

2 **Diethylene glycol - draft Poisons Information Monograph for**  
3 **peer review**

4  
5 **CHEMICAL SUBSTANCES**

6  
7  
8 **1. NAME**

9  
10 **1.1 Substance**

11  
12 Diethylene Glycol

13  
14 **1.2 Group**

15  
16 Polyalcohols - Glycol

17  
18 **1.3 Synonyms**

19  
20 Diethylenglykol (Czech); Dihydroxydiethyl ether; Dihydroxyethylether;  
21 Ethylene diglycol;  
22 Bis(2-Hydroxyethyl)Ether; DEG; Dicol; Diethylene ether; Diethylene glycol;  
23 Digenos; Diglycol; Digol;  $\beta$ ,  $\beta$ '-Dihydroxydiethyl ether; 1,5-Dihydroxy-3-  
24 oxapentane; Glycol ether; Glycol ethyl ether;  
25 2,2'-Oxybis[ethanol]; 2,2'-Oxydiethanol; 2,2'-Oxyethanol; 2-(2-  
26 Hydroxyethoxy)ethanol; 2-Hydroxyethoxyethanol; 3-Oxapentamethylene-1,5-  
27 diol; 3-Oxapentane-1,5-diol; Bis(- $\beta$  hydroxyethyl) ether; Bis(2-hydroxyethyl)  
28 ether; DEG; Dicol; Digenos; Diglycol; Digol; Ethylene diglycol;

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31  
32 **1.4 Identification numbers**

33 **1.4.1 CAS number**

34  
35 111-46-6

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38 **1.4.2 Other numbers**

39 No data available.

40  
41  
42 **1.5 Main brand names, main trade names**

43 Brecolane NDG; Deactivator E; Dissolvant APV;  
44 NSC 36391; TL4N

45  
46 **1.6 Main manufacturers, main importers**

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2 **2. SUMMARY**

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4 **2.1 Main risks and target organs**

5  
6 The main risk is severe metabolic acidosis with CNS depression, respiratory  
7 failure and acute renal failure.

8  
9 **2.2 Summary of clinical effects**

10  
11 Profound metabolic acidosis, oliguria progressing to anuria, CNS depression,  
12 and risk of respiratory failure are major concerns following ingestion of  
13 diethylene glycol. There is also risk of hepatotoxicity and cardiac arrhythmias.  
14 Death due to sudden cardiorespiratory arrest may occasionally occur.

15  
16 Initial symptoms include headache, severe nausea, vomiting, abdominal  
17 pain, diarrhoea, drowsiness, and tachypnoea. These may be accompanied or  
18 closely followed by flank pain, marked CNS depression, seizures, metabolic  
19 acidosis, anuria, oedema, and other evidence of severe renal and hepatic  
20 injury. Patients may also develop hypertension, tachycardia, pulmonary  
21 crepitations, and a subnormal temperature.

22  
23 Time to onset of symptoms following ingestion is variable. Typically, initial  
24 symptoms of gastrointestinal upset and altered mental status develop  
25 within 24 hours of ingestion. The first symptoms are often nausea and  
26 vomiting, which may not commence after the first dose, but, once started,  
27 become more severe with repeat exposures. More severe renal  
28 effects, metabolic acidosis, and neurological effects may develop 1 to 3 days  
29 following the onset of the initial symptoms. (Severe metabolic acidosis is  
30 characteristically absent until renal failure becomes evident or the patient is  
31 moribund). Oliguria may be preceded by a transient phase of polyuria.

32  
33 **2.3 Diagnosis**

34 The diagnosis is based on history of exposure, clinical features and laboratory  
35 findings.

36 Profound metabolic acidosis, oliguria progressing to anuria, CNS depression,  
37 and risk of respiratory failure are major concerns following ingestion of  
38 diethylene glycol.

39 Severe metabolic acidosis with elevated anion and osmolal gap is typical. The  
40 degree of metabolic acidosis is related to the severity of poisoning.

41  
42  
43 **2.3 First aid measures and management principles**

44  
45 Standard first aid measures.  
46

1 Support of renal function and correction of acidosis is critical, and  
2 management of respiratory depression, seizures, and dysrhythmias may also  
3 be important. Initial stabilization may require airway protection and monitored  
4 administration of IV fluids. Gastric decontamination via nasogastric aspiration  
5 can be considered.

6  
7 Antidotes in the form of either ethanol or fomepizole have been suggested to  
8 inhibit the metabolism of diethylene glycol to its metabolites. Thiamine and  
9 pyridoxine may be indicated as therapeutic adjuncts. Symptomatic patients,  
10 especially those with acidosis or renal dysfunction, should receive  
11 haemodialysis to reverse acidosis and/or reduce glycol and toxic metabolite  
12 levels.

13  
14 Delayed neurological sequelae have been reported, usually in the form of  
15 optic neuritis, or cranial and peripheral neuropathies. Often delayed effects  
16 are unpredictable, some may have resolution of their neurological signs over a  
17 matter of weeks or months, others may die with fulminant encephalopathy.  
18 Follow up including further symptomatic treatment may be required.

### 20 21 **3. PHYSICO-CHEMICAL PROPERTIES**

#### 22 23 **3.1 Origin of the substance**

24  
25 Derived from ethylene oxide

#### 26 27 **3.2 Chemical structure**

##### 28 • ***Structural formula***

29  
30  $\text{HO} - \text{CH}_2 - \text{CH}_2 - \text{O} - \text{CH}_2 - \text{CH}_2 - \text{OH}$

##### 31 32 33 • ***Molecular formula***

34  
35  $\text{C}_4 \text{H}_{10} \text{O}_3$

##### 36 37 • ***Molecular weight***

38  
39 106.1

##### 40 41 • ***Structural name(s)***

42  
43 Ethanol, 2,2'-oxybis-

1  
2 **3.3 Physical properties**  
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4  
5 **3.3.1 Colour**  
6

