described in this report, it is unlikely that glutaraldehyde will pose a significant health and safety risk to the public or a significant risk to the environment.

21. Recommendations

Glutaraldehyde has a number of hazardous properties to justify its classification as a hazardous substance according to the Approved Criteria,[109] (see section 21.1). Under the National Commission's *National Model Regulationals and National Code of Practice for the Control of Workplace Hazardous Substances*,[107] duties are placed on suppliers, employers and employees regarding the provision of information, assessment of the workplace, and the implementation and operation of proper control measures.

As all States and Territories are committed to adoption of the regulations for workplace hazardous substances, it is recommended that suppliers and employers fulfil their obligations under the regulations in a manner consistent with the recommendations in this report. The recommendations have been framed to assist with the implementation of these model regulations and therefore they cover matters such as information provision and suitable control strategies in the various industries where glutaraldehyde is used.

21.1 Hazard classification;

The classification of glutaraldehyde at various concentrations in accordance with the Approved Criteria[109] is based on the assessment of the health effects of glutaraldehyde at those concentrations. Glutaraldehyde is commercially available in Australia at concentrations up to approximately 50% w/w, so the recommended classifications and corresponding risk phrases for these mixtures are listed in Table 31 (see Appendix 1 for a list of risk phrases).

In the classification of glutaraldehyde, products which contain other hazardous substances, for example, x-ray film processing solutions, the health effects of all the ingredients need to be taken into account.

It is recommended that suppliers incorporate health hazard information consistent with the classification of glutaraldehyde in their MSDS and labels.

The evidence for the respiratory sensitising effect of glutaraldehyde is not sufficient to recommend classification under the Approved Criteria,[109] but it is recommended that the position be further reviewed, particularly when the criteria for respiratory sensitisation are amended by the EEC, and if evidence becomes available to confirm a respiratory sensitisation effect.

Similarly, the acute inhalational toxicity classification should be reviewed when more data is available.

It is recommended that the risk phrases determined from this assessment report be added to the List[108] in order to assist implementation of the Model Regulations.

Table 31

Classifications for glutaraldehyde at various concentrations

Glutaraldehyde classification	*Concentration*	*Mixture classification*	*Risk phrase*
Corrosive	> 25%	Corrosive	R34
	> 1-25%	Skin Irritant	R38
Serious Eye Damage	> 5%	Serious Eye Damage	R41
	> 0.1-5%	Eye Irritant	R36
Respiratory Irritant	≥ 1%	Respiratory Irritant	R37
Skin Sensitiser	≥ 1%	Skin Sensitiser	R43
Toxic (Inhalation)	> 25%	Toxic	R23
	1-25%	Harmful	R20
Harmful (Skin)	≥ 25%	Harmful	R21
Toxic (Oral)	≥ 50%	Toxic	R25
	5- < 50%	Harmful	R22

21.2 Hazard communication

21.2.1 Labels and MSDS

A survey of the labels and MSDS of glutaraldehyde-containing products indicated that many were below the standard normally considered appropriate under the National Commission's codes of practice. It is recommended that:

- labels be reviewed and upgraded where necessary, with the risk and safety phrases and/or directions reflecting the health and safety risks present during the normal or reasonably foreseeable use of the product; and
- MSDS be reviewed and upgraded where necessary in accordance with the information in this report and the National Commission's Code of Practice for the *Preparation of Material Safety Data Sheets*.[114]

It is also recommended that the following statements be included on MSDS for glutaraldehyde products:

- 'Occupational asthma and/or rhinitis have been indicated in a number of workers exposed to glutaraldehyde.'
- 'The results of more recent assays have generally shown that glutaraldehyde is mutagenic *in vitro*. *In vivo* tests to date have been negative. Consequently glutaraldehyde does not meet the criteria for classification as a mutagen.'

In view of the differing labelling requirements for some products under the various regulatory codes and schedules, it is recommended that the relevant regulatory authorities use this assessment report of the hazards of glutaraldehyde as a basis for reviewing their labelling requirements. Such a review is particularly necessary in the case of the SUSDP[112] where no warnings of sensitisation or corrosivity are currently required.

A small number of glutaraldehyde-containing products are sometimes used in spray form, significantly increasing the risk of exposure unless proper precautions are taken. It is recommended that the use of glutaraldehyde-containing products in spray form be reduced as much as possible. However, where spray use is still necessary, it is recommended that the product should carry an appropriate warning such as the following on the label:

CAUTION: AVOID BREATHING SPRAY,

and that the proper control measures, detailed in section 21.3, should be implemented.

21.2.2 Other information

For the health care industry, it is recommended that safe use guidelines, similar in style to those available in some States, be provided for health care workplaces in each of the States and Territories. The guidelines should include information about the health effects of glutaraldehyde and detailed guidance on the control measures available to minimise exposure (see section 21.3).

It is also recommended that safe use guidance be provided for the use of glutaraldehyde in dentistry.

In other industries, some end-users are not aware of the health effects of glutaraldehyde nor the hazards present during its use. Therefore, industry specific safe use guidelines, similar in style to those available for the health care industry, are recommended for the tanning, animal housing and water treatment industries.

For the other minor uses of glutaraldehyde, for example, in microscopy, in toilet sanitation and in air duct disinfection, guidance material from suppliers is recommended for availability at each workplace.

For the sake of uniformity, it is recommended that, wherever possible, guidelines be produced for use on a national basis.

21.2.3 Training and education

In accordance with the national model regulations, workers potentially exposed to glutaraldehyde need to be trained in the safe work practices which are appropriate to their particular workplace, and that a record of training be kept.

Because of the incidence of adverse health effects occurring in the past and the widespread use of glutaraldehyde in a number of different industries, the training should be as specific as possible. Use of information in the safe use guidelines for that industry is recommended to facilitate those training needs.

21.3 Control of occupational exposure

As glutaraldehyde is a hazardous substance, it is recommended that worker exposure be reduced as much as possible by the implementation of effective control measures in accordance with the hierarchy of control measures detailed in *the National Model Regulations and Code of Practice for the Control of Workplace Hazardous Substances*.[107]

Where the replacement of glutaraldehyde may be considered in some application, the health effects and hazards of any substitute need to be taken into account to ensure that glutaraldehyde is not being replaced by a more hazardous substance.

Where possible, control measures, especially engineering controls, should be implemented at the design stage. Engineering controls such as ventilation should be installed by qualified professionals to ensure that specifications and Australian standards are met and that any new installation is compatible with existing systems.

It is recommended that all workplaces handling glutaraldehyde employ safe work practices to minimise exposure during routine operations, and to quickly reduce exposure in the case of spillage or during maintenance. Good housekeeping and personal hygiene is required in all workplaces. Appropriate safe work practices are listed in section 16.12.6.

Where other control measures are inappropriate or impractical, then PPE must be used. If PPE is to be used, then it should be selected and maintained in accordance with the relevant Australian Standards. Detailed guidance on the appropriate PPE for glutaraldehyde is given in section 16.12.7. The type of personal protection must be appropriate to the concentration of glutaraldehyde in the product and to the particular use of the product. PPE must be properly stored and maintained.

Control measures available in Australia are detailed in section 16.12. Recommended control measures by use and industry are detailed below.

21.3.1 Formulation of glutaraldehyde products

As glutaraldehyde is usually handled in large quantities and as a concentrate in the formulation of glutaraldehyde products, it is recommended that the process be enclosed, with the mixing vessel and glutaraldehyde transfer system sealed.

The discharge of product, for example, to a filling line, should also be enclosed as much as possible. If this is not achievable, then local exhaust ventilation is required.

Good dilution ventilation in accordance with Australian Standards is necessary in all production areas, with each ventilation rate having the capacity to be increased substantially in case of spillage.

All ventilation systems must be regularly examined, tested and maintained.

Total loss ventilation is recommended, but if the use of recirculated air cannot be avoided, filters, for example, carbon adsorption, must be used. If carbon filters are used, their performance must be monitored to ensure that they are replaced before chemical breakthrough occurs.

In production areas, procedures must be in place to handle spills and leaks.

If required, PPE should consist of the items listed below for the use of glutaraldehyde as a disinfectant. If PPE is required in handling glutaraldehyde concentrate, then goggles, long gloves, overalls and respiratory protection are essential.

21.3.2 Use as cold disinfectant

All instruments and equipment must be thoroughly cleaned before disinfection with glutaraldehyde.

