DIETHANOLAMINE

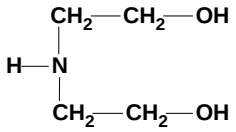
1. Exposure Data

1.1 Chemical and physical data

1.1.1 *Nomenclature*

Chem. Abstr. Serv. Reg. No.: 111-42-2
Deleted CAS Reg. No.: 8033-73-6
Chem. Abstr. Name: 2,2′-Iminobis[ethanol]
IUPAC Systematic Name: 2,2′-Iminodiethanol
Synonyms: Bis(hydroxyethyl)amine; bis(2-hydroxyethyl)amine; *N*,*N*-bis(2-hydroxyethyl)amine; DEA; *N*,*N*-diethanolamine; 2,2′-dihydroxydiethylamine; di-(β-hydroxyethyl)amine; di(2-hydroxyethyl)amine; diolamine; 2-(2-hydroxyethyl-amino)ethanol; iminodiethanol; *N*,*N*′-iminodiethanol; 2,2′-iminodi-1-ethanol

1.1.2 *Structural and molecular formulae and relative molecular mass*



$C_4H_{11}NO_2$ Relative molecular mass: 105.14

1.1.3 *Chemical and physical properties of the pure substance*

(*a*) *Description*: Deliquescent prisms; colourless, viscous liquid with a mild ammonia odour (Budavari, 1998; Dow Chemical Company, 1999)
(*b*) *Boiling-point*: 268.8 °C (Lide & Milne, 1996)
(*c*) *Melting-point*: 28 °C (Lide & Milne, 1996)
(*d*) *Density*: 1.0966 g/cm^3 at 20 °C (Lide & Milne, 1996)
(*e*) *Spectroscopy data*: Infrared (proton [5830]; grating [33038]), nuclear magnetic resonance (proton [6575]; C-13 [2936]) and mass spectral data have been reported (Sadtler Research Laboratories, 1980; Lide & Milne, 1996)
(*f*) *Solubility*: Very soluble in water (954 g/L) and ethanol; slightly soluble in benzene and diethyl ether (Lide & Milne, 1996; Verschueren, 1996)

(*g*) *Volatility*: Vapour pressure, < 0.01 mm Hg [1.33 Pa] at 20 °C; relative vapour density (air = 1), 3.6; flash-point, 149 °C (Verschueren, 1996)
(*h*) *Stability*: Incompatible with some metals, halogenated organics, nitrites, strong acids and strong oxidizers (Dow Chemical Company, 1999)
(*i*) *Octanol/water partition coefficient (P)*: log P, –2.18 (Verschueren, 1996)
(*j*) *Conversion factor*[1]: $mg/m^3 = 4.30 \times ppm$

1.1.4 *Technical products and impurities*

Diethanolamine is commercially available with the following specifications: purity, 99.3% min.; monoethanolamine, 0.45% max.; triethanolamine (see monograph in this volume), 0.25% max.; and water content, 0.15% max. (Dow Chemical Company, 1998a). Diethanolamine is also available as a blend of 85% diethanolamine and 15% deionized water which is a low freeze-grade product for use in colder temperatures (Dow Chemical Company, 1998b).

1.1.5 *Analysis*

Diethanolamine can be determined in workplace air by drawing the air sample through aqueous hexanesulfonic acid and analysing by ion chromatography. The limit of detection for this method is 13 µg per sample (Eller, 1994).

Diethanolamine can be determined in water samples by gas chromatography (GC) and by high-performance liquid chromatography (HPLC) with fluorescence detection (Melnick *et al.*, 1994a,b; Pietsch *et al.*, 1997); in metalworking and cutting fluids by GC–mass selective detection of silylated derivatives, by isotachophoresis, by capillary zone electrophoresis with indirect ultraviolet detection, and by spectrophotometry (Kenyon *et al.*, 1993; Fernando, 1995; Schubert *et al.*, 1996; Sollenberg, 1997); and in cosmetics and pharmaceuticals by GC with flame ionization detection, by ion-exclusive chromatography, and by reversed-phase HPLC (Fukui *et al.*, 1992; Maurer *et al.*, 1996; Chou, 1998).

1.2 Production

Ethanolamines became available commercially in the early 1930s; they assumed steadily growing commercial importance as intermediates after 1945, because of the large-scale production of ethylene oxide. Since the mid-1970s, economical production of very pure, colourless ethanolamines has been possible. Ethanolamines are produced on an industrial scale exclusively by reaction of ethylene oxide (see IARC, 1994) with excess ammonia. This reaction takes place slowly but is accelerated by water. An

[1] Calculated from: mg/m^3 = (relative molecular mass/24.45) × ppm, assuming a temperature of 25 °C and a pressure of 101 kPa

anhydrous procedure uses a fixed-bed ion-exchange resin catalyst (Hammer *et al*., 1987).

Worldwide production of ethanolamines in 1985 was approximately (thousand tonnes per year): United States, 220; western Europe, 145; south-east Asia, 40; South America, 18; eastern Europe, 4. About 50% of world production of ethanolamines in 1985 was monoethanolamine, 30–35% diethanolamine and 15–20% triethanolamine (Hammer *et al*., 1987). Estimated annual production of diethanolamine in the United States is presented in Table 1.

Table 1. Estimated annual production of diethanolamine in the USA (thousand tonnes)

Year	1960	1965	1970	1975	1980	1985	1989[a]
Production	24	35	42	39	56	76	92

From Bollmeier (1992)
[a] National Toxicology Program (1992)

Information available in 1999 indicated that diethanolamine was manufactured by seven companies in the United States, three companies each in China and Germany, two companies each in France and India, and one company each in Belgium, Brazil, Canada, Iran, Japan, Mexico, Netherlands, the Russian Federation, Spain, Sweden and the United Kingdom (Chemical Information Services, 1999).