7 Clear, colourless

8 **3.3.2 State/Form**  
9

10 liquid-viscous fluid

11 **3.3.3 Description**  
12

13 Practically odourless, Initially it has a sweetish taste with a bitter aftertaste

14 Solubility in Water: miscible; Ethanol: miscible

15 Ether: miscible; Ethylene glycol: miscible

16 Benzene: practically insoluble

17 Carbon tetrachloride: practically insoluble  
18  
19

- 20
- 21 • boiling point 25°C
  - 22 • melting point -6.5 to -8°C
  - 23 • flash point 124 to 143°C
  - 24 • autoignition temperature °C
  - 25 • vapour pressure (0.07 mmHg at 20 °C)
  - 26 • Specific gravity (water =1) 1.12
  - 27 • Flammability limits 3 to 7%

28 (Cavender & Sowinski 1994, Budivari 1996, Lewis 1996)  
29

30 **3.4 Hazardous characteristics**  
31

32 Reacts violently with strong oxidants.  
33

34 **4. USES**  
35

36 **4.1 Uses**

37 **4.1.1 Uses**  
38

39 Diethylene glycol is found as a component in antifreeze and gas conditioning  
40 formulations, brake fluids, cosmetics, lubricants, mould-release agents, inks,  
41 book-binding adhesives, and dyeing agents. It is used as a softening agent for  
42 textiles, and as a plasticizer for cork, adhesives, paper, and packaging  
43 materials.  
44

45 It may be used in the production of diethylene glycol dinitrate, triethylene  
46 glycol, polyurethane, resins, morpholine, and diethylene glycol esters and  
47 ethers. Furthermore it has been used in natural gas processing, as a solvent,  
48 and as a humectant for tobacco, casein, and synthetic sponges.  
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#### **4.1.2 Description**

### **4.2 High risk circumstance of poisoning**

Medicines adulterated with diethylene glycol have caused mass fatalities. Diethylene glycol contamination of wine and toothpaste has also occurred and has the potential to cause poisoning.

### **4.3 Occupationally exposed populations**

Due to its low volatility, diethylene glycol is not an occupational hazard.

## **5. ROUTES OF EXPOSURE**

### **5.1 Oral**

The usual route of exposure, readily absorbed.

### **5.2 Inhalation**

Absorbed, but little risk because of low volatility.

### **5.3 Dermal**

Low absorption requiring application to large surface areas to reach toxic dose. Prolonged contact to broken skin is however potentially toxic.

### **5.4 Eye**

Local irritation.

### **5.5 Parenteral**

Possible but no reports.

### **5.6 Other**

No data available.

1  
2 **6. KINETICS**

3  
4 **6.1 Absorption by route of exposure**

5  
6 There is limited information available regarding the human kinetics of  
7 diethylene glycol; the majority of information derives from experimental  
8 studies in other species.

9  
10 Oral absorption is rapid. In rats peak plasma levels were reached after 25 to  
11 120 minutes (Heilmair et al 1993).

12 Dermal absorption is minimal but greater if the skin is damaged or contact is  
13 prolonged and extensive (Cantarell et al 1987).

14  
15 Inhalational Absorption: Diethylene glycol has a very low vapour pressure but  
16 can be absorbed through the respiratory system under some circumstances  
17 (Heilmair et al 1993).

18  
19  
20 **6.2 Distribution by route of exposure**

21 Diethylene glycol is widely distributed. The distribution time depends on the  
22 blood flow to the area.

23  
24 In rats after oral administration it was distributed into kidneys, brain, spleen,  
25 liver, muscle, and adipose tissue (Heilmair et al 1993).

26  
27 Diethylene glycol crosses the blood brain barrier.

28  
29 In rats dosed with 5 mL/kg pure DEG, narcosis was observed after 20 minutes  
30 (Heilmair et al 1993).

31  
32 **6.3 Biological half-life by route of exposure**

33 The elimination half-life of 3.6 hours was determined in rats following oral  
34 dosing (Heilmair et al 1993).

35  
36 **6.4 Metabolism**

37 In rats approximately 14 to 41% of DEG is converted to 2-hydroxyethoxyacetic  
38 acid (HEAA) (Lenk et al 1989). There was no evidence of oxalic acid  
39 formation (unlike ethylene glycol metabolism) (Wiener and Richardson 1989).  
40 The major metabolic pathway is by alcohol dehydrogenase to 2-  
41 hydroxyethoxyacetaldehyde, then by aldehyde dehydrogenase to the toxic  
42 metabolite HEAA (Wiener and Richardson 1989).

43  
44 **6.5 Elimination and excretion**

45 A portion of diethylene glycol is excreted unchanged and the remainder  
46 appears as its metabolite, HEAA (Wiener and Richardson 1989).

47  
48 One study in rats showed greater than half was excreted unchanged, with 10  
49 to 30% appearing as HEAA. Approximately 80% was eliminated within 24  
50 hours (Mathews et al 1991).

## 7. TOXICOLOGY

### 7.1 Mode of action

The precise toxic mechanism of diethylene glycol remains to be fully elucidated. It was initially thought it was metabolized to ethylene glycol, with the latter being the cause of acute toxicity (Durand et al 1976, Herbert et al 1978). However, further studies determined that diethylene glycol is not metabolized to ethylene glycol, probably because of its stable ether linkage (Wiener and Richardson 1989). Neither has oxalate formation been demonstrated, either in patients (Alfred et al 2005, Cantarell 1987, Drut et al 1994) or in the laboratory (Heilmair et al 1993, Wiener and Richardson 1989), lending further support to the argument that degradation to ethylene glycol does not occur.

Diethylene glycol can be metabolized via oxidation by alcohol dehydrogenase (ADH) to (2-hydroxyethoxy)acetaldehyde, which is then rapidly metabolized by aldehyde dehydrogenase (ALDH) to 2-hydroxyethoxy)acetic acid (HEAA) (Wiener and Richardson 1989). It has been suggested that HEAA and other unidentified metabolites may be the mediators of toxicity in poisoning (Alfred et al 2005, Wiener and Richardson 1989).