Elimination or substitution

The use of glutaraldehyde in general surface disinfection, for example, the cleaning of bench-tops, is not recommended, so it should be eliminated where possible by more thorough cleaning with soap and water or replaced by a non-hazardous substance.

The substitution of glutaraldehyde should be approached with caution, as many of the alternatives are hazardous substances and/or less efficacious against micro-organisms.

Enclosure

Operations involving glutaraldehyde in x-ray film processing should be enclosed. Automatic mixers and automatic processors with exhaust outlets should be used where possible.

Engineering controls

Where the purchase of automatic equipment cannot be justified, good LEV is essential to minimise exposure (see section 16.12.4).

LEV for fixed work stations should consist of properly constructed and maintained fume cupboards. Mobile units must have lids or covers and be fitted with vapour extractors and carbon adsorption filters, which must be monitored to ensure that they are replaced before chemical breakthrough occurs.

Good dilution ventilation to a standard consistent with the relevant Australian Standards is essential in all work areas.

Safe work practices

The following safe work practices are recommended for the use of glutaraldehyde as a disinfectant:

- clear labelling of all containers, including those used in decanting when the solution is not consumed immediately;
- proper storage of solutions in designated cupboards away from heat sources;
- use of the minimum amount of glutaraldehyde for the task;
- avoidance of heat or ultrasonics, as glutaraldehyde vapours may be generated;
- care taken during the soaking procedure, including use of syringes, so that any splashing is avoided;
- lids or covers on soaking baths at all times;
- avoidance of transporting open containers of disinfectant;
- proper rinsing of instruments and soaking baths with clean running water after disinfection;
- use of solutions only in ventilated work areas;
- no decanting of glutaraldehyde solutions from soaking containers back into bottles;
- prompt clean-up of spills; and
- the deposit of disposable items, for example, gloves and syringes, into sealed containers prior to collection.

Personal protective equipment

Personal protective equipment recommended for the use of glutaraldehyde disinfectant solutions are:

- chemical safety goggles or safety spectacles with sideshields;
- elbow-length nitrile or butyl rubber gloves; double layers of surgical latex rubber gloves may be used for short contact times (<10 min.);
- aprons made from impervious material such as those used in the manufacture of gloves, with protection of the arms and legs essential; and
- in case of spills and leaks, half-face respirator with organic vapour cartridge.

21.3.3 Use in x-ray film processing

Enclosure

Operations involving glutaraldehyde in x-ray film processing should be enclosed, with automatic mixers and processors with exhaust outlets to be used where possible.

Engineering controls

The exhaust air from automatic processors must be completely removed from the work area by connection to an exhaust ventilation system independent of the dilution ventilation system. Discharge should be to atmosphere at a safe location.

If the use of an automatic mixer and/or processor is impractical or unjustifiable on economic grounds, then all mixing and processing operations involving glutaraldehyde must be carried out with effective local exhaust ventilation, preferably in a fume cupboard (see section 16.12.4).

Effective dilution ventilation is essential in all work areas, with the area under slightly negative pressure to prevent the escape of chemical vapours to adjacent work areas.

To minimise evaporation of the chemicals, including glutaraldehyde, the dark room and processing temperatures should be kept as low as possible while attaining the desired photographic results.

Safe work practices

Recommended safe working practices for the use of glutaraldehyde in x-ray film processing include:

- location of mixing tanks in a well ventilated area, preferably in a fume cupboard;
- proper storage of solutions in designated cupboards away from heat;
- avoidance of splashing and generation of vapours during mixing;
- covering of tanks (with tight-fitting lids) at all times;
- avoidance of carrying open tanks or containers of chemicals, especially when they are full;
- careful handling of processor rollers and tanks and other processing equipment so that spillage and skin contact are avoided;
- provision of adequate wash trough for cleaning tasks, for example, washing of processor rollers and tanks, with location of trough close to equipment;
- minimal direct handling of wet films;
- prompt clean-up of contaminated areas; and
- proper maintenance of automatic mixers and processors to prevent vapour generation, for example, through overheating and leaking pipes and connections.

Personal protective equipment

PPE is required when filling, emptying or maintaining automatic mixers and processors and when working with solutions during manual operations. Eye protection and gloves should be worn at all times and respiratory protection is required during spillage and maintenance of equipment.

The recommended PPE for the handling of x-ray processing solutions is:

- chemical safety goggles or safety spectacles with sideshields;
- long nitrile or butyl rubber gloves;
- laboratory coat or overalls, with protection for the arms and legs; and
- in case of spills or leakage, a half-face respirator with organic vapour filter.

21.3.4 Use in tanning

Control measures similar to those used in the manufacture of glutaraldehyde products are required for the use of glutaraldehyde in tanning (see section 21.3.1). Mixing vessels should be covered and sealed if possible to minimise vapour generation. The transfer of glutaraldehyde to the mixer should proceed via a sealed system, and all operations should be carried out with good ventilation.

Procedures for handling spills must be in place, and personal protective equipment (see section 21.3.2) should be worn during all operations involving possible exposure to glutaraldehyde.

21.3.5 Use in water treatment

The addition of glutaraldehyde solutions to cooling water systems is generally carried out in the field.

If automatic feed systems are used, then the proper safe handling procedures should be followed in filling and emptying the containers and connecting them to the dosing system.

Manual dosing should be carried out wearing the proper personal protective equipment, that is, goggles, gloves, overalls and protective footwear. Respiratory protection is required if glutaraldehyde vapours are generated.

The dilution of concentrated glutaraldehyde solutions should be carried out under proper local exhaust ventilation rather than at the site of water treatment.

21.3.6 Use in animal housing

The application of glutaraldehyde solutions in animal housing is generally carried out in the field, with the solutions used in spray form (see section 21.2.1), as a wash or as a foam.

Recommended safe work practices for the use of glutaraldehyde as a wash or as a foam in animal housing are:

- proper storage of solutions in designated areas away from heat sources;
- proper labelling of all containers, including those used in decanting when the solution is not consumed immediately;
- cleaning of all equipment after use, and storage in a designated area;
- clearing area of animals or birds before disinfection and for appropriate period after disinfection;
- availability of MSDS to workers carrying out disinfection; and
- good housekeeping in the work area.

The following personal protective equipment is to be worn during application as a wash or foam:

- chemical goggles or faceshield;
- long-sleeved gloves of impervious material such as butyl or nitrile rubber;
- overalls; and
- rubber boots.

In the application of glutaraldehyde solutions in spray form, all the above safe work practices need to be followed, with additional care in the clearing of the work area of other workers and animals and birds. In addition to the PPE stipulated above, long-sleeved overalls, hood and respiratory protection, for example, a half-face cartridge respirator, are required, with the type of respiratory protection dependent on the duration of application.

The use of glutaraldehyde on animals or birds is not recommended.

21.4 Atmospheric monitoring

Where an assessment of the workplace indicates that there is a significant risk of exposure to glutaraldehyde, it is recommended that an atmospheric monitoring program for glutaraldehyde be implemented as a means of measuring occupational exposure and as a monitor of the effectiveness of control measures in the workplace. The program should be in proportion to the risk of exposure, taking into account the quantity and concentration of glutaraldehyde used, the frequency of use and the number of workers potentially exposed.

If the level of exposure to glutaraldehyde is not known, it is recommended that a small number of analyses be conducted initially to establish a baseline for assessment of the workplace and to determine whether improved control measures and/or regular monitoring are necessary. For example, no atmospheric monitoring results for exposure to glutaraldehyde in the tanning industry were available during the PEC assessment period.

Where atmospheric monitoring is required, both personal and fixed-point monitoring should be carried out, and proven analytical procedures should be used (see Chapter 6).

The frequency of monitoring required will also depend on the results obtained. Once control measures have been shown to be effective, then the frequency can be reduced.

21.5 Emergency response plan

It is recommended that a written emergency response plan be provided in all workplaces where significant quantities of glutaraldehyde are used. The essential items in a good emergency response plan are listed in section 16.4.

21.6 Disposal

It is recommended that no special environmental controls beyond those that currently prevail across Australia are considered necessary. Spent solutions disposed of to sewer should be flushed with copious amounts of water. Glutaraldehyde must not be discharged to surface waters, storm water drains or septic systems.

21.7 Regulatory controls

21.7.1 Exposure standard

The current Australian exposure standard for glutaraldehyde, set by the National Commission, is 0.2 ppm v/v (0.82 mg/m^3) as a peak limitation and with a sensitiser notation. The standard, which is based on the irritant effect of glutaraldehyde on the upper respiratory tract, has been listed for review since 1991.