1.3 Use

Diethanolamine is used as surface-active agent in metal-cutting fluids and oils (see General Remarks), as a corrosion inhibitor, as a dispersant in agricultural chemical formulations, and as an intermediate in the production of other compounds such as fatty acid condensates of diethanolamine which are extensively used in soaps and cosmetics as emulsifiers, thickeners, wetting agents and detergents (Beyer *et al.*, 1983). In the cosmetic formulations, the concentration of diethanolamine may range from 1 to 25% (National Toxicology Program, 1999a).

Other applications of diethanolamine are in adhesives, antistatic agents, cement and concrete work, coatings, electroplating, an epoxy hardener, a fuel-gelling agent, printing inks, metal cleaning and lubricating, mining, natural gas treatment, paint and pigments, paper, petroleum and coal production, a pharmaceutical intermediate and an ointment-emulsifier, polymers and polymer production, rubber processing, soldering flux, textile finishing and polyurethane production and use (Hammer *et al*., 1987; Bollmeier, 1992; Knaak *et al.*, 1997; Dow Chemical Company, 1998b). Table 2 presents estimates of percentages used in major applications in the United States (Knaak *et al.*, 1997).

Table 2. Major uses of diethanolamine in the United States

Applications	Percentage of production
Surfactants	39
Gas purification	30
Textile processing	15
Metalworking fluids	10
Miscellaneous	8
Laundry detergents	2
Agricultural chemicals	2

From Knaak *et al*. (1997)

Free diethanolamine is reported to be a contaminant in fatty acid-diethanolamine condensates (amides of coconut oil acid, oleic acid and lauric acid) at levels ranging from < 1% to nearly 10% (National Toxicology Program, 1999b,c,d). Diethanolamine also occurs as a contaminant in triethanolamine products (National Toxicology Program, 1999e).

1.4 Occurrence

1.4.1 *Natural occurrence*

Diethanolamine is not known to occur as a natural product.

1.4.2 *Occupational exposure*

Diethanolamine is present in machining and grinding fluids and has been detected in workplace air in the metal manufacturing industry. It was present in bulk cutting fluids at levels ranging from 4 to 5% (Kenyon *et al*., 1993). Diethanolamine has also been reported to be present in wetting fluids used in road paving. A level of 0.05 mg/m^3 was detected in a stationary sample at a slurry machine discharging a bitumen emulsion containing 0.2% of the amine. All personal exposures were below the detection limit (0.02 mg/m^3) (Levin *et al*., 1994). In a German study (1992–94), diethanolamine was measured in samples of metalworking fluids in a range of 0–44% (n = 69). The number of samples with diethanolamine present steadily declined from 90% to 60% over the study period (Pfeiffer *et al*., 1996).

According to the 1981–83 National Occupational Exposure Survey (NOES, 1999), as many as 800 000 workers (many of whom were metalworkers) in the United States were potentially exposed to diethanolamine (see General Remarks).

1.4.3 *Environmental occurrence*

Production of diethanolamine and its wide use in industrial and consumer products may result in its release to the environment (Yordy & Alexander, 1981; Beyer *et al*., 1983; Environment Canada, 1995; Mathews *et al*., 1995; Knaak *et al*., 1997).

(*a*) *Air*

According to the Environmental Protection Agency Toxics Release Inventory, air emissions of diethanolamine from 358 industrial facilities in 1994 were approximately 149 200 kg in the United States (Environmental Protection Agency, 1996). According to the National Pollutant Release Inventory (NPRI) of Canada, on-site releases of diethanolamine to air from 74 facilities amounted to about 40 000 kg (Environment Canada, 1995).

(*b*) *Water*

Surface water discharges of diethanolamine from 358 industrial facilities in 1994 in the United States amounted to 100 350 kg, as reported in the Toxics Release Inventory (Environmental Protection Agency, 1996). On-site releases of diethanolamine (and its salts) to water from 74 facilities in Canada amounted to about 26 000 kg, as reported to the NPRI (Environment Canada, 1995).

Because of the spectrum of industrial and consumer uses of diethanolamine and its miscibility with water, large amounts of the chemical can be discharged into wastewater and sewage in an unaltered form (Yordy & Alexander, 1981; Mathews *et al*., 1995).

(*c*) *Soil*

Releases of diethanolamine to land and underground from 358 industrial facilities in the United States in 1994 (as reported to the Toxics Release Inventory) amounted to 77 050 kg and 36 850 kg respectively (Environmental Protection Agency, 1996). Canadian on-site releases of diethanolamine (and its salts) to land and underground amounted to about 118 000 kg and 497 000 kg, respectively, as reported to the NPRI (Environment Canada, 1995).

1.5 Regulations and guidelines

Occupational exposure limits and guidelines for diethanolamine are presented in Table 3.

The Food and Drug Administration permits the use of diethanolamine as a component of adhesives in food packaging, as an indirect food additive, as a component of the uncoated or coated food contact surface of paper and paperboard for use with dry solid foods with no free fat or oil on the surface, and for use only as an adjuvant to control pulp absorbance and pitch content in the manufacture of paper and paperboard or for use only in paper mill boilers in the United States (Food and Drug Administration, 1999).

Table 3. Occupational exposure limits and guidelines for diethanolamine[a]

Country	Year	Concentration (mg/ m^3)	Interpretation[b]
Australia	1993	15	TWA
Belgium	1993	15	TWA
Denmark	1993	15	TWA
France	1993	15	TWA
Ireland	1997	15	TWA
Netherlands	1997	2	TWA
Russian Federation	1993	5 (sk)	STEL
Switzerland	1993	15	TWA
United Kingdom	1997	15	TWA
United States			
ACGIH[c]	1999	2	TWA
NIOSH	1999	15	TWA

[a] From American Conference of Governmental Industrial Hygienists (1999); National Library of Medicine (1999)
[b] TWA, time-weighted average; STEL, short-term exposure limit; sk, skin notation
[c] These countries follow the recommendations of the ACGIH threshold limit values: Bulgaria, Colombia, Jordan, Republic of Korea, New Zealand, Singapore and Viet Nam