Suggested possible mechanisms include membrane destabilization through phospholipid or ion channel effects, osmotic metabolite accumulation, and transcellular fluid shifts (Alfred et al 2005). It is believed that the two hydroxyl groups in the diethylene glycol molecule may account for much of the renal (and hepatic) hydropic degeneration (Scalzo 1996), characterised by severe vacuolation and profound swelling of the epithelium of the convoluted tubules, which can produce complete obliteration of the lumen.

Metabolic acid base derangements result in metabolic acidosis which is enhanced due to concomitant rise in lactate (Heilmair et al 1993).

### 7.2 Toxicity

#### 7.2.1 Human data

##### 7.2.1.1 Adults

There is a range in human susceptibility to diethylene glycol, (Geiling and Cannon 1938) and the minimum dose capable of being significantly toxic is not well established.

It has been suggested that 140 mg/kg (1 mL/kg of a 14% solution) is a toxic dose (Brophy et al 2000) and ~ 1 mL/kg a typical lethal dose, (Cavender and Sowinski 1994) but some data (more so in adults) indicate lower doses than 140 mg/kg can be toxic or even fatal. Lethal doses have been estimated as 14 to 56 mg/kg or more for adults (Ferrari and Giannuzzi 2005).

1 One estimated fatal dose range (after typological correction) (Schep &  
2 Slaughter 2005) is 14 to 175 mg/kg (14 to 44 mg/kg or 56 to 175 mg/kg  
3 respectively, depending whether individuals' ingestions estimated as 5 or 20  
4 mL in total of product).

5  
6 It is clear that fatalities can occur at lower doses than ~ 1 mL/kg (one largely  
7 unsubstantiated estimate of a typical human lethal dose) (Cavender &  
8 Sowinski 1994). On the other hand, no effects were noted following an  
9 average dose of ~ 11 mg (range 2 to 22 mg) obtained via contaminated  
10 polyethylene glycol (in the context of whole bowel irrigation) (Woolf & Pearson  
11 1995). This suggests the minimal toxic dose is certainly more than 11 to 22  
12 mg, or over ~ 0.18 to 0.36 mg/kg in adults.

13  
14 In adults involved in one series, estimated cumulative nonfatal doses ranged  
15 from 0.72 to 173 g (1 to 240 mL of a 72% solution), and estimated cumulative  
16 fatal doses ranged from 14.4 to 172.8 g (20 to 240 mL of a 72% solution).  
17 (Calvery & Klumpp 1939) The minimum fatal dose (14.4 g) would represent ~  
18 206 mg/kg in a 70 kg adult; but it is clear that considerably higher doses can  
19 be survived. The mean estimated fatal dose was ~ 71 g. (Calvery & Klumpp  
20 1939)

#### 21 22 23 7.2.1.2 Children

24  
25 Estimated fatal doses in one paediatric series ranged from 0.22 to 4.42 mL/kg  
26 (mean 1.34 mL/kg) (O'Brien et al 1998). Corresponding doses in w/w  
27 units (given its specific gravity of 1.12) are 246 to 4950 mg/kg (mean 1500  
28 mg/kg). However these were maximum possible amounts (assuming one child  
29 received all bottle's missing contents) and some may be over-estimates  
30 (under-estimating toxicity).

31  
32 In children (between 7 months and 16 years) involved in one series, estimated  
33 cumulative nonfatal doses ranged from 2.2 to 75.6 g (3 to 105 mL of a 72%  
34 solution), and estimated cumulative fatal doses ranged from 3.6 to 86.4 g (5 to  
35 120 mL of a 72% solution) (Calvery and Klumpp 1939). There appears  
36 considerable overlap, but individual doses in terms of mg/kg were not  
37 given. However it is clear considerable doses can be survived. The mean  
38 estimated fatal dose was ~ 38 g (Calvery and Klumpp 1939).

#### 39 40 7.2.2 Relevant animal data

41		
42	LD50 Oral, Rat	12.6 to 20.8 g/kg
43	LD50 Oral, Mouse	13.3 to 26.5 g/kg
44	LD50 Oral, Guinea Pig	8.7 to 14 g/kg
45	LD50 Oral, Rabbit	4.4 to 26.9 g/kg
46	LD50 Oral, Dog	9 g/kg
47	LD50 Oral, Cat	3.3 g/kg
48		
49	LD50 IP, Rat	7.7 g/kg
50	LD50 IP, Mouse	9.7 g/kg

LD50 SC, Rat	18.8 g/kg
LD50 SC, Mouse	5 g/kg
LD50 IV, Rat	6.6 g/kg
LD50 IM, Rat	7.8 g/kg
LD50 Dermal, Rabbit	13.3 g/kg (Cavender & Sowinski 1994)

### 7.2.3 Relevant in vitro data

### 7.2.4 Workplace standards

TLV not established. MAK: 10 ppm, 44 mg/m<sup>3</sup>

### 7.2.5 Acceptable daily intake (ADI)

Diethylene glycol has been evaluated by the SCF as a component in food packaging materials. A group TDI of 0-0.5 mg/kg bw was allocated (SCF, 1986).

An ADI has not been set by the FAO/WHO Joint Expert Committee on Food Additives: this compound is not to be used in foods (FAO/WHO 2007).

## 7.3 Carcinogenicity

Not classified as a human carcinogen

## 7.4 Teratogenicity

The effects of human exposure to diethylene glycol during pregnancy are unknown.

Diethylene glycol has been shown to be teratogenic in animals.