In view of the results of animal testing and the human experience, where irritant effects have been observed at or below the current exposure standard, particularly after repeated exposure, it is recommended that the following exposure limits for glutaraldehyde be considered by the National Commission's Exposure Standards Expert Working Group in their review:

- STEL (15 min.) 0.15 ppm (0.62 mg/m^3);
- TWA (8 hr) 0.1 ppm (0.41 mg/m^3);

with a skin sensitiser notation.

21.7.2 Health surveillance

It is not recommended that glutaraldehyde be added to schedule 3 of *the National Model Regulations for the Control of Workplace Hazardous Substances*,[107] but under the regulations, employers will need to provide health surveillance in workplaces where the assessment shows that exposure to glutaraldehyde may result in a substance-related health effect such as contact dermatitis.

As early diagnosis of glutaraldehyde-induced health effects is important, it is recommended that workers potentially exposed to glutaraldehyde should undergo a pre-placement medical check as a baseline to assist in identifying future signs of skin or respiratory disease.

If the workplace assessment indicates that health surveillance is required, then it is recommended that the following medical tests should be considered by occupational physicians:

- patch testing in accordance with accepted standard procedures;
- PEFR measurements;
- spirometry for the measurement of FVC and FEV_1; and
- bronchial challenge testing where appropriate.

So that an adequate record of occupational disease is compiled, it is recommended that cases of skin and respiratory disease in workers exposed to glutaraldehyde be fully evaluated and that the case studies be reported in the scientific and/or medical literature. Available case reports should be sent to Worksafe Australia.

21.7.3 Aquaculture;

Although not reported by any of the applicants during the assessment period, there is some evidence that glutaraldehyde may be used in aquaculture in Australia.[11] It is recommended that the National Registration Authority for Agricultural and Veterinary Chemicals use the health and environmental effects information in this report to assist with any review of the use of glutaraldehyde in aquaculture.

21.8 Further testing

In carrying out the assessment of glutaraldehyde, some items of toxicological, ecotoxicological and technical information were unavailable, either because testing was not completed or because testing had not been carried out. It is recommended that testing be carried out, or completed, in the following areas:

- a two-year inhalation study (the NTP is expected to begin a study in 1994);
- comparative acute inhalational toxicity studies at various temperatures (repeat LC^{50} studies at ambient and elevated temperatures currently being carried out);
- detailed vapour generation studies at various temperatures for various strengths of solution to improve the corrrelation between strength of solution and vapour concentration (as ppm) above solution;
- improve the reliability of the vapour generation procedure for the purposes of inhalational toxicity testing;
- anaerobic aquatic metabolism and bacterial inhibition tests (currently being carried out); and
- studies into the mechanism and cause of occupational asthma in workers exposed to glutaraldehyde.

22. Secondary notification;

Under section 65 of the Act, the secondary notification of a chemical may be required if there has been a change in circumstances which warrants a reassessment of any of the hazards of the chemical.

In the case of glutaraldehyde, a secondary notification may be required if:

- it is manufactured in Australia;
- a new use arises, for example, in cosmetics; or
- significant new information about the health and/or environmental effects becomes available.

Risk phrases

R20 Harmful by inhalation

R21 Harmful in contact with skin

R22 Harmful if swallowed

R23 Toxic by inhalation

R24 Toxic in contact with skin

R25 Toxic if swallowed

R26 Very Toxic by inhalation

R27 Very Toxic in contact with skin

R28 Very Toxic if swallowed

R34 Causes burns (Corrosive)

R35 Causes severe burns (Very Corrosive)

R36 Irritating to eyes

R37 Irritating to respiratory system

R38 Irritating to skin

R39 Danger of very serious irreversible effects

R40 Possible risk of irreversible effects

R41 Risk of serious damage to eyes

R42 May cause sensitisation by inhalation

R43 May cause sensitisation by skin contact

R45 May cause cancer

R46 May cause heritable genetic damage

R47 May cause birth defects

R48 Danger of serious damage to health by prolonged exposure

R49 May cause cancer by inhalation

MSDS submitted

Product Name	*Supplier*	*% Glutaraldehyde*
Raw Materials		
50% w/w glutaraldehyde	Union Carbide	50%
approx 50% glutaraldehyde	BASF	50%
approx 25% glutaraldehyde	BASF	50%
Glutaraldehyde 25%	ICI Pharmaceuticals	25%
Disinfectants		
Aldecyde 28	ICI Pharmaceuticals	2.3%
Aidal	Whiteley Chemicals	1%
Aidal Plus	Whiteley Chemicals	2%
Wavicide 01	Whiteley Chemicals	2.1%
Cidex	Johnson & Johnson Medical	2%
Cidex Long-Life	Johnson & Johnson Medical	2%
General Biocides		
Sepacid	BASF	50%
Protectol GDA	BASF	50%
Protectol GDA 25%	BASF	25%
Actisan	Gibson Chemicals	15%
Formula 936N	Gibson Chemicals	2%
Formula 9365N	Gibson Chemicals	2%
Formula 9465N	Gibson Chemicals	2.5%
Uconex Antimicrobial 350	Union Carbide	50%
Ucarcide Antimicrobial 125	Union Carbide	25%
Germ-Out	SterileAir	2%

Product Name	*Supplier*	*% Glutaraldehyde*
X-ray Photography		
Industrex Developer Replenisher Part C	Kodak Australasia	10-15% 20-25% (as bisulfite)
Duraflo RT Developer Replenisher Part B	Kodak Australasia	5-10% (as bisulfite)
Rapid-X-Developer Replenisher	Ilford	3-7%
Ilfotec-RT-Developer Replenisher	Ilford	1-5%
Cronex	DuPont	5-10%
Cronex High Stability Developer/Replenisher Working Strength	DuPont	0.5-1.5% (as bisulfite)
Cronex High Stability Developer/Replenisher Part C	DuPont	5-10% 10-30% (as bisulfite)
RP X-Omat Developer/ Replenisher Part C	Kodak	40-45%
RD III Developer/ Replenisher Part C	Ilford	3-7%
G135 Developer Part C	Agfa-Gevaert	10-20% (as bisulfite)
Tanning		
Relugan GT 50	BASF	50%
Relugan GT 25%	BASF	25%
Derugan 2000	T R Chemicals	unknown
Derugan 2020	T R Chemicals	

Product Name	*Supplier*	*% Glutaraldehyde*
Water Treatment		
Biomate 5792	Grace Dearborn	8.1%
Biomate 733	Grace Dearborn	30-60%
Nalco 7338	Nalco Australia	45%
Piror Slimicide 825	Union Carbide	25%
Aqucar Microbiocide 545	Union Carbide	45%
Animal Housing		
Microcide/GPC8	Pfizer	12.4%
Keymix Glutacide	International Animal Health	15%
Safe Guard	Campbell Bros	5.3%
Embalming		
DSD (Dodge Sterilant & Disinfectant)	Hickey & Co P/L	2%

Labels submitted

The following table lists the labels which were submitted during the assessment period. The suppliers of the products listed can be obtained from the list of MSDS in Appendix 2.

The approximate risk and safety phrases on the labels relating to health effects have also been listed. In some cases, the term 'poisonous' has been used on labels in accordance with requirements of the SUSDP,[112] for example, 'poisonous if inhaled'. For the purposes of comparison in this table, a similar EC risk phrase has been indicated, for example, 'Toxic by inhalation' for 'poisonous if inhaled'.

Product Name	*% Glut.*	*Risk Phrases*	*Safety Phrases*
Disinfectants			
Aidal	1%	—	S24,25,37,50
Aidal Plus	2%	R43	S24,50
Wavicide 01	2.1%	R43	S24,50
Aldecyde 28	2%	R20,21,36,38	S23,24,25,37,39
Cidex	2%	R22,38,41,43	S24,39,51
Cidex Long-Life	2%	R22,38,41,43	S24,39,51
Glutarall	2.1%	R36,43	S24,50,51
(Colgate-Orapharm)			
General Biocides			
Ucarcide 225	25%	R20,21,22 34,41,43	S23,24,25,36,37, 39
*Actisan	15%	R23,24,36, 38,43	S23,24,25,37,39
*Formula 936N	2%	R43	S23,24,25
*Formula 9365N	2%	R43	S23,24,25
*Formula 9465N	2.5%	R43	S23,24,25

Product Name	*% Glut.*	*Risk Phrases*	*Safety Phrases*
X-ray Photography			
Kodak RP X-Omat	50%	R20	S22,24,51
Part C			
Cronex HSD/R Part C	14%	R34	S24,25,37,39
Ilford Rapid X-D Part C	5%	—	—
Hanimex RD III Part C	5%	—	—
Water Treatment			
Nalco 7338	45%	R34,51	S23,37,39
Aqucar 545	45%	R20,21,22,34, 41,43	S23,24,25,36, 37,39
Biomate 5792	8.1%	R34	—
Animal Housing			
Keymix Glutacide	15.1%	R23,24,36,37, 38	S23,24,25,37,39
Microcide/GPC8	12.4%	—	S23,39,50

* Domestic end-use products.