2. Studies of Cancer in Humans

The Working Group was not aware of any study that specifically examined the risk of cancer among persons exposed to diethanolamine. However, ethanolamines have been used as additives for metalworking fluids since the 1950s and are present in wetting fluids used in asphalt paving. Results from cohort and case–control studies of asphalt and road-maintenance workers suggest elevations in the risk of several cancers, including lung, stomach, non-melanoma skin cancer and leukaemia (reviewed by Partanen & Boffetta, 1994). These groups of workers are also exposed to known or suspected carcinogens present in road paving and roofing materials (see Table 4). These compounds include benzene (Group 1) (IARC, 1987a), 1,3-butadiene (Group 2A) (IARC, 1999) and coal-tar pitches (Group 1) (IARC, 1987b). In the light of these concomitant exposures, any observed risk elevations cannot be specifically attributed to diethanolamine or to any other constituent of the complex mixtures. The Working Group, therefore, did not make a detailed evaluation of these studies.

There are three major types of metalworking fluid; straight (generally mineral oils), soluble (straight oils diluted with water and additives) and synthetic (water and addi-

Table 4. Degrees of evidence for carcinogenicity in humans and experimental animals and overall evaluation of carcinogenicity to humans for agents to which asphalt workers and roofers may be or may have been exposed, as evaluated by IARC as of 1993[a]

Agent [CAS No.]	Human	Animal	Overall evaluation
Asbestos [1332-21-4]	S	S	1
Benzene [71-43-2]	S	S	1
Bitumens [8052-42-4], undiluted, steam-refined (straight-run)	I	L	3
Bitumens [92062-05-0], undiluted, cracking-residue	I	L	3
Bitumens [64742-93-4], undiluted, air refined (air-blown)	I	L	3
Extracts of steam-refined bitumens	I	S	2B
Extracts of air-refined bitumens	I	S	2B
1,3-Butadiene [106-99-0]	L	S	2A
Coal-tars [8007-45-2]	S	S	1
Coal-tar pitches [65996-93-2]	S	S	1
Diesel engine exhaust	L	S	2A
Gasoline	I	L	2B
Gasoline engine exhaust	I	I	2B
Kerosene [8008-20-6]	I	I	3
Petroleum solvents	I	I	3
Polyaromatic hydrocarbons			
Anthracene [120-12-7]	I	I	3
Phenanthrene [85-01-8]	I	I	3
Fluoranthene [206-44-0]	I	I	3
Pyrene [129-00-0]	I	I	3
Chrysene [218-01-0]	I	L	3
Benzo[*a*]pyrene [50-32-8]	I	S	2A
Benz[*a*]anthracene [56-55-3]	I	S	2A
Perylene [198-55-0]	I	I	3
Benzo[*b*]fluoranthene	I	S	2B
Benzo[*j*]fluoranthene	I	S	2B
Benzo[*k*]fluoranthene [207-08-9]	I	S	2B
Anthanthrene [191-26-4]	I	L	3
Silica, crystalline [7631-86-9]	L	S	2A
Solar radiation	S	S	1
Styrene [100-42-5]	I	L	2B

From Partanen and Boffetta (1994)

[a] I, inadequate evidence; L, limited evidence; S, sufficient evidence. Overall evaluation: 1, carcinogenic to humans; 2A, probably carcinogenic to humans; 2B, possibly carcinogenic to humans; 3, not classifiable as to its carcinogenicity to humans.

tives) (see General Remarks). Ethanolamines, either diethanolamine or triethanolamine, are very common additives to both soluble and synthetic metalworking fluids (see Sections 1.3 and 1.4.2). Metalworking fluids are complex mixtures that may vary considerably depending on the type of fluid and the additives used. These mixtures may contain many potential carcinogens and, in particular, there is potential for exposure to *N*-nitrosodiethanolamine (see monograph in this volume) in all of the studies considered. A number of studies have examined the risk of cancer among workers exposed to metalworking fluids. Only studies which stated that ethanolamines (no studies indicated diethanolamine alone) were used as additives or that presented results for workers primarily exposed to soluble or synthetic fluids were considered by the Working Group. The characteristics of these studies are presented in Table 5 and a summary of the results for specific cancer sites is presented in Table 6. The use of ethanolamines and nitrites together as additives to metalworking fluids can lead to the formation of *N*-nitrosodiethanolamine. Studies stating that ethanolamines and nitrites were used as additives or which presented results for exposure to nitrosamines are described in detail in the monograph in this volume on *N*-nitrosodiethanolamine. The other studies are described in detail below.

Järvholm and Lavenius (1987) examined the risk for cancer among Swedish men employed for at least five years and any time between 1950 and 1966 in the grinding or turning departments of a company producing bearing rings. This was an extension of an earlier study reported by Järvholm *et al*. (1981) in which a two-fold excess of stomach cancer morbidity was reported among workers in the grinding department during 1958–76. A total of 792 employees met the entrance criteria (4.4% were lost to follow-up). Of these, 559 men had been employed in the grinding department where soluble and some synthetic oils (acid-refined from 1940–75 and solvent-refined mineral oils from 1975) were used. Ethanolamines were introduced as additives in the metalworking fluids used in the department in the mid-1950s. Mortality and cancer incidence follow-up was conducted from 1958 until 1983 and expected numbers were calculated using reference rates from the same city. There were 209 deaths (standardized mortality ratio (SMR), [0.83]; 95% confidence interval (CI), 0.71–0.94) and 67 incident cancers (standardized incidence ratio (SIR), [0.69]; 95% CI, 0.54–0.87) in the full cohort. Among the subcohort of 559 workers in grinding departments, there were 41 incident cancers (SIR, [0.63]; 95% CI, 0.45–0.86), with the only notable excess being for stomach cancer (SIR, [1.5]; 95% CI, 0.7–3.0). [The Working Group noted that part of this cohort was also studied in relation to exposure to *N*-nitrosodiethanolamine. The results of this investigation (Järvholm *et al*., 1986) are reported in the monograph on *N*-nitrosodiethanolamine in this volume.]