Effects in pregnant mice fed 3.5% diethylene glycol for 14 weeks included: Statistically significant decreases in:

- Litters per pair
- Live pups per litter
- Proportion of pups born alive
- Live pup weight (Williams et al 1990)

Craniofacial abnormalities in 95% of dead pups including:

- Cleft palate

- Exencephaly (Williams et al 1990)

## **7.5 Mutagenicity**

No data available

## **7.6 Interactions**

# **8. TOXICOLOGICAL ANALYSES AND BIOMEDICAL INVESTIGATIONS**

## **8.1 Material sampling plan**

### **8.1.1 Sampling and specimen collection**

- 8.1.1.1 Toxicological analyses
- 8.1.1.2 Biomedical analyses
- 8.1.1.3 Arterial blood gas analysis
- 8.1.1.4 Haematological analyses
- 8.1.1.5 Other (unspecified) analyses

### **8.1.2 Storage of laboratory samples and specimens**

- 8.1.2.1 Toxicological analyses
- 8.1.2.2 Biomedical analyses
- 8.1.2.3 Arterial blood gas analysis
- 8.1.2.4 Haematological analyses
- 8.1.2.5 Other (unspecified) analyses

### **8.1.3 Transport of laboratory samples and specimens**

- 8.1.3.1 Toxicological analyses
- 8.1.3.2 Biomedical analyses
- 8.1.3.3 Arterial blood gas analysis
- 8.1.3.4 Haematological analyses
- 8.1.3.5 Other (unspecified) analyses

## **8.2 Toxicological Analyses and their Interpretation**

### **8.2.1 Tests on toxic ingredient(s) of material**

- 8.2.1.1 Simple Qualitative Test(s)
- 8.2.1.2 Advanced Qualitative Confirmation Test(s)
- 8.2.1.3 Simple Quantitative Method(s)
- 8.2.1.4 Advanced Quantitative Method(s)

### **8.2.2 Tests for biological specimens**

- 8.2.2.1 Simple Qualitative Test(s)
- 8.2.2.2 Advanced Qualitative Confirmation Test(s)
- 8.2.2.3 Simple Quantitative Method(s)
- 8.2.2.4 Advanced Quantitative Method(s)
- 8.2.2.5 Other Dedicated Method(s)

### **8.2.3 Interpretation of toxicological analyses**

## **8.3 Biomedical investigations and their interpretation**

### **8.3.1 Biochemical analysis**

- 8.3.1.1 Blood, plasma or serum
  - "Basic analyses"
  - "Dedicated analyses"
  - "Optional analyses"

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#### 8.3.1.2Urine

"Basic analyses"

"Dedicated analyses"

"Optional analyses"

#### 8.3.1.3Other fluids

### **8.3.2 Arterial blood gas analyses**

### **8.3.3 Haematological analyses**

"Basic analyses"

"Dedicated analyses"

"Optional analyses"

### **8.3.4 Interpretation of biomedical investigations**

## **8.4 Other biomedical (diagnostic) investigations and their interpretation**

## **8.5 Overall interpretation of all toxicological analyses and toxicological investigations**

## **8.6 References**

# **9. CLINICAL EFFECTS**

## **9.1 Acute poisoning**

### **9.1.1 Ingestion**

Profound metabolic acidosis, oliguria progressing to anuria, CNS depression, and risk of respiratory failure are major concerns following ingestion of diethylene glycol. There is also risk of hepatotoxicity and cardiac arrhythmias. Death due to sudden cardiorespiratory arrest may occasionally occur.

Initial symptoms include headache, severe nausea, vomiting, abdominal pain, diarrhoea, drowsiness, and tachypnoea. These may be accompanied or closely followed by flank pain, marked CNS depression, seizures, metabolic acidosis, anuria, oedema, and other evidence of severe renal and hepatic injury. Patients may also develop hypertension, tachycardia, pulmonary crepitations, and a subnormal temperature (Geiling & Cannon 1938). Less commonly, anorexia, bradycardia, epistaxis and mydriasis are reported. The onset of symptoms usually heralds rapid deterioration (Yip 2004).

### **9.1.2 Inhalation**

Diethylene glycol's vapour pressure at room temperature is so low that in situations of uncomplicated use, toxic concentrations are not possible, and poisoning via inhalation is uncommon. However significant inhalational exposures may occur with heated material or where mist or fogs are generated, and it may present a risk in some such industrial settings if correct safety equipment is not utilized (Cavender and Sowinski 1994).

1                                   **9.1.3 Skin exposure**

2  
3 Diethylene glycol does not significantly irritate the skin (Cavender and  
4 Sowinski 1994).

5  
6 It is slowly absorbed through intact skin; however only in cases of extensive  
7 and prolonged skin contact would systemic effects be expected (Cavender  
8 and Sowinski 1994).

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10  
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12                                   **9.1.4 Eye contact**

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14  
15 No appreciable ocular irritation has been reported following exposure in  
16 animals. No cases of injury to human eyes have been reported (Grant and  
17 Schuman 1993). Significant corneal damage would not be expected  
18 (Cavender and Sowinski 1994).

19  
20                                   **9.1.5 Parenteral exposure**

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22  
23 No data available

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25                                   **9.1.6 Other**

26  
27  
28 No data available

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30                                   **9.2 Chronic poisoning**

31                                   **9.2.1 Ingestion**

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34  
35 The severity of effect in rats receiving diethylene glycol in their diets for 2  
36 years was clearly dose related (Cavender & Sowinski 1994). The purity of the  
37 diethylene glycol was not outlined and some effects may have been due to  
38 other contaminants (Calcium oxalate formation is probably due to ethylene  
39 glycol).

40  
41 1% diethylene glycol resulted in minor growth depression; formation of  
42 bladder stones (comprising mainly calcium oxalate); slight kidney damage

43  
44 2% diethylene glycol resulted in similar effects as in rats fed 1% diethylene  
45 glycol, but with more pronounced kidney damage and slight liver damage.