Risk phrases

See Appendix 1.

Safety phrases

S23	Do not breath vapour/spray.
S24	Avoid contact with skin.
S25	Avoid contact with eyes.
S36	Wear suitable protective clothing.
S37	Wear suitable gloves.
S39	Wear eye/face protection.
S50	Do not mix with/
S51	Use only in well-ventilated areas.

Survey of health care establishments using glutaraldehyde

A4.1 Tasmania

The questionnaire sent to health care establishments in Tasmania by the Department of State Development and Resources revealed that the following establishments used glutaraldehyde:

Burnie Hospital, Burnie.

Emmerton Park, Smithton (aged care).

Eskleigh Memorial Home, Perth.

Hobart Pathology, Hobart.

Launceston General Hospital.

Launceston Presbyterian Homes for the Aged.

Melaleuca Home for the Aged, Devonport.

Nazareth House, St Leonards.

Northern Tasmanian Pathology Service, Launceston.

Queen Victoria Hospital, Launceston:

- used as disinfectant for laparoscopes in gynaecology theatre until theatre closed in January 1993.

Rosebery District Hospital, Rosebery.

Royal Hobart Hospital:

- Anatomical Pathology Dept:
  - in electron microscopy;
  - used in fume cupboard;
- Microbiology Dept:
  - as disinfectant.

St Helens District Hospital, St Helens:

- used as disinfectant for only six weeks.

St Helens Private Hospital, Hobart:

- as disinfectant;
- monitoring carried out, with concentrations below 0.1 ppm.

St John's Private Hospital, Hobart.

St Luke's Private Hospital, Launceston:

- specially designed laminar flow unit installed for disinfection of endoscopes;
- written policy on use and storage.

St Vincent's Private Hospital, Launceston:

- used as disinfectant in operating suite and endoscopy unit.

Tasmanian Dental Technicians and Dental ProsthesistsAssociation, Howrah.

Webster Nursing Home and Campbell Town District Hospital, Campbell Town.

A4.2 South Australia

The survey carried out by the South Australian Occupational Health and Safety Commission resulted in replies from the following health care establishments. Observed adverse health effects after exposure to glutaraldehyde are also detailed.

Balaklava Soldiers' Memorial District Hospital:

- disinfection of arthroscopes.

Burra Burra Hospital:

- 1% solution used for disinfection of endoscopes and laparoscopes once per month.

Flinders Medical Centre, Bedford Park

- 1% and 2% solutions used in endoscopy unit;
- sore eyes and throat in 1 nurse, and facial rash on one nurse.

Glenside Hospital, Adelaide:

- used in small amounts as disinfectant in Eye and Dental Clinics;
- PPE includes goggles, chemical resistant gloves and gown.

Hillcrest Hospital, Adelaide:

- used in eye clinic for disinfection of heat sensitive tonometer prisms;
- used in well-ventilated area, but without LEV;
- PPE includes visor, nitrile gloves and long-sleeved plastic-lined gowns.

Hutchinson Hospital, Gawler:

- used in disinfection of laparoscopes;
- PPE includes elbow length gloves and safety glasses.

Lameroo District Hospital.

Loxton Hospital.

Lyell McEwin Health Service, Elizabeth Vale:

- used as 1% and 2% solutions in disinfection of fibre optic scopes, endoscope blades and ultrasound probes;
- used in x-ray film developer;
- automixers located in fume cupboards installed to minimise exposure;
- PPE includes gowns with long sleeves, gloves, face masks or safety glasses.

Millicent and District Hospital:

- used in operating theatre for disinfection.

Modbury Hospital.

- Mount Gambier Hospital.
- 2% solution used for disinfection of colonoscopes:
- pump system, fume cupboard and exhaust fans installed for mixing and pouring operations;
- eye irritation in 1 nurse.

Murray Bridge Soldiers' Memorial Hospital:

- five workers potentially exposed, but on an infrequent basis;
- contact dermatitis observed in two workers, but short term only;

Noarlunga Health Services.

Peterborough Soldiers' Memorial Hospital:

- used for endoscope disinfection once per month.

Port Augusta Hospital:

- soaking dishes and other containers fully covered or sealed;
- mixing and pouring avoided in inadequately ventilated areas;
- PPE includes nitrile gloves, aprons and face shields or goggles;
- spill kit, including cartridge respirators, readily accessible;
- emergency eye shower bottles readily available;
- eye irritation in one nurse.

Port Pirie Regional Health Service:

- adverse health effects observed in four of six theatre staff:
- eye irritation in one nurse;
- nose and throat irritation in two nurses;
- chest tightness in one nurse;
- headache in three nurses;
- dermatitis of hands and feet in one nurse.

Renmark and Paringa District Hospital, Renmark:

- 1% solution used for disinfection of endoscopes.
- Riverland Regional Health Services, Berri:
- used in endoscopy unit up to twice per week.

Royal Adelaide Hospital:

- developed a comprehensive Occupational Health Policy Document;
- implemented a number of engineering controls to minimise exposure;
- 18 confirmed cases in period 1986-93, including:
    - dermatitis on hands or arms of six nurses and one technical officer,
    - red blotches on skin of four nurses,
    - whole body rash on 1 nurse,

- coughing and/or sore throat in two nurses,
- occupational asthma in 1 nurse,
- eye burn in 1 nurse,
- nausea and lethargy in 1 nurse.

Streaky Bay Hospital:

- 2% solution used to clean cytoscopy equipment twice per year;
- x-ray developers used.

The Queen Elizabeth Hospital, Adelaide:

- used in operating theatres, endoscopy room and day surgery suite;
- report of respiratory irritant effects in endoscopy room;
- exposure minimised by installation of fume extraction hoods and better drainage.

Waikerie Hospital and Health Services:

- used in disinfection of laparoscopes and laryngoscopes.

Whyalla Hospital and Health Services:

- safe work practices introduced to eliminate occupational symptoms, include:
  - enclosed automatic cleaning system situated under large extractor hood, exhausted to outside building;
  - disposal into closed drums of sawdust and burnt;
  - rotation of staff in endoscopy unit;
  - enclosed soaking system;
- facial dermatitis in 1 physician from disinfection of eyepiece;
- rhinitis and itchy eyes in 1 anaesthetist, 1 surgeon and 2 nurses:
- wheezy bronchitis in one nurse.
- Women's and Children's Hospital:
- eye irritation in three workers.

Example of MSDS for concentrated glutaraldehyde

Company: UNION CARBIDE CHEMICALS (AUST) PTY LTD.
Address: SUITE 1, 1-7 JORDAN STREET
GLADESVILLE, NSW-2111
Tel. No: (02)879 6066

Emergency:(02)879 6066

Issued :13/05/93
U.N. NO: 1760
Hazchem Code:2R
Packing Grp:II
Hazard Class:8
EPG:G1
Poison Sch.: 6
Page : 1

Glutaraldehyde (50% by weight)

Union Carbide urges each customer or recipient of this MSDS to study it carefully to become aware of and understand the hazards associated with the product. The reader should consider consulting reference works or individuals who are experts in ventilation, toxicology, and fire prevention, as necessary or appropriate to use and understand the data contained in this MSDS.

To promote safe handling, each customer or recipient should: (1) notify its employees, agents, contractors and others whom it knows or believes will use this material or the information in this MSDS and any other information regarding hazards or safety; (2) furnish this same information to each of its customers for the product; and (3) request its customers to notify their employees, customers, and other users of the product of this information.