Eisen *et al*. (1992) performed a cohort mortality study of 46 384 workers employed for three or more years before 1985 in three United States auto parts manufacturing facilities. Exposure to all three types of metalworking fluid (straight oils (insoluble or cutting oils), soluble oils (water-miscible or emulsifier oils) and synthetic oils (chemical fluids, containing ethanolamines)), the last two introduced in the 1940s, existed and no

Table 5. Characteristics of studies on diethanolamine exposure

Study/country	Study design	Study population	Follow-up period	Potential exposures
Järvholm & Lavenius (1987) Sweden	Cohort	792 men employed > 5 years, any time 1950–66 in the grinding and turning departments of a bearing rings company (may overlap with Järvholm *et al.*, 1986)	1958–83	Analysis of the subgroup of 559 grinders exposed to soluble or synthetic oils
Eisen *et al.* (1992)[a] USA	Cohort	46 384 employed for > 3 years before 1985 at three auto parts manufacturing facilities	1941–84	All three types of metalworking fluid; no analysis by sub-group
Tolbert *et al.* (1992) USA	Cohort	33 619 (two of the three facilities in Eisen *et al*., 1992)	1941–84	Analysis of three sub-groups exposed to each type of metalworking fluid by years of exposure
Eisen *et al.* (1994) USA	Nested case–control of laryngeal cancer	108 fatal and incident cases; 538 controls (study base: Eisen *et al.*, 1992 cohort)	1941–84	Cumulative exposure to straight and soluble types of metalworking fluid and metalworking fluid particulate exposure during grinding; duration of exposure to metalworking fluid and other components.
Sullivan *et al*. (1998) USA	Nested case–control of oesophageal cancer	53 fatal cases; 971 controls (study base: Eisen *et al*., 1992 cohort)	1941–84	Cumulative exposure to the three types of metalworking fluid; duration of exposure to metalworking fluid and other components, incl. nitrosamines.

[a] The results of this study were not considered by the Working Group, but it is included because it forms the study base of the nested case–control studies considered.

Table 6. Results of epidemiological studies of cohorts exposed to soluble and synthetic metalworking fluids

Reference	Stomach		Oesophagus		Larynx		Leukaemia		Pancreas		All cancer		All mortality	
	Obs.	SMR/ PMR	Obs.	SMR/ PMR/OR	Obs.	SMR/ PMR/OR	Obs.	SMR/ PMR	Obs.	SMR/ PMR	Obs.	SMR/ PMR	Obs.	SMR/ PMR
Järvholm & Lavenius (1987) (incidence)														
All grinders (SIR)	8	[1.5] (0.7–3.0)	2	[2.0] (0.2–7.2)	NR		NR		NR		41	[0.63] (0.45–0.86)		
> 20 years latency (SIR)	7	[1.7] (0.7–3.5)	2	[2.4] (0.3–8.8)	NR		NR		NR		33	[0.66] (0.46–0.93)		
Tolbert *et al.* (1992) (mortality)														
Synthetic oils														
White males	21	1.3 (0.8–2.0)	8	0.99 (0.4–1.9)	8	1.6 (0.7–3.1)	16	1.2 (0.7–2.0)	19	1.03 (0.6–1.6)	333	0.97 (0.87–1.1)	1632	1.01 (0.96–1.1)
Soluble oils														
White males	99	1.2 (1.0–1.4)	35	1.03 (0.7–1.4)	30	1.4 (1.0–2.0)	75	1.3 (1.0–1.7)	61	0.8 (0.6–1.0)	1479	1.02 (0.97–1.1)	7287	1.00 (0.98–1.03)
Black males	17	1.0 (0.6–1.6)	10	0.7 (0.3–1.3)	6	1.5 (0.5–3.2)	4	0.7 (0.2–1.9)	19	1.6 (1.0–2.5)	200	0.90 (0.78–1.0)	922	0.81 (0.76–0.87)
Eisen *et al.* (1994) (mortality)														
Soluble fluids (mg/m^3–years)														
0	NA		NA		9	1.00	NA		NA		NA		NA	
0.1–2.0					41	1.34 (0.6–3.0)								
> 2.0–6.0					29	1.22 (0.5–2.9)								
> 6.0					29	1.16 (0.5–2.7)								
Sullivan *et al.* (1998) (20-year lag) (mortality)														
5 mg/m^3–years synthetic oil	NA		–	2.8 (1.1–7.5)	NA		NA		NA		NA		NA	
5 mg/m^3–years soluble oil			–	1.0 (1.0–1.1)										

NA, not applicable; NR, not reported

separate analyses for subgroups were presented (Tolbert *et al.*, 1992). This cohort formed the study base for the three subsequent studies in this monograph.