46  
47 4% diethylene glycol resulted in some mortality, marked growth depression,  
48 numerous bladder stones, significant kidney damage and moderate liver  
49 damage

50

1                                   **9.2.2 Inhalation**

2  
3 No data available  
4

5  
6                                   **9.2.3 Skin exposure**

7  
8 Patients with damaged skin are much more at risk and symptoms similar to  
9 those following ingestion may occur. Fatalities in burn patients have been  
10 attributed to low level contamination of their topical treatments. Poisoning was  
11 possibly due to a combination of already damaged skin, the large surface  
12 areas being treated, and repeated application of the product (Cantarell et al  
13 1987).  
14

15                                   **9.2.4 Eye contact**

16  
17 No data available  
18

19                                   **9.2.5 Parenteral exposure**

20  
21 No data available  
22

23                                   **9.2.6 Other**

24  
25 No data available  
26

27                                   **9.3 Course, prognosis, cause of death**

28  
29 Profound metabolic acidosis, oliguria progressing to anuria, CNS depression,  
30 and risk of respiratory failure are major concerns following ingestion of  
31 diethylene glycol. There is also risk of hepatotoxicity and cardiac arrhythmias.  
32 Death due to sudden cardiorespiratory arrest may occasionally occur.  
33

34 Initial symptoms include headache, severe nausea, vomiting, abdominal  
35 pain, diarrhoea, drowsiness, and tachypnoea. These may be accompanied or  
36 closely followed by flank pain, marked CNS depression, seizures, metabolic  
37 acidosis, anuria, oedema, and other evidence of severe renal and hepatic  
38 injury. Patients may also develop hypertension, tachycardia, pulmonary  
39 crepitations, and a subnormal temperature (Geiling & Cannon 1938). Less  
40 commonly, anorexia, bradycardia, epistaxis and mydriasis are reported. The  
41 onset of symptoms usually heralds rapid deterioration (Yip 2004).  
42

43 Various neurological effects are described, including optic neuritis, cranial and  
44 peripheral neuropathies, and recurrent seizures. Such effects may be  
45 delayed at least a week (Alfred et al 2005).  
46

47 Time to onset of symptoms following ingestion is variable. Typically, initial  
48 symptoms of gastrointestinal upset and altered mental status develop  
49 within 24 hours of ingestion (Doyle et al 1998). The first symptoms are often  
50 nausea and vomiting, which may not commence after the first dose, but, once

1 started, become more severe with repeat exposures. More severe renal  
2 effects, metabolic acidosis, and neurological effects may develop 1 to 3 days  
3 following the onset of the initial symptoms. (Severe metabolic acidosis is  
4 characteristically absent until renal failure becomes evident or the patient is  
5 moribund). Oliguria may be preceded by a transient phase of polyuria.

6  
7 However symptom onset may be slower, with initial GI symptoms delayed for  
8 two days and renal effects delayed for six days (Doyle et al 1998, Rollins et al  
9 2002). In such cases, the delayed onset was likely secondary to concurrent  
10 ingestion of ethanol.

11  
12 Death usually occurs 2 to 7 days after the onset of anuria (Leech 1937).  
13  
14  
15

## 16 17 **9.4 Systematic description of clinical effects**

### 18 19 **9.4.1 Cardiovascular**

20  
21 Hypotension (Borron et al 1997)  
22 Hypertension (Doyle et al 1998)  
23 Tachycardia  
24 Bradycardia  
25 Cardiac dysrhythmias  
26

### 27 28 **9.4.2 Respiratory**

29  
30 Tachypnoea (secondary to metabolic acidosis)  
31 Dyspnoea (Cavender & Sowinski 1994, O'Brien et al 1998)  
32 Respiratory depression  
33 Respiratory failure (Alfred et al 2005, O'Brien et al 1998)  
34 Pulmonary oedema (Leech 1937)  
35

### 36 37 **9.4.3 Neurological**

#### 38 **9.4.3.1 Central nervous system (CNS)**

39  
40 Lethargy (Hasbani et al 2005)  
41 Weakness (Rollins et al 2002)  
42 Dizziness  
43 Headache  
44 Malaise (Leech 1937)  
45 CNS depression  
46 Unresponsiveness  
47 Tremors (Heilmair et al 1993)  
48 Optic neuritis (Scalzo 1996, O'Brien et al 1998)  
49 Seizures (Wax 1995, Borron et al 1997)  
50 Encephalopathy (O'Brien et al 1998, Hari et al 2006)

1 Coma (Cantarell et al 1987, Wax 1995, Scalzo 1996, Borron et al 1997)  
2 Paralysis (Rollins et al 2002)  
3 Hyporeflexia (Rollins et al 2002)

- 4
- 5
- 6 9.4.3.2 Peripheral nervous system
- 7 9.4.3.3 Autonomic nervous system
- 8 9.4.3.4 Skeletal and smooth muscle
- 9

#### 10 11 **9.4.4 Gastrointestinal**

12  
13  
14 Nausea  
15 Vomiting (Doyle et al 1998)  
16 Haematemesis  
17 Diarrhoea (Leech 1937)  
18 Abdominal or costovertebral pain (Wax 1995, Scalzo 1996, O'Brien et al 1998)  
19 Melaena  
20 Anorexia (Cavender & Sowinski 1994)  
21 Pancreatitis

#### 22 23 **9.4.5 Hepatic**

24  
25  
26 Liver damage may occur following diethylene glycol exposure (unlike with  
27 ethylene glycol).  
28 Jaundice  
29 Hepatomegaly  
30 Hepatic pathology (typically centrilobular hydropic degeneration) (Cantarell et  
31 al 1987, Wax 1995, Hanif et al 1995, Bowie & McKenzie 1972)

#### 32 33 **9.4.6 Urinary**

##### 34 35 9.4.6.1 Renal

36  
37  
38 Thirst  
39 Diuresis (initially)  
40 Oliguria (Wilkinson 1967)  
41 Flank pain (Wax 1994)  
42 Anuria (Leech 1937, O'Brien et al 1998)  
43 Proteinuria (Wax 1995, Hanif et al 1995)  
44 Acute renal failure (O'Brien et al 1998, Hari et al 2006)

45  
46 Note: Calcium oxalate crystal deposition does not occur, unlike with ethylene  
47 glycol (Rollins et al 2002, Cantarell et al 1987, Wiener & Richardson 1989)  
48 Instead, the typical histopathological finding is renal cortical infarction and/or  
49 necrosis with haemorrhage, and severe vacuolation of the convoluted tubule  
50 epithelium.

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9.4.6.2 Other

**9.4.7 Endocrine and reproductive systems**

**9.4.8 Dermatological**

Diethylene glycol does not significantly irritate the skin (Cavender and Sowinski 1994).