I. IDENTIFICATION

PRODUCT NAME: Glutaraldehyde (50% by weight)

CHEMICAL NAME: Glutaraldehyde, 50% aqueous solution

CHEMICAL FAMILY: Aldehydes

FORMULA: OHCC3H6CHO

MOLECULAR WEIGHT: 100.12

SYNONYMS: Glutaral, glutaric dialdehyde

CAS # AND NAME:
See Section III, "Ingredients"

II. PHYSICAL DATA (Determined on typical material)

BOILING POINT, 760 mm Hg: ~100.5 C (~213 F)
SPECIFIC GRAVITY(H2O = 1): 1.129 AT 20/20 C

EMERGENCY PHONE NUMBER

SYDNEY: (02) 879 6066 OUTSIDE SYDNEY METROPOLITAN AREA: 008 027 955
OR YOUR STATE POISONS INFORMATION CENTRE WHERE MEDICAL ADVICE IS REQUIRED.

UNION CARBIDE CHEMICALS (AUSTRALIA) PTY LIMITED
SUITE 1, 1ST FLOOR 1-7 JORDAN STREET, GLADESVILLE NSW 2111 AUSTRALIA

PRODUCT NAME: Glutaraldehyde (50% by weight)

FREEZING POINT: --21 C (--5.8 F)

VAPOR PRESSURE AT 20'C: ~16 mmHg

VAPOR DENSITY (air = 1): 1.05

EVAPORATION RATE:
(Butyl Acetate = 1): 1.02

SOLUBILITY IN WATER by wt: 100% AT 20 C

APPEARANCE: Transparent colorless

ODOR: Characteristic
Aldehyde

PHYSICAL STATE: Liquid

III. INGREDIENTS

%	MATERIAL	CAS#	EXPOSURE LIMIT
50	Glutaraldehyde	111-30-8	See Section V
~50	Water	7732-18-5	None established
0.5	Methanol	67-56-1	See Section V

IV. FIRE AND EXPLOSION HAZARD DATA

FLASH POINT (test method(s)):
None
Tag Closed Cup ASTM D 56

None
Tag Open Cup ASTM D 1310

FLAMMABLE LIMITS IN AIR, by volume:

LOWER: Not Determined, Aqueous System
UPPER: Not Determined, Aqueous System

EXTINGUISHING MEDIA:
Non-flammable (aqueous solution): After water evaporates, remaining material will burn. Use alcohol-type or all-purpose-type foam, applied by manufacturer's recommended techniques for large fires. Use carbon dioxide or dry chemical media for small fires.

SPECIAL FIRE FIGHTING PROCEDURES:
Use self-contained breathing apparatus and protective clothing.

PRODUCT NAME: Glutaraldehyde (50% by weight)

UNUSUAL FIRE AND EXPLOSION HAZARDS:
None

V. HEALTH HAZARD DATA

TLV AND SOURCE:
Glutaraldehyde: 0.2 ppmv Ceiling, OSHA & ACGIH
Methanol: 200 ppm TWA (skin), OSHA & ACGIH
250 ppm STEL (skin), OSHA & ACGIH

EFFECTS OF SINGLE OVEREXPOSURE:

SWALLOWING:
Moderately toxic.
May cause moderate to marked irritation or chemical burns of the mouth, throat, esophagus, and stomach, with discomfort or pain in the mouth, throat, chest, and abdomen, nausea, vomiting, diarrhea, dizziness, faintness, drowsiness, weakness, thirst, circulatory collapse, and coma.

SKIN ABSORPTION:
Prolonged or widespread contact may result in the absorption of potentially harmful amounts of material.

INHALATION:
Vapor is irritating to the respiratory tract, causing stinging sensations in the nose and throat, discharge from the nose, possibly bleeding from the nose, coughing, chest discomfort and tightness, difficulty with breathing, and headache.

SKIN CONTACT:
Brief contact will cause itching with mild to moderate local redness and possibly swelling. Prolonged contact may result in pain, severe redness and swelling, with ulceration, tissue destruction, and possibly bleeding into the inflamed area.

EYE CONTACT:
Liquid will cause a severe and persistent conjunctivitis, seen as excess redness and marked swelling of the conjunctiva with profuse discharge. Severe corneal injury may develop, which could permanently impair vision if prompt first-aid and medical treatment are not obtained. Vapor will cause stinging sensations in the eye with excess tear production, blinking, and possibly a slight excess redness of the conjunctiva.

EFFECTS OF REPEATED OVEREXPOSURE:
Repeated skin contact may cause a cumulative dermatitis.

MEDICAL CONDITIONS AGGRAVATED BY OVEREXPOSURE:
Skin contact may aggravate an existing dermatitis.
Inhalation of material may aggravate asthma and inflammatory or fibrotic pulmonary disease.

SIGNIFICANT LABORATORY DATA WITH POSSIBLE RELEVANCE TO HUMAN HEALTH HAZARD EVALUATION:
Laboratory studies have shown that glutaraldehyde is not teratogenic, and

several studies have shown the material not to be a mutagen. Preliminary, as yet not quality assured, histopathological findings in the 24-month sacrifice of a combined oncogenicity/chronic toxicity study in Fischer 344 rats given glutaraldehyde in drinking water (50, 250, and 1000 ppm) showed an increase in the incidence of the spontaneously occurring large granular cell lymphocytic leukemia (LGL) at all dosages compared with the controls only for the female rats. Male rats had the same incidence in controls and at all levels of exposures. Since the incidence of this leukemia was low in the control female rats, comparison with other control data and further statistical analyses are currently being undertaken in order to further define the relevance of this study.

OTHER EFFECTS OF OVEREXPOSURE:
May cause skin sensitization in a small portion of individuals and present as an allergic contact dermatitis. This usually results from contact with the liquid, but occasionally there may be a reaction to glutaraldehyde vapor.

EMERGENCY AND FIRST AID PROCEDURES:

SWALLOWING:
DO NOT INDUCE VOMITING. Do not give anything to drink. Obtain medical attention without delay.

SKIN:
Immediately remove contaminated clothing and shoes. Wash skin with soap and water. Obtain medical attention. Wash clothing before reuse. Discard contaminated leather articles such as shoes and belt.

INHALATION:
Remove to fresh air. Give artificial respiration if not breathing. If breathing is difficult, oxygen may be given by qualified personnel. Obtain medical attention.

EYES:
Immediately flush eyes with water and continue washing for at least 15 minutes. Obtain medical attention without delay, preferably from an ophthalmologist.

NOTES TO PHYSICIAN:
The hazards of this material are due mainly to its severely irritant properties on skin and mucosal surfaces.
Moderately toxic by swallowing.
Moderately toxic by absorption across the skin.
Due to the severely irritating or corrosive nature of the material, swallowing may lead to ulceration and inflammation of the upper alimentary tract with hemorrhage and fluid loss. Also, perforation of the esophagus or stomach may occur, leading to mediastinitis or peritonitis and the resultant complications.
The stomach should be evacuated carefully in case of ingestion.
Any material aspirated during vomiting may cause lung injury. Therefore, emesis should not be induced mechanically or pharmacologically. If it is considered necessary to evacuate the stomach contents, this should be done by means least likely to cause aspiration (e.g., gastric lavage after endotracheal intubation).

VI. REACTIVITY DATA

PRODUCT NAME: Glutaraldehyde (50% by weight)

STABILITY: Stable

CONDITIONS TO AVOID:
Avoid high temperature and evaporation of water.

INCOMPATIBILITY (materials to avoid):
Strong alkalies and acids catalyze an aldol-type condensation (exothermic, but not expected to be violent).

HAZARDOUS COMBUSTION OR DECOMPOSITION PRODUCTS:
Burning can produce the following products:
Carbon monoxide and/or carbon dioxide.
Carbon monoxide is highly toxic if inhaled; carbon dioxide in sufficient concentrations can act as an asphyxiant.

HAZARDOUS POLYMERIZATION: Will Not Occur

CONDITIONS TO AVOID:
Temperatures above 100 degrees C.
Although polymerization may occur, it is not hazardous.

VII. SPILL OR LEAK PROCEDURES

STEPS TO BE TAKEN IF MATERIAL IS RELEASED OR SPILLED:
Wear suitable protective equipment. Toxic to fish; avoid discharge to natural waters. Very low concentrations (10 ppm or less) can be degraded in a biological treatment system. Thus, small spills can be flushed with large quantities of water.
Large quantities or 'slugs' can be harmful to the treatment system.
Thus, large spills should be collected for disposal. It may also be possible to decontaminate spilled material by careful application of aqueous sodium hydroxide or dibasic ammonium phosphate solution. Depending on conditions, considerable heat and fumes can be liberated by the decontamination reaction.