Tolbert *et al*. (1992) reported the results of a cohort study of 33 619 persons who had worked for at least three years before 1985 in two of the three facilities studied by Eisen *et al*. (1992) where metalworking fluids were used extensively. Mortality was followed from 1941 to 1984 and vital status could be determined for 94% of the cohort at the end of follow-up. In total, 9349 deaths were identified and death certificates were obtained for 92%. Plant records and industrial hygiene data were used in combination with detailed work history records to identify which persons were exposed to different types of machining fluid and their duration of exposure. Among white men exposed to soluble oils (n = 23 488), there were 7287 deaths (SMR, 1.00) and small excesses were observed for cancers of the stomach (SMR, 1.2; 95% CI, 1.0–1.4), larynx (SMR, 1.4; 95% CI, 1.0–2.0) and brain (SMR, 1.2; 95% CI, 0.9–1.7) and leukaemia (SMR, 1.3; 95% CI, 1.0–1.7). Among white men exposed to synthetic fluids (n = 8446), there were 1632 deaths (SMR, 1.01) and small excesses were observed for cancers of the stomach (SMR, 1.3; 95% CI, 0.8–2.0) and larynx (SMR, 1.6; 95% CI, 0.7–3.1) and leukaemia (SMR, 1.2; 95% CI, 0.7–2.0). Among black men exposed to soluble oils (n = 4964), there were 922 deaths (SMR, 0.81) and small excesses were observed for pancreatic cancer (SMR, 1.6; 95% CI, 1.0–2.5) and laryngeal cancer (SMR, 1.5; 95% CI, 0.5–3.2). Results for black men exposed to synthetic fluids or women exposed to any fluids were not presented because of small numbers. Poisson regression analyses were performed to examine the relationships between duration of exposure to each of the three types of metalworking fluid and specific cancer sites after adjustment for plant, sex, race, length of follow-up, year of birth and age at risk. With the exception of statistically significantly negative associations between lung cancer and synthetic fluids (p = 0.006) (for soluble oils, p = 0.09), no strong dose–response relationship was observed. Mild excesses were observed among persons exposed to soluble fluids for 20 or more years for stomach cancer (rate ratio, 1.2; 95% CI, 0.7–2.1) and pancreatic cancer (rate ratio, 1.4; 95% CI, 0.5–3.7). Slightly larger excesses were observed among persons exposed to synthetic fluids for eight or more years for colon cancer (rate ratio, 1.6; 95% CI, 0.8–3.4) and pancreatic cancer (rate ratio, 2.0; 95% CI, 0.9–4.7).

Eisen *et al*. (1994) reported the results of a nested case–control study of laryngeal cancer among the members of the cohort studied by Eisen *et al*. (1992). Potential cases were individuals who had, or died from, laryngeal cancer between 1941 and 1984 and people with laryngeal cancer identified using regional tumour registries or based on other information included on death certificates. Cases were verified using tumour registry or hospital records and a total of 108 cases were eligible for inclusion (all but one being squamous-cell carcinomas). Incidence density sampling was used to select five controls for each case matched on the basis of year of birth, plant, race and sex. Exposure was assessed based on air sampling data, plant records and interviews with plant personnel. Indices of exposure were developed for duration and cumulative

exposure to the straight and soluble metalworking fluids and duration of exposure to biocides, sulfur and various metals. Matched analyses were performed using conditional logistic regression models with additional adjustment for time since hire. The risk for laryngeal cancer was not found to be associated with either cumulative level (mg/m^3–years) or duration of exposure to soluble metalworking fluids. The relationship with exposure to synthetic fluids or ethanolamines was not presented.

Sullivan *et al*. (1998) conducted a nested case–control study of oesophageal cancer among the members of the cohort studied by Eisen *et al*. (1992). Potential cases were 60 individuals who died of oesophageal cancer between 1941 and 1984. Incidence density sampling was used to select 20 controls for each case matched on the basis of year of birth, plant, race and sex, but because of missing data, 53 cases and 971 controls remained. Work history data and an exposure matrix developed for the study were used to assign exposure. The same indices of exposure were used as those described for Eisen *et al*. (1994), with the addition of duration and cumulative exposure to synthetic fluids and duration of exposure to nitrosamines. Matched analyses were performed using conditional logistic regression with additional adjustment for time since hire. Lagging was used to account for latency. After allowing for a 20-year latency, oesophageal cancer was associated with cumulative exposure to synthetic fluids (odds ratio, 2.8; 95% CI, 1.1–7.5 for 5 mg/m^3–years) and duration of exposure to synthetic fluids (odds ratio, 3.3; 95% CI, 1.1–9.6 for five years). Analyses for exposure specifically to ethanolamines and the risk for oesophageal cancer were not presented. [The Working Group noted that in the last studies, data on tobacco smoking and alcohol drinking were not directly presented.]

The Working Group was aware of several other cohort and proportionate mortality studies which included workers exposed to metalworking fluids but did not include analyses of sub-groups of workers exposed to soluble or synthetic fluids. The Working Group was also aware of a number of population-based case–control studies that reported risks associated with exposure to unspecified metalworking fluids or employment in occupations with potential exposure to metalworking fluids. However, these studies were not considered informative for the evaluation because of the unknown probability of exposure to ethanolamines and the potential for confounding from exposure to other known or suspected carcinogens.

[The Working Group noted that the mixed and varying exposures may explain the variability of the results of the different studies and also make it very difficult to ascribe the excesses of cancer observed to any single agent.]

3. Studies of Cancer in Experimental Animals

3.1 Skin application

3.1.1 *Mouse*

Groups of 50 male and 50 female B6C3F_1 mice, six weeks of age, were administered 0, 40, 80 or 160 mg/kg bw diethanolamine (purity, > 99%) in 95% ethanol by dermal application on five days per week for two years. Survival of dosed male mice was similar to that of the vehicle control group, but survival of dosed female mice was reduced (44/50, 33/50, 33/50 and 23/50 for the control, low-, mid- and high-dose groups, respectively). The mean body weights of the mid- and high-dose males were lower than those of the vehicle controls after weeks 88 and 77, respectively. The mean body weights of the low- and mid-dose females were lower than those of the vehicle controls from week 73, but those of the high-dose females were reduced compared with the vehicle controls from week 53. In male mice, the incidences of hepatocellular adenoma and of hepatocellular adenoma and carcinoma (combined) in all dosed groups were significantly greater than those in the vehicle control group (hepatocellular adenoma: 31/50, 42/50, 49/50 and 45/50 ($p < 0.001$, Poly-3 trend test); hepatocellular carcinoma: 12/50, 17/50, 33/50 and 34/50 ($p < 0.001$, Poly-3 trend test), for the control, low-, mid- and high-dose groups, respectively). In addition, the incidences of hepatoblastoma in the mid- and high-dose groups were significantly increased compared with the vehicle control (0/50, 2/50, 8/50 ($p = 0.004$) and 5/50 ($p = 0.028$, pairwise comparisons) in the control, low-, mid- and high-dose groups, respectively). In the female mice, the incidences of hepatocellular neoplasms were significantly higher than those in the vehicle control group (hepatocellular adenoma: 32/50, 50/50, 48/50 and 48/50 ($p < 0.001$, Poly-3 trend test); hepatocellular carcinoma: 5/50, 19/50, 38/50 and 42/50 ($p < 0.001$, Poly-3 trend test) in the control, low-, mid- and high-dose groups, respectively). Renal tubule adenomas in males showed a marginal increase after standard single-section examination (1/50, 4/50, 6/50 and 6/50 ($p = 0.05$, Poly-3 trend test) in the control, low-, mid- and high-dose groups, respectively). When combining single with extended step-sectioning, the incidences were: 1/50, 6/50, 8/50 and 7/50 ($p = 0.055$, Poly-3 trend test) for the control, low-, mid- and high-dose groups, respectively (National Toxicology Program, 1999a).