**9.4.9 Eye, ear, nose, throat: local effects**

Pupillary dilation (O'Brien et al 1998)  
Optic neuritis (Scalzo 1996, O'Brien et al 1998)  
Retinal oedema  
Epistaxis

**9.4.10 Haematological**

Leukocytosis  
Anaemia (decreased hematocrit) (Ferrari & Giannuzzi 2005)

**9.4.11 Immunological**

No data available

**9.4.12 Metabolic**

9.4.12.1 Acid-base disturbances

Increased anion gap metabolic acidosis (Cantarell et al 1987, Hanif et al 1995, Vale & Buckley 1985)  
Increased osmolal gap (Borron et al 1997)

NB. A normal anion or osmolal gap does not rule out diethylene glycol ingestion.

9.4.12.2 Fluid and electrolyte disturbances

Hyperkalaemia (Singh et al 2001)

9.4.12.3 Others

Subnormal temperature

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#### **9.4.13 Allergic reactions**

No data available

#### **9.4.14 Other clinical effects**

No data available

#### **9.4.15 Special risks**

### **9.5 Other**

### **9.6 Summary**

## **10. MANAGEMENT**

### **10.1 General principles**

Diethylene glycol can produce significant morbidity and mortality, particularly in patients with delayed presentation, (Doyle et al 1998) and there is as yet no well proven successful therapeutic approach (Woolf 1998). However support of renal function and correction of acidosis is critical, and management of respiratory depression, seizures, and dysrhythmias may also be important. Antidotes in the form of either ethanol or fomepizole have been suggested to inhibit the metabolism of diethylene glycol to its metabolites. (Alfred et al 2005, Borron et al 1997). Thiamine and pyridoxine may be indicated as therapeutic adjuncts. Symptomatic patients, especially those with acidosis or renal dysfunction, should receive haemodialysis to reverse acidosis and/or reduce glycol and toxic metabolite levels.

### **10.2 Life supportive procedures and symptomatic/specific treatment**

Initial stabilization may require airway protection and monitored administration of IV fluids. Supportive care is often required for acidosis, impaired renal function, and CNS depression or other neurotoxicity. Gastrointestinal fluid losses may lead to hypotension, and fluid and electrolyte balance must be maintained, while avoiding overload. Administration of sodium bicarbonate to return base excess to normal is recommended. Large quantities may be required, and iatrogenic hypernatraemia can be a risk, which should be monitored. The kidneys are typically affected, and close monitoring and support of renal function is required. In the event of acute renal failure, haemodialysis is required until recovery; it is also indicated in severe cases of acidosis. Hepatotoxicity is also common (unlike with ethylene glycol), and monitoring and supportive therapies may be required.

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### **10.3 Decontamination**

Gastric decontamination via nasogastric aspiration can be considered, however, benefit is unproven, and the risks potentially out-weigh gain. Other forms of decontamination are not recommended.

### **10.4 Enhanced elimination**

Symptomatic patients, especially those with acidosis or renal dysfunction, should receive haemodialysis to reverse acidosis and/or reduce glycol and toxic metabolite levels.

### **10.5 Antidote treatment**

#### **10.5.1 Adults**

There are two alternative antidotes, which act by competing with or blocking the alcohol dehydrogenase-mediated metabolism of diethylene glycol: ethanol, fomepizole.

#### **Ethanol**

Ethanol is recommended for adult ingestion of greater than > 10 mg/kg, or if dose unknown, in combination with an osmolal gap of greater than 10 mOsm/L.

It is also recommended for a history or clinical suspicion of diethylene glycol poisoning, and at least two of the following:

- Arterial pH < 7.3
- Serum bicarbonate < 20 mmol/L (20 mEq/L)
- Osmolal gap > 10 mOsm/L (Barceloux et al 1999)

Ethanol is effective because it has a much greater affinity for alcohol dehydrogenase than diethylene glycol. However, ethanol is sometimes technically difficult to administer because of its rapid and unpredictable rate of metabolism. A loading dose followed by titrated maintenance therapy is necessary.

1 Suggested dosing regimen:

	Oral	Intravenous
Loading dose	1 mL/kg of 95% ethanol, diluted	10 mL/kg of 10% ethanol in 5% dextrose over 30 minutes
Maintenance dose	0.1 – 0.2 mL/kg/hour of 95% ethanol, diluted	1-2 mL/kg of 10% ethanol in 5% dextrose over 30 minutes

2 Notes:

3 In an emergency, an equivalent amount of any alcoholic drink may be  
4 administered orally.

5 The maintenance dosing needs to be adjusted according blood ethanol  
6 concentration, ideally measured hourly, to maintain the concentration >100  
7 mg/dL.

8 Prolonged ethanol administration may cause hypoglycaemia, especially in  
9 children, and frequent blood glucose determinations are mandatory. If  
10 haemodialysis is started, the ethanol infusion should be increased.

11 Ethanol administration may be discontinued when the patient is asymptomatic  
12 with a normal arterial pH.

13

14 **Fomepizole**

15

16 While availability is limited by purchase price, fomepizole appears preferable  
17 to ethanol. It is more particularly indicated in those with altered mental status,  
18 patients suffering hepatic disease, or those critically ill but lacking confirmation  
19 of poisoning. Its administration to paediatric patients avoids the disadvantages  
20 of ethanol (e.g. inebriation, hypoglycaemia).

21

22 Fomepizole is recommended for adult ingestion of greater than > 10 mg/kg, or  
23 if dose unknown, in combination with an osmolal gap of greater than 10  
24 mOsm/L.

25

26 It is also recommended for a history or clinical suspicion of diethylene glycol  
27 poisoning, and at least two of the following

28

- Arterial pH < 7.3

29

- Serum bicarbonate < 20 mmol/L (20 mEq/L)

30

- Osmolal gap > 10 mOsm/L

31

32 Particular indications are:

33

- Altered mental status

34

- Hepatic disease

35

- Critically ill patients lacking confirmation of diethylene glycol toxicity

36

(Antizol medicines datasheet 2000)

1  
2 **Dose and Administration**

3  
4 **Loading dose**

5 15 mg/kg diluted in 100 mL of normal saline or 5% dextrose in water and  
6 administered by IV infusion over 30 minutes

7  
8 **Maintenance doses**

9 10 mg/kg should be administered every 12 hours for 4 doses, then;  
10 15 mg/kg every 12 hours thereafter if indicated

11  
12 Maintenance fomepizole should be administered in the same fashion as the  
13 loading dose. Dosing requirements will change if haemodialysis is required

14  
15 Fomepizole may be discontinued when the patient is asymptomatic with a  
16 normal arterial pH.