WASTE DISPOSAL METHOD:
Atomize into a very hot incinerator fire or mix with a suitable flammable solvent, and incinerate where permitted under appropriate Federal, State, and local regulations. High water content may dampen flame.

VIII. SPECIAL PROTECTION

RESPIRATORY PROTECTION (specify type):
Use self-contained breathing apparatus in high vapor concentrations.
If self-contained breathing apparatus is not available, a MSHA/NIOSH approved air purifying respirator equipped with an organic vapor cartridge should be used.

VENTILATION:
General (mechanical) room ventilation is expected to be satisfactory where this product is stored and handled in closed equipment.

PROTECTIVE GLOVES:
Rubber
Nitrile (NBR)

PRODUCT NAME: Glutaraldehyde (50% by weight)

Butyl
Polyethylene

EYE PROTECTION:
Monogoggles or Faceshield

OTHER PROTECTIVE EQUIPMENT:
Chemical Apron
Eye Bath, Safety Shower
Rubber Boots

IX. SPECIAL PRECAUTIONS

PRECAUTIONS TO BE TAKEN IN HANDLING AND STORAGE:
DANGER: CORROSIVE - CAUSES IRREVERSIBLE EYE DAMAGE.
CAUSES SKIN BURNS.
HARMFUL IF INHALED.
HARMFUL IF SWALLOWED.
HARMFUL IF ABSORBED THROUGH SKIN.
MAY CAUSE SKIN SENSITIZATION.
Do not get in eyes, on skin, on clothing.
Avoid breathing vapor.
Do not swallow.
Wear goggles, protective clothing, and rubber gloves.
Wash thoroughly with soap and water after handling.
Remove contaminated clothing and wash before reuse.
FOR INDUSTRY USE ONLY

OTHER PRECAUTIONS:
Laboratory studies, using an odor test panel, indicated glutaraldehyde vapors in air may be 'irritating' to humans at about 0.3 ppm in air; the TLV has been established as 0.2 ppm ceiling. Thus, if vapors are concentrated enough to be irritating, the TLV is probably being exceeded.

Must not be used in the form of a spray or aerosol.

X. REGULATORY INFORMATION

STATUS ON SUBSTANCE LISTS:
The concentrations shown are maximum or ceiling levels (weight %) to be used for calculations for regulations. Trade Secrets are indicated by "TS".

FEDERAL EPA

Comprehensive Environmental Response Compensation, and Liability Act of 1980 (CERCLA) requires notification of the National Response Center of release of quantities of Hazardous Substances equal to or greater than the reportable quantities (RQs) in 40 CFR 302.4.
Components present in this product at a level which could require reporting under the statute are:
*** NONE ***

PRODUCT NAME: Glutaraldehyde (50% by weight)

Superfund Amendments and Reauthorization Act of 1986 (SARA) Title III requires emergency planning based on Threshold Planning Quantities (TPQs) and release reporting based on Reportable Quantities (RQs) in 40 CFR 355 (used for SARA 302, 311 and 312).

Components present in this product at a level which could require reporting under the statute are:

*** NONE ***

Superfund Amendments and Reauthorization Act of 1986 (SARA) Title III requires submission of annual reports of release of toxic chemicals that appear in 40 CFR 372 (for SARA 313). This information must be included in all MSDSs that are copied and distributed for this material.

Components present in this product at a level which could require reporting under the statute are:

*** NONE ***

TSCA INVENTORY STATUS:

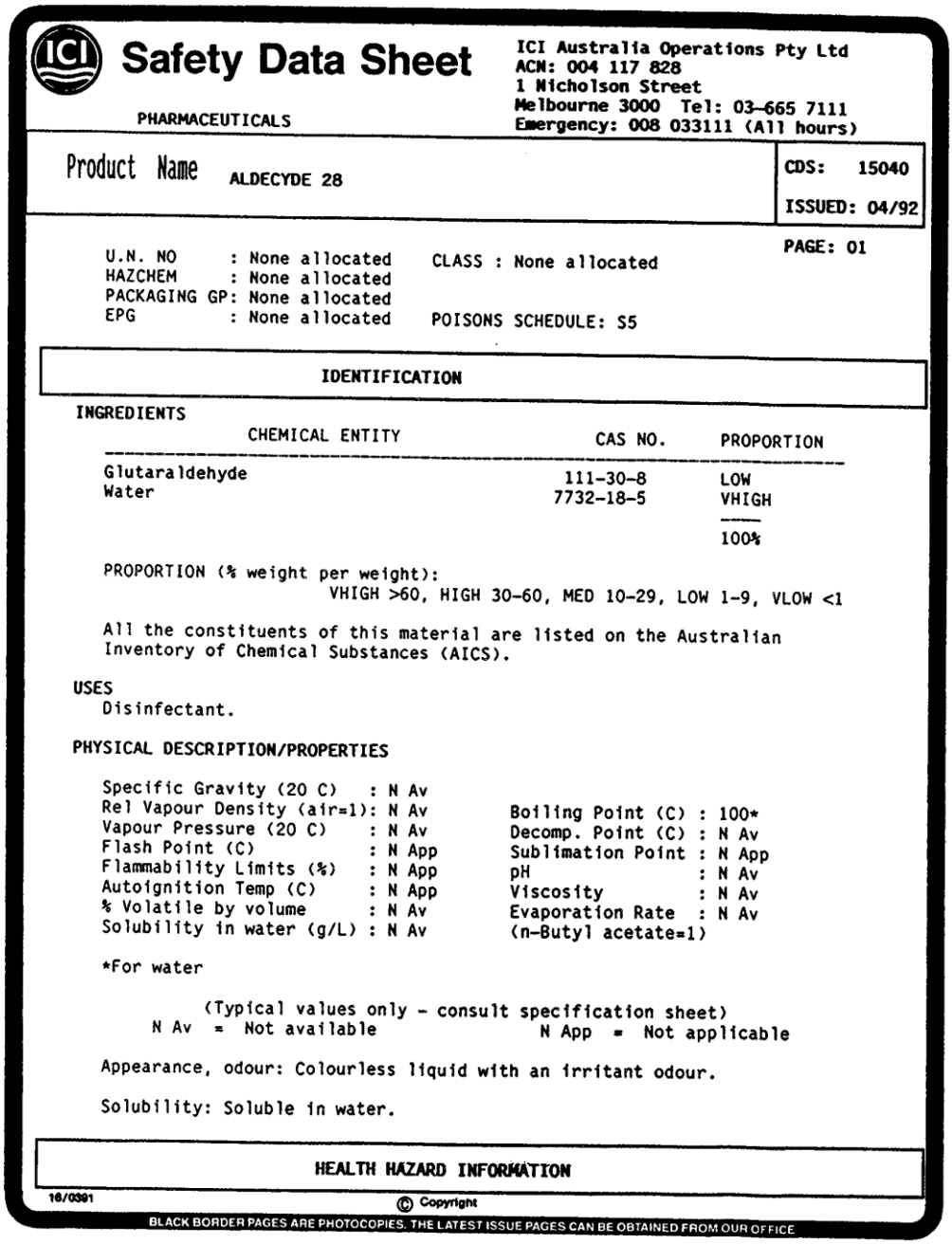
The ingredients of this product are on the TSCA inventory.

NOTE ----

The opinions expressed herein are those of qualified experts within Union Carbide. We believe that the information contained herein is current as of the date of this Material Safety Data Sheet. Since the use of this information and of these opinions and the conditions of the use of the product are not within the control of Union Carbide, it is the user's obligation to determine the conditions of safe use of the product.

Date: 07/29/92
REVISION DATE: 05/13/93 Printed in Australia
REVISED SECTIONS
The information in this MSDS has been updated.
Please review all sections.
PRODUCT: 40544
F NUMBER: B0387G

Example of MSDS for diluted glutaraldehyde



Safety Data Sheet

PHARMACEUTICALS

ICI Australia Operations Pty Ltd
ACN: 004 117 828
1 Nicholson Street
Melbourne 3000 Tel: 03-665 7111
Emergency: 008 033111 (All hours)

Product Name ALDECYDE 28

CDS: 15040
ISSUED: 04/92

PAGE: 01

U.N. NO : None allocated CLASS : None allocated
HAZCHEM : None allocated
PACKAGING GP: None allocated
EPG : None allocated POISONS SCHEDULE: S5

IDENTIFICATION

INGREDIENTS

CHEMICAL ENTITY	CAS NO.	PROPORTION
Glutaraldehyde	111-30-8	LOW
Water	7732-18-5	VHIGH
		100%

PROPORTION (% weight per weight):
VHIGH >60, HIGH 30-60, MED 10-29, LOW 1-9, VLOW <1

All the constituents of this material are listed on the Australian Inventory of Chemical Substances (AICS).