3.1.2 *Rat*

Groups of 50 male and 50 female Fischer 344/N rats, six weeks of age, were administered diethanolamine (purity, > 99%) in 95% ethanol by dermal application on five days per week for two years. Males received 0, 16, 32 or 64 mg/kg bw and females 0, 8, 16 or 32 mg/kg bw. Survival rates for dosed male and female groups were similar to those of corresponding vehicle control groups. The mean body weight

of the high-dose male group was lower than that of the vehicle controls from week 8 and the mean body weight of the high-dose female group was lower than that of the vehicle controls from week 97. There were no increases in tumours in treated groups compared with the vehicle controls (National Toxicology Program, 1999a).

3.2 Genetically modified mouse

Groups of 15–20 female Tg.AC mice, which carry a zeta-globin promoted v-Ha-*ras* gene on an FVB background, 14 weeks of age, were administered diethanolamine topically in 95% ethanol (the diethanolamine used was from the same chemical batch as that used in the mouse National Toxicology Program study (National Toxicology Program, 1999a). The diethanolamine was administered in 200-µL volumes, five times per week for 20 weeks. The concurrent negative control groups were treated with 200 µL 95% ethanol. The positive control group was treated with 1.25 µg 12-*O*-tetradecanoylphorbol 13-acetate (TPA; approximately 99% pure) twice per week for 20 weeks. The doses of diethanolamine selected were based on the maximum tolerated dose used earlier (National Toxicology Program, 1999a) and were 5, 10 or 20 mg diethanolamine per mouse per application (higher than the MTD). Survival was high in both the control (90%) and treated groups (80–95%). Lesions were diagnosed as papillomas when they reached at least 1 mm in diameter and persisted for three weeks. Animals that did not survive until the end of week 10 were not included in the data summaries or calculations. Six weeks after the last application, all surviving mice were killed. There was no evidence of chronic irritation or ulceration at the site of application. In contrast to the positive controls, which developed multiple papillomas in 18/20 animals, there was no increase in the incidence of skin tumours in diethanolamine-treated animals in this model (Spalding *et al.*, 2000).

[The Working Group was aware of three carcinogenicity bioassays (dermal application studies) in B6C3F_1 mice and Fischer 344/N rats of fatty acid-diethanolamine condensates conducted by the National Toxicology Program. These were coconut oil acid, lauric acid and oleic acid diethanolamine condensates (National Toxicology Program, 1999b,c,d). The same three condensates were also tested in the transgenic Tg.AC and *p53*$^{+/-}$ mouse models (Spalding *et al.*, 2000). The Working Group concluded that these studies could not be used in the evaluation of the carcinogenicity of diethanolamine *per se*. This judgement was based on the fact that the substances tested were complex mixtures of imprecise composition, that the actual diethanolamine content had not been measured in any of the three studies and therefore the precise levels of exposure were indeterminable, and the fact that these studies were not designed as, and did not represent, conventional or adequate carcinogenesis bioassays of diethanolamine.]

4. Other Data Relevant to an Evaluation of Carcinogenicity and its Mechanisms

4.1 Absorption, distribution, metabolism and excretion

4.1.1 *Humans*

No data were available to the Working Group.

4.1.2 *Experimental systems*

(*a*) *Absorption and distribution*

Data on the toxicokinetics of diethanolamine have been reviewed (Beyer *et al*., 1983; Melnick & Tomaszewski, 1990; Gillner & Loeper, 1995; Knaak *et al*., 1997).

Evidence of dermal absorption and the effect of grooming were reported by Stott *et al.* (2000). Diethanolamine was administered (160 mg/kg bw per day) to $B6C3F_1$ mice by dermal application (with or without access to the application site) or by oral gavage for two weeks. After the final dose (1–2 h), the blood levels of diethanolamine were 5, 6.6 and 7.7 μg/g for dermal (collared mice), oral + dermal (grooming allowed) and oral gavage treatment, respectively. The dermal dosing method for diethanolamine (90 mg/mL in ethanol; 1.78 mL/kg bw per 4-cm^2 area) was the same as in the carcinogenicity bioassay (Section 3.1.1; National Toxicology Program, 1999a).

Skin penetration rates and permeability constants (k_p) for ^{14}C-labelled diethanolamine (Table 7) were determined *in vitro* using full-thickness skin preparations from rats, mice, rabbits and humans (female mammoplasty patients). Human skin proved to be the best barrier against aqueous diethanolamine (37%, w/w) followed by rat, rabbit and mouse skin when the chemical was applied as an 'infinite dose' (20 mg/cm^2 to cm^2 of skin for 6 h). The total absorbed dose from aqueous diethanolamine was greater (0.23–6.68%) than that from undiluted material (0.02–1.3%) (Sun *et al*., 1996).

Dermal doses of [^{14}C]diethanolamine applied in 95% ethanol (for 48 h) to a 1-cm^2 area of $B6C3F_1$ mouse skin (8–81 mg/kg bw, 15 μL volume, and protected non-occlusively by a dome of wire mesh) were more efficiently absorbed (27–58%) than the test doses (2–28 mg/kg bw, 25 μl volume) applied to a 2-cm^2 area of Fischer 344 rat skin (3–16%) (Mathews *et al.*, 1997).