17  
18  
19 **10.5.2 Children**

20  
21 **Ethanol**

22  
23 Ethanol is recommended for ingestion by a child of any amount of 100% pure  
24 diethylene glycol or greater than 20 mg/kg from "mixed" products in  
25 combination with an osmolal gap of greater than 10 mOsm/L

26  
27 It is also recommended for a history or clinical suspicion of diethylene glycol  
28 poisoning, and at least two of the following:

- 29 - Arterial pH < 7.3  
30 - Serum bicarbonate < 20 mmol/L (20 mEq/L)  
31 - Osmolal gap > 10 mOsm/L (Barceloux et al 1999)

32  
33 Intravenous ethanol maintenance dose:

34  
35 5% w/v solution: 3.6 mL/kg/h

36  
37 10 % w/v solution: 1.8 mL/kg/h

38  
39 Ethanol administration may be discontinued when the patient is asymptomatic  
40 with a normal arterial pH.

41  
42 Hypoglycaemia may occur, especially in children (Bates et al 1997). Once an  
43 infusion has been commenced blood glucose levels must be determined on a  
44 frequent basis (every 20 to 60 minutes). It may be necessary to add dextrose  
45 to intravenous solutions, or give glucose if ethanol is being administered orally  
46 (Parfitt 1999)

## 1 Fomepizole

2  
3 While availability is limited by purchase price, fomepizole appears preferable  
4 to ethanol. It is more particularly indicated in those with altered mental status,  
5 patients suffering hepatic disease, or those critically ill but lacking confirmation  
6 of poisoning. Its administration to paediatric patients avoids the disadvantages  
7 of ethanol (e.g. inebriation, hypoglycaemia).

8  
9 Fomepizole is recommended for ingestion by a child of any amount of  
10 100% pure diethylene glycol or greater than 20 mg/kg from "mixed" products  
11 in combination with an osmolal gap of greater than 10 mOsm/L.

12  
13 It is also recommended for a history or clinical suspicion of diethylene glycol  
14 poisoning, and at least two of the following:

- 15 - Arterial pH < 7.3
- 16 - Serum bicarbonate < 20 mmol/L (20 mEq/L)
- 17 - Osmolal gap > 10 mOsm/L

18  
19 Particular indications:

- 20 - Altered mental status
- 21 - Hepatic disease
- 22 - Critically ill patients lacking confirmation of diethylene glycol toxicity
- 23 - Paediatric patients (avoids the inebriation and hypoglycaemia that  
24 may occur with ethanol administration) (Antizol medicines datasheet  
25 2000)

26  
27 Dose and Administration

28  
29 Loading dose

30 15 mg/kg diluted in 100 mL of normal saline or 5% dextrose in water and  
31 administered by IV infusion over 30 minutes

32  
33 Maintenance doses

34 10 mg/kg should be administered every 12 hours for 4 doses, then;  
35 15 mg/kg every 12 hours thereafter if indicated

36  
37 Maintenance fomepizole should be administered in the same fashion as the  
38 loading dose. Dosing requirements will change if haemodialysis is required

39  
40 Fomepizole may be discontinued when the patient is asymptomatic with a  
41 normal arterial pH.

## 42 43 44 **10.6 Management discussion**

45  
46 There are some uncertainties regarding the role of diethylene glycol as  
47 opposed to its metabolites in the adverse renal (and neurological) effects.  
48 Some have raised concern that the parent compound may induce renal  
49 toxicity (Scalzo 1996), but some of the important toxic effects are thought  
50 more related to the metabolites.

1  
2 Therefore use of antidotes to reduce its conversion to these metabolites,  
3 which is presumed to occur via the alcohol dehydrogenase (ADH) pathway  
4 (as documented in rodents), is theoretically favoured and generally  
5 recommended (Alfred et al 2005, Brophy et al 2000). This can be  
6 accomplished by either effective competitors for ADH (such as ethanol) or  
7 inhibitors of ADH (such as 4-methylpyrazole; fomepizole).

8  
9 There is some (limited) clinical evidence to suggest both these agents can  
10 play a useful role (Borron et al 1997, Vassiliadis et al 1999). Both act by  
11 blocking the action of alcohol dehydrogenase on diethylene glycol, thus  
12 reducing its conversion to toxic (acid) metabolites.

13  
14 Ethanol has long been regarded as an effective intervention for toxic alcohol  
15 and glycol poisoning and it is cheap and readily available (Wacker et al  
16 1965). Fomepizole has proven efficacy in ethylene glycol poisoning (Brent et  
17 al 1999), but is expensive.

18  
19 Thiamine and pyridoxine may be indicated as therapeutic adjuncts. No data  
20 exists to support this assumption, but they may benefit those with a history of  
21 ethanol abuse or inadequate nutrition (e.g. those vitamin deficient).

22  
23 There is limited information regarding use of haemodialysis for diethylene  
24 glycol intoxication; however it appears to effectively enhance the excretion of  
25 diethylene glycol and its toxic metabolites, reducing the required duration of  
26 antidote use and improving patient outcome (Brophy et al 2000).

27  
28 Most available data regarding glycol toxicity relates to ethylene glycol  
29 (Barceloux et al 1999) but similar regimens should be used for diethylene  
30 glycol. If dialysis is prolonged, monitor for hypophosphataemia and treat if  
31 necessary.

32  
33 Haemodialysis is indicated in all clearly symptomatic ingestions of diethylene  
34 glycol (or systemic poisoning via other routes). It is especially indicated in  
35 patients with metabolic acidosis of pH < 7.25 to 7.30, and in those with renal  
36 dysfunction (Yip 2004, Alfred et al 2005).