USES
Disinfectant.

PHYSICAL DESCRIPTION/PROPERTIES

Specific Gravity (20 C)	: N Av		
Rel Vapour Density (air=1)	: N Av	Boiling Point (C)	: 100*
Vapour Pressure (20 C)	: N Av	Decomp. Point (C)	: N Av
Flash Point (C)	: N App	Sublimation Point	: N App
Flammability Limits (%)	: N App	pH	: N Av
Autoignition Temp (C)	: N App	Viscosity	: N Av
% Volatile by volume	: N Av	Evaporation Rate (n-Butyl acetate=1)	: N Av
Solubility in water (g/L)	: N Av		

*For water

(Typical values only - consult specification sheet)
N Av = Not available N App = Not applicable

Appearance, odour: Colourless liquid with an irritant odour.

Solubility: Soluble in water.

HEALTH HAZARD INFORMATION

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Safety Data Sheet

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HEALTH EFFECTS

No adverse health effects expected if the product is handled in accordance with this Safety Data Sheet and the product label. Symptoms that may arise if the product is mishandled are:

ACUTE EFFECTS
SWALLOWED: Swallowing can result in nausea and vomiting.

EYE: An eye irritant.

SKIN: Contact with skin may result in irritation. Repeated or prolonged skin contact may lead to allergic contact dermatitis.

INHALED: Harmful if inhaled.

CHRONIC EFFECTS
No information available for product.

FIRST AID

SWALLOWED: Rinse mouth with water. Do NOT induce vomiting. Give water or milk, then raw egg. Seek immediate medical assistance.

EYE: Immediately irrigate with copious quantities of water for at least 15 minutes. Eyelids to be held open. Remove clothing if contaminated and wash skin. Seek immediate medical assistance.

SKIN: Wash contaminated skin with plenty of water. Remove contaminated clothing and wash before re-use. If swelling, redness, blistering, or irritation occurs seek medical advice.

INHALED: Remove victim from exposure - avoid becoming a casualty. Seek medical advice if effects persist.

ADVICE TO DOCTOR

Treat symptomatically.

TOXICITY

No LD50 data available for product.

Cases of occupational allergic contact dermatitis have been reported for this product (3).

For glutaraldehyde, a component:

Oral LD50(rat): 134 mg/kg (1)
Dermal LD50(rabbit): 2560 mg/kg (1)
Inhalation LC50(rat): 5000 ppm/4h (2)

SKIN (rabbit): Severe irritant (1)
EYES (rabbit): Severe irritant (1)

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Safety Data Sheet

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Product Name ALDECYDE 28

CDS: 15040
ISSUED: 04/92

TOXICITY (CONT.)

Mice exposed to 33 ppm for 24 hours have shown toxic effects on the liver (2).

PRECAUTIONS FOR USE

EXPOSURE STANDARDS

No value assigned for this specific material by the National Occupational Health and Safety Commission (Worksafe Australia).

For constituent: Glutaraldehyde
Exposure Standard (TWA): 0.2 ppm; 0.82 mg/m3 Peak Limitation and 'Sen' notice

As published by the National Occupational Health and Safety Commission (Worksafe Australia).

Peak Limitation - a ceiling concentration which should not be exceeded over a measurement period which should be as short as possible but not exceeding 15 minutes.

'Sen' notice - sensitiser. The substance can cause a specific immune response in some people. An affected individual may subsequently react to exposure to minute levels of that substance.

Exposure Standard (TWA) is the time-weighted average airborne concentration over an eight-hour working day, for a five-day working week over an entire working life. According to current knowledge this concentration should neither impair the health of, nor cause undue discomfort to, nearly all workers.

ENGINEERING CONTROLS

Ensure ventilation is adequate to maintain air concentrations below exposure standards. Keep containers closed when not in use.

PERSONAL PROTECTION

ICI PERSONAL PROTECTION GUIDE (NO. 2, 1990): CODE C -
OVERALLS, SAFETY SHOES, GOGGLES, GLOVES(S)
Avoid skin and eye contact. Do not inhale vapour. Wear overalls, chemical goggles and impervious gloves. Always wash hands before smoking, eating, drinking or using the toilet.

FLAMMABILITY

Non-combustible material.

Safety Data Sheet

PHARMACEUTICALS

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SAFE HANDLING INFORMATION

STORAGE AND TRANSPORT

Not defined as a Dangerous Good by the Australian Code for the Transport of Dangerous Goods by Road and Rail.
This material is a Scheduled Poison (S5) and must be stored, maintained and used in accordance with the relevant regulations.

No special storage precautions required.

SPILLS

Wear protective equipment to prevent skin and eye contamination and inhalation of vapours. Use absorbent (soil, sand, vermiculite or other inert material eg. paper cloth). Collect and seal in properly labelled containers for disposal. Wash area down with excess water.

DISPOSAL

Refer to State Land Waste Management Authority.

FIRE/EXPLOSION HAZARDS

Not combustible.

ENVIRONMENTAL IMPACT

Avoid contaminating waterways.

OTHER INFORMATION & REFERENCES

PRINCIPAL REFERENCES

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CONTACT POINT: Toxicology Information Section,
ICI Australia Operations Pty Ltd (03) 665 7143.

Issue Date: 28/APR/92/DRF Supersedes Issue Date: 04/89

Safety Data Sheets are current for a maximum of three years but may be updated more frequently. Please ensure that you have a current copy.

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Safety Data Sheet

PHARMACEUTICALS

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ISSUED: 04/92

All information contained in this Data Sheet is as accurate and up-to-date as possible. Since ICI Australia Limited and its subsidiary companies cannot anticipate or control the conditions under which this information may be used, each user should review the information in the specific context of the intended application.

ICI Australia Limited and its subsidiary companies will not be responsible for damages of any nature resulting from use of or reliance upon the information. No expressed or implied warranties are given other than those implied mandatorily by Commonwealth, State or Territory legislation.

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Glossary

Acetal	An organic compound formed by the combination of an aldehyde with an alcohol.
ACGIH	American Conference of Governmental Industrial Hygenists.
ADG Code	*The Australian Code for the Transport of Dangerous Goods by Road and Rail*.
AICS	Australian Inventory of Chemical Substances.
Approved Criteria	The National *Commission's Approved Criteria for Classifying Hazardous Substances*.
Arthroscopy	Examination of the interior of a joint, for example, the knee, with an instrument called an arthroscope.
AST	Aspartate aminotansferase.
Asthma	A condition marked by recurrent episodes of wheezing and/or breathlessness characterised by a significant increase in resistance to air flow.
ASTM	American Society of Testing Materials.
Atopy	An inherited tendency to develop some form of allergy.
Basophilia	A blue or gray discolouration of immature blood cells.
Blepharospasm	Spasm of the eyelids causing more or less complete closure of the eyelids.
BOD	Biochemical oxygen demand.
^{14}C	A radioactive isotope of carbon which is used in the radio isotope labelling of a molecule.
Carbonyl group	The carbon-oxygen double bond occurring in organic compounds such as aldehydes and ketones.
Carcinogenicity	The tendency to produce cancer.
CHO cells	Chinese hamster ovary cells used for *in vitro* mutagenicity testing to detect clastogenic agents and agents causing sister chromatid exchange (SCE).
Chromosomal aberration	A change which results from damage expressed in both sister chromatids at the same site.
Chromosome	A structure in the nucleus of animal cells containing a substance (DNA) which transmits genetic (hereditary) information.
Clastogenic	Giving rise to, or inducing, breakages in chromosomes.
Conjunctival	Refers to the delicate mucous membrane that lines the eyelids and eyeball.
Corpora lutea	Yellow glandular masses in the ovary formed by ovarian follicles that have matured and discharged their ova.
CPK	Creatinine phosphokinase.