Dermal absorption was also studied in rats. [^{14}C]Diethanolamine was applied to 19.5 cm^2 of the dorsal skin (20 mg/cm^2, 1500 mg/kg bw) and covered for 48 h (no washing) or for 6 h before it was removed by washing. Absorbed [^{14}C]diethanolamine was determined in 48-h urine and faeces and from sampled tissues. Unwashed rats absorbed 1.4% and washed animals 0.64% of the dose, while the majority of [^{14}C]diethanolamine was recovered in the occlusive wrappings (80%) and in skin of the dose site (3.6%). The radioactivity was found in carcass, liver or kidneys but very little in urine (0.11%), faeces or blood (Waechter *et al.*, 1995, cited by Knaak *et al.*, 1997).

Table 7. Skin penetration characteristics of undiluted and aqueous solutions of [^{14}C]diethanolamine

Species	Cumulative dose absorbed (%)	Lag time (h)[a]	Steady-state penetration rate[b] (μg/cm^2/h)	Permeability constant, k_p[c] (cm/h × 10^{-4})
Undiluted diethanolamine				
Rat	0.04 ± 0.01[d]	0.6	1.8	0.02
Mouse	1.30 ± 1.15[d]	0.9	46.3	0.42
Rabbit	0.02 ± 0.01[d]	1.3	0.9	0.01
Human	0.08 ± 0.03[e]	3.2	5.7	0.05
Aqueous diethanolamine (37% w/w)				
Rat	0.56 ± 0.43[d]	0.8	23.0	0.60
Mouse	6.68 ± 5.28[d]	0.8	294.4	7.62
Rabbit	2.81 ± 2.39[d]	1.5	132.2	3.42
Human	0.23 ± 0.09[e]	2.4	12.7	0.34

From Sun *et al*. (1996)

[a] Extrapolated from the intercept of the linear segment (regression) line with the abscissa

[b] Penetration rate at steady state, derived from the slope of the linear segment of a plot of the cumulative mg/cm^2 absorbed versus time

[c] k_p = Steady-state penetration rate (mg/cm^2/h) / Initial concentration (mg/cm^3)

[d] Mean ± SE (n = 3)

[e] Mean ± SE (n = 6)

Combined data from several studies (cited above) showed that in rats the absorption rate increased linearly with the [^{14}C]diethanolamine dose (single), and that a 100-fold increase in the dose of diethanolamine (188–19 720 μg/cm^2) resulted in a 450-fold increase in absorption rate (0.113–45.0 μg/cm^2 per h) (Knaak *et al*., 1997).

Non-radiolabelled diethanolamine was applied to the dorsal skin of rats (1500 mg/kg bw, *ca.* 20 mg/cm^2 to 25 cm^2 of skin and covered) once per day for 6 h per day for three or six days. [^{14}C]Diethanolamine (1500 mg/kg bw) was then applied to the skin for a 48-h penetration test. Animals in the three-day and six-day pretreatment groups absorbed 21% and 41% of the applied dose, respectively. Liver, kidney or carcass contained the majority of absorbed radioactivity, urine from three-day and six-day groups contained 4.3% and 13%, respectively, and less than 0.3% was found in brain, fat or heart (Waechter *et al.*, 1995, cited by Knaak *et al.*, 1997).

[^{14}C]Diethanolamine (7 mg/kg bw) was given orally to male Fischer 344 rats once or by daily repeat dosing for up to eight weeks. Single oral doses (0.7–200 mg/kg bw) were well absorbed but excreted very slowly. About 20–30% of oral and intravenous doses (7 mg/kg bw) was found in urine (mainly as unchanged diethanolamine), with less than 3% in faeces and only 0.2% or less was exhaled (CO_2) within 48 h. Most of the diethanolamine was retained in tissues at high concentrations. The tissue-to-blood

ratios were 150–200 for the liver and kidney, 30–40 for the lung and spleen and 10–20 for the heart, brain and muscle. Tissue radioactivity was found mainly in aqueous extracts (up to 90%) and 5–10% was organic-extractable (Mathews *et al*., 1995, 1997).