## 37 38 39 40 41 **11. ILLUSTRATIVE CASES**

### 42 43 **11.1 Case reports from literature**

44  
45 (1) An unknown amount of 28% diethylene glycol was ingested by a 28 year  
46 old male. Signs and symptoms included vomiting, abdominal pain, acidosis,  
47 renal failure, lethargy, encephalopathy and quadriplegia.

48  
49 Supportive care included haemodialysis.

50

1 Several months of recovery were required. At the time of discharge he had  
2 some residual neurological effects, required the aid of a walker, and was  
3 dialysis dependent (Hasbani et al 2005).

4  
5 (2) Approximately 235 mL of 100% diethylene glycol was ingested by a 56  
6 year old male. Two days post ingestion he developed gastrointestinal  
7 complaints, confusion, renal failure, respiratory arrest. On day 8 he developed  
8 ascending paralysis. Supportive care, included fomepizole and haemodialysis.  
9 Despite treatment the patient died (Rollins et al 2002)

10  
11 (3) Two to three cups of 100% diethylene glycol were ingested by three adult  
12 males. They experienced epigastric pain, vomiting, acute renal failure,  
13 hypertension, hepatic dysfunction. They presented to hospital 6 days following  
14 ingestion. Peritoneal dialysis was performed . Despite treatment all 3 died  
15 between 3rd and 12th day after admission (Doyle et al 1998)

16  
17 (4) Two to three glasses of unknown strength diethylene glycol were ingested  
18 by a 25 year old male. This caused nausea, vomiting, acidosis, acute renal  
19 failure, bulbar palsy, peripheral neuropathy. He received supportive care,  
20 including haemodialysis. He remained dialysis dependent and neurological  
21 signs improved over time but did not resolve completely (Alfred et al 2005)

22  
23 (5) Five cups of unknown strength diethylene glycol were ingested by a 19  
24 year old male. He experienced nausea, vomiting, acidosis, elevated anion and  
25 osmolar gap, acute renal failure. He received supportive care, including  
26 ethanol therapy and haemodialysis. He developed cerebral oedema, died 19  
27 days post ingestion (Alfred et al 2005)

28  
29 (6) An unknown amount of brake fluid containing diethylene glycol was  
30 ingested by a 17 month old female. She had a hoarse cough, was drooling  
31 and vomited. Emesis was induced by her parent. Upon arrival at hospital she  
32 was administered activated charcoal and fomepizole, and underwent  
33 haemodialysis. No further symptoms occurred. She was discharged well 2  
34 days post ingestion (Brophy et al 2000)

35  
36 Diethylene glycol has been responsible for a number of mass poisonings:

- 37 • The most infamous incident was the 1937 Elixir Sulfanilamide disaster  
38 in the USA, in which 107 people died after taking sulfanilamide  
39 dissolved in diethylene glycol. This episode was the impetus for the US  
40 Federal Food, Drug, and Cosmetic Act of 1938 (Wax 1995).
- 41 • In recent years, deaths from medicines adulterated with diethylene  
42 glycol have been reported from South Africa, India, Nigeria, Argentina,  
43 Haiti, and Panama. In Haiti in 1996, 85 children died due to glycerine  
44 contaminated with diethylene glycol in a paracetamol syrup produced  
45 by Pharval Laboratories, a Haitian company, which did not use  
46 standard quality assurance procedures to verify the purity of the  
47 glycerine (which was supplied by a Dutch company, Vos, from a

1 manufacturer in China, but the point of contamination with DEG was  
2 never determined) (O'Brien et al 1998).

- 3 • In 1985 a small number of producers of Austrian wine were found to be  
4 adulterating their product with diethylene glycol in order to give the  
5 wine a sweeter and more full-bodied taste (Anon 1985). The amount  
6 added was not high enough to be acutely toxic (one would have to  
7 ingest about 28 bottles per day for two weeks); however, exports of  
8 Austrian wine collapsed.
  
- 9 • In 1990, in Bangladesh, 339 children developed kidney failure, and  
10 most of them died, after being given paracetamol (acetaminophen)  
11 syrup contaminated with diethylene glycol (Hanif et al 1995).
  
- 12 • Toxic syrup: In October 2006 the CDC and the Ministry of Health of  
13 Panama detected toxic levels of diethylene glycol in a sugarless liquid  
14 expectorant during an investigation of 46 deaths from a syndrome  
15 characterized by gastrointestinal symptoms, renal failure and paralysis.  
16 Almost all the victims were hypertension and diabetes patients in their  
17 40s to 80s. The source of the contamination was found to be diethylene  
18 glycol labelled as glycerine.
  
- 19
  
- 20 • In May 2007, a Panamanian discovered that toothpaste sold in his  
21 country was labelled as containing DEG, the same ingredient that had  
22 tainted cough syrup and killed 138 Panamanians in 2006. Panamanian  
23 officials discovered that the toothpaste had come from China and  
24 initiated a global response (Barr et al 2007).
  
- 25 • In June 2007, phoney Colgate toothpaste imported from China was  
26 found to be contaminated with DEG, and several people in eastern US  
27 reported experiencing headaches and pain after using the toothpaste.

## 28 11.2 Cases registered by centre

## 30 12. Additional information

### 32 12.1 Availability of antidotes

### 34 12.2 Specific preventive measures

### 36 12.3 Other

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26  
27 **14. AUTHOR(S), REVIEWER(S), DATE(S) (INCLUDING UPDATES),**  
28 **COMPLETE ADDRESS(ES)**

29  
30  
31 Dr Wayne A Temple  
32 Director,  
33 National Poisons Centre  
34 Department of Preventive and Social Medicine  
35 Dunedin School of Medicine  
36 University of Otago  
37 PO Box 913  
38 Dunedin  
39 New Zealand

40  
41 Phone number 64-3-4797244  
42 Email wayne.temple@otago.ac.nz  
43 Fax 64-3-4770509

44  
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