Cross-linker	A compound, group, or element which joins 2 chains of polymer molecules.
Cyanohydrin	A compound formed by the addition of hydrocyanic acid to an aldehyde or ketone.
Cyclophosphamide	A drug used in the treatment of many types of malignancies.
Dentin	The substance which surrounds the tooth pulp, covered by enamel on the crown and by cementum on the roots of the teeth.
Dermatitis	Inflammation of the skin.
DNA	Deoxyribonucleicacid, carrier of genetic information.
DNCB	2,4-dinitrochlorobenzene.
EC_{50}	The concentration of a substance in water that has an effect on 50% of exposed organisms, relative to unexposed controls.
Embryotoxicity	The toxicity of a substance to the developing embryo (2 to 8 weeks).
Endoscopy	Visual inspection of any cavity in the body using an instrument called an endoscope.
Epidemiological	Relating to the study of the relationships determining the frequency and distribution of a disease in a human community.
Epidermis	The outermost layer of the skin.
Erythema	Redness of the skin which may result from a variety of causes.
Erythrocytes	Red blood cells.
FCA	Freund's complete adjuvant.
FIFRA	*Federal Insecticide, Fungicide and Rodenticide Act 1975* (USA).
FEV_1	Forced expiratory volume in one second.
Foetotoxicity	The toxicity of a substance to the foetus.
Fundus	That portion of a hollow organ furthest from its mouth.
FVC	Forced vital capacity.
Gastritis	Inflammation of the stomach.
Gavage	Forced feeding through a tube passed into the stomach.
Genotoxicity	The tendency to cause damage to genetic material such as DNA.
Glutaconyl CoA	The oxidation product of glutaric acid after undergoing enzymatic changes.
GPU	Glutaraldehyde production unit.
HETA	Hazard Evaluations and Technical Assistance branch of NIOSH.
Hepatitis	Inflammation of the liver.

HPLC	High performance liquid chromatography (or chromatograph), an analytical technique (or instrument) based on the separation of compounds for measurement.
HPV	High production volume. Refers to a program of the OECD for chemicals where there is a high risk of exposure to humans or the environment because production volumes are in excess of 1000 te/yr.
Hydrazone	An organic compound formed from the reaction of an aldehyde or ketone with the chemical phenylhydrazine.
Hyperaemia	An excess of blood in any part of the body.
Hyperplasia	Abnormal multiplication or increase in the number of normal cells.
Hypersensitivity	A state of heightened reactivity to an antigen resulting from previous sensitisation.
IC_{50}	The concentration of a substance in water that produces a 50% inhibition of the growth of bacteria, relative to unexposed controls.
Ileum	The lowest part of the small intestine.
In vitro toxicity test	A test conducted outside the body of the organism, for example, with cell cultures.
In vivo toxicity test	A test carried out within the living body of an experimental animal.
Iritis	Inflammation of the iris (membrane behind the cornea).
IUPAC	International Union for Pure and Applied Chemistry.
Keratinised	Coated with a protein which is not soluble in the stomach.
Lacrimation	Secretion and discharge of tears.
Laryngeal	Pertaining to the larynx.
LC_{50}	The median lethal concentration, that is, the concentration of a substance that is estimated to produce death in 50% of test organisms; it is used for estimating the acute lethality of chemicals to aquatic organisms or of air-borne chemicals to terrestrial animals.
LD_{50}	The median lethal dose, that is, the single dose of a substance that can produce death in 50% of test animals.
Lesion	A discontinuity of tissue or loss of function of a part of the body as a result of disease or trauma.
Leukaemia	A progressive, malignant disease of the blood-forming organs characterised by excessive white blood cells and their precursors in the blood and bone marrow.
LEV	Local exhaust ventilation.
LGLL	Large granular cell lymphatic leukaemia.
The List	The National Commission's *Designated List of Hazardous Substances*.

Lymphatic	Pertaining to the vessels which convey the clear fluid derived from the tissues of the body to the bloodstream.
Lymphoma	A cancerous disease of the lymphatic tissues.
Margo plicatus	The marginal fold in a membrane.
MBTH	3-methyl-2-benzothiazolinone hydrazone.
MED	Minimal erythemal dose.
Medicament	A medicinal substance or agent.
Metaplasia	A change from normal to abnormal cells in a tissue.
Micronucleus	A type of nucleus which functions in sexual reproduction in lower forms of living organisms.
Mitotic cells	Cells which have divided.
MMEF	Maximum mid-expiratory flow rate.
MSDS	Material Safety Data Sheet.
Mutagenicity	The property of being able to induce a change in the genetic pattern in cells.
National Commission	The National Occupational Health and Safety Commission.
Necropsy	The examination of the organs and body tissues of a dead animal to determine the cause of death or pathological conditions.
NHMRC	The National Health and Medical Research Council.
NIOSH	The United States-based National Institute of Occupational Safety and Health.
NOAEL	No observed adverse effect level. The highest dose level of a substance that, in a given toxicity test, causes no observable adverse effect in the test animal.
NOEL	No observable effect level.
Normoerythrocyte	A red blood cell of normal size.
NOS	Not otherwise specified.
NTP	The United States-based National Toxicology Program.
Occluded dressing	A dressing which is covered or closely fitting.
Occupational asthma	A respiratory disease characterised by variable bronchial obstruction and variable hyperactivity caused by specific agents inhaled at work.
OECD	The Organisation for Economic Cooperation and Development.
Oedema	Swelling.
Oncogenic	Giving rise to tumours.
Ophthalmological	Pertaining to the eye.
Osmolality	The property of a solution which depends on the concentration of the solute per unit of solvent.

Oxime	A compound formed by the action of a hydroxylamine on an aldehyde or ketone.
Palpitations	Unduly rapid heart beat.
Patch test	A skin test used to determine allergic manifestations in an individual.
PCE	Polychromatic erythrocyte.
PEFR	Peak expiratory flow rate.
Percutaneous	Performed through the skin.
Perinasal	Around the area of the nose.
Periocular	Around the area of the eyes.
Pharmacokinetic	Pertaining to the action of drugs in the body over a period of time.
Photoallergy	An allergic type of sensitivity to light.
Photosensitisation	The development of abnormally increased reactivity of the skin to sunlight.
Phototoxicity	Increase of sunburn response to ultraviolet light, without any allergic effect.
Piloerection	Erection of the hair.
Polychromatic	Exhibiting many colours.
Post coitum	After the sexual act.
PPE	Personal protective equipment.
Pulpotomy	Excision of a portion of the pulp (of the tooth).
Pylorus	The distal opening of the stomach through which the stomach contents are emptied into the duodenum.
RD_{50}	The concentration of a substance which produces a 50% decrease in respiratory rate.
Refractive index	The number which gives a measure of the change in angle of light beam passing from a medium of different density.
Respiratory allergy	The clinical disease (or adverse reaction) mediated by an immune response to an antigen.
Respiratory sensitisation	An immune status resulting from an immune response to an antigen.
Rhinitis	A disease that invokes inflammation of the nasal mucous membrane, characterised by periods of nasal discharge, sneezing and congestion.
S9 fraction	An enzyme preparation used in *in vitro* toxicity testing for the purpose of determining whether the test substance requires metabolic activation to exert its mutagenic effect.
SCE	See sister chromatid exchange.
Schiff base	A class of compounds derived by the chemical reaction of aldehydes or ketones with primary amines.

SIDS	Screening information data set (for HPV chemicals).
Sinusitis	Inflammation of the air-containing spaces (sinuses) in the face.
Sister chromatids	The two spiral filaments of a chromosome.
Sister chromatid exchange (SCE)	The reciprocal exchange of DNA between two sister chromatids of a duplicating chromosome.
SLRL	Sex-linked recessive lethal.
SMR	Standardised mortality rate.
Sporicidal	Capable of destroying spores.
Squamous	Scaly or plate-like.
STEL	Short term exposure limit.
Stratum corneum	The horny outermost layer of the skin containing dead cells.
SUSDP	The National Health and Medical Research Council's *Standard for the Uniform Scheduling of Drugs and Poisons*.
SWORD	Surveillance of Work-related and Occupational Respiratory Disease. A reporting scheme, run by the Epidemiological Research Unit of the London Chest Hospital in collaboration with the Society of Occupational Medicine and the British Thoracic Society.
Synovial	Pertaining to the secretion of a transparent viscid fluid (synovia) from a joint cavity, for example, in the knee.
Teratogenicity	The property of causing defects in the reproduction process, resulting either in reduced productivity due to foetal or embryonic mortality, or in birth defects.
Thioester	An ester in which sulfur replaces oxygen.
TLV	Threshold limit value.
Tonometer	An instrument used to measure the pressure of the eyeball.
Troposphere	The lowest level of the atmosphere, between the Earth's surface and the stratosphere.
TWA	Time-weighted average.
ULLI	Unit length labelling index.
USEPA	United States Environmental Protection Agency.
Virucidal	Capable of destroying a virus.