(*b*) *Metabolism and excretion*

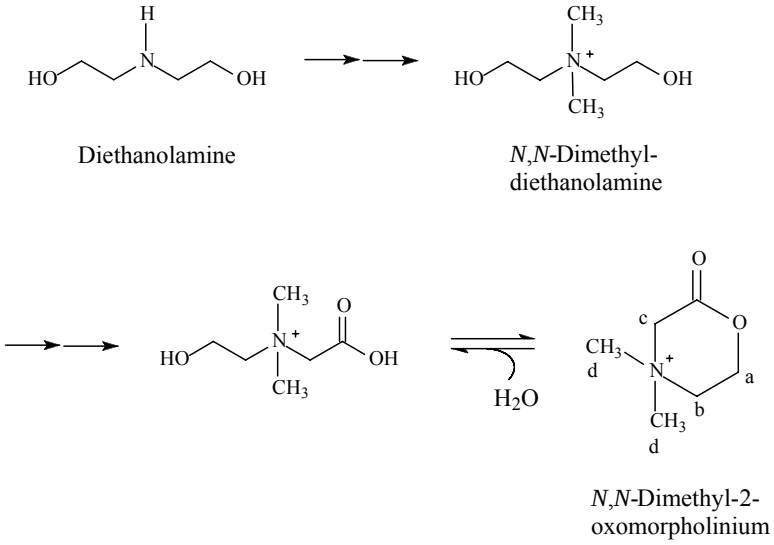
Diethanolamine is incorporated into membrane phospholipids (Artom *et al*., 1949, 1958) and interacts with lipid metabolism *in vivo*, for example by inhibiting incorporation of ethanolamine and choline into phospholipids in rat liver and kidney. The synthesis of liver phospholipids *in vitro* was competitively inhibited by diethanolamine (K_i ~ 3 mM). Diethanolamine was a less effective precursor (K_m = 12 mM) in phospholipid synthesis than the natural substrates choline (K_m = 0.076 mM) and ethanolamine (K_m = 0.054 mM) (Barbee & Hartung, 1979a). The catabolism of diethanolamine-containing lipids was slower than that of the corresponding choline- and ethanolamine-containing derivatives (Artom *et al*., 1958; Barbee & Hartung, 1979a). Diethanolamine is conserved and metabolized by biosynthetic routes common to ethanolamine, resulting in *O*-phosphorylated, *N*-methylated and *N*,*N*-dimethylated derivatives that are incorporated as polar head groups into aberrant phospholipids which are, in turn, incorporated into critical membranes (Mathews *et al.*, 1997). Functional and structural alterations induced by diethanolamine in liver mitochondria may ensue from its adverse effects on lipid metabolism in subcellular membranes (Barbee & Hartung, 1979b). About 30% of the diethanolamine-derived phospholipids in rat liver were ceramides (sphingomyelins) and about 70% were phosphoglycerides following a single oral dose of diethanolamine (7 mg/kg bw). After repeated administration (7 mg/kg bw on five days per week for eight weeks), the bioaccumulation of diethanolamine to plateau levels at between four and eight weeks was accompanied by an increasing degree of methylation and accumulation of aberrant sphingomyelinoid lipids in tissues. The highest concentrations of diethanolamine-associated radioactivity measured 72 h after the final dose given in the eight-week period were found in the liver (0.3 mg equivalent/g). The blood was a notable exception in that it continued to bioaccumulate diethanolamine throughout the eight-week dosing period. Uptake, retention and metabolism of diethanolamine in human and rat liver slices are reported to be similar (Mathews *et al*., 1995, 1997).

Hepatic levels of choline, phosphocholine and glycerophosphocholine were reduced as much as 64, 84 and 70%, respectively in male B6C3F_1 mice after two weeks' administration of diethanolamine (160 mg/kg bw per day) via oral gavage or skin painting. These levels were inversely related to the blood diethanolamine levels (uptake) after the final dose. In contrast, the hepatic levels of sphingomyelin were increased relative to those in control mice, and were directly correlated with blood diethanolamine levels (Stott *et al.*, 2000).

The metabolism of diethanolamine leading to urinary elimination is illustrated in Figure 1. After single oral and intravenous administrations of diethanolamine to Fischer 344 rats, the compound is excreted predominantly unchanged in urine, only a small

portion being found as its mono- and dimethylated derivatives. As a result of progressive methylation after repeated oral administration (eight weeks), the relative amounts of *N*-methyldiethanolamine and *N*,*N*-dimethyl-2-oxomorpholinium appearing together with unchanged diethanolamine in urine increased markedly. The quaternized lactone was formed from *N*,*N*-dimethyldiethanolamine *in vivo* and in incubations with rat liver microsomes *in vitro* (Mathews *et al*., 1995, 1997).

Figure 1. Proposed pathway of diethanolamine metabolism in the rat, based on urinary excretion data from an eight-week oral dosing study (7 mg/kg bw per day, five days per week for eight weeks)



From Mathews *et al.* (1997)

After four weeks' repeated administration of [^{14}C]diethanolamine (7 mg/kg bw per day on five days per week) to rats, the urinary excretion of radiolabel (during the 'washout phase') was followed for another four weeks. The log-linear response with time was a first-order process with a whole-body elimination half-life of about six days (Mathews *et al*., 1997).

Excretion of *N*-nitrosodiethanolamine in urine was evident in Sprague-Dawley rats receiving diethanolamine via the skin (100–400 mg/animal) and sodium nitrite in the drinking water (2000 ppm [mg/L]) for six days but not in the absence of sodium nitrite (Preussmann *et al.*, 1981). *N*-Nitrosodiethanolamine was detected in a gastric rinse of rats treated with 100 µmol diethanolamine [59 mg/kg bw] and 400 µmol sodium nitrite [153 mg/kg bw] by gavage (Konishi *et al.*, 1987). No evidence of formation of *N*-nitrosodiethanolamine *in vivo* was found, however, in B6C3F$_1$ mice treated with diethanolamine (160 mg/kg bw per day) and sodium nitrite (140 ppm in drinking-water; 40 mg/kg bw) (Stott *et al.*, 2000).

4.2 Toxic effects

4.2.1 *Humans*

The only experimental data available on human exposure to airborne diethanolamine come from clinical provocation tests. Diethanolamine-induced occupational asthma was diagnosed following specific bronchial provocation tests in an exposure chamber. The positive reaction was observed in a 39-year-old male metal worker after a 30-min or 45-min inhalation exposure to aerosols from a warmed cutting fluid (40 °C) containing 0.15% diethanolamine and 0.32% triethanolamine, as well as after a 15-min exposure to pure diethanolamine at aerosol concentrations of 0.75 and 1.0 mg/m^3 (Piipari *et al.*, 1998).

4.2.2 *Experimental systems*

The toxicity of diethanolamine (as well as of mono- and triethanolamine) has been reviewed (Knaak *et al*., 1997).

In Swiss Webster mice, the LD_{50} for diethanolamine (by intraperitoneal injection) was 2.3 g/kg bw. At this dose, marked liver changes, including extensive vacuolization and fat droplets, were observed 4 h after dosing. By 24 h, no vacuoles were visible in hepatocytes and fatty droplets were reduced in number (Blum *et al.*, 1972).

Extensive information is available on toxic effects following oral and dermal application of diethanolamine in a 13-week subchronic study (National Toxicology Program, 1992; Melnick *et al*., 1994a,b). Groups of 10 male Fischer 344/N rats were given 0, 320, 630, 1250, 2500 or 5000 ppm [mg/L] diethanolamine in the drinking-water (equivalent to 25–440 mg/kg bw per day), while groups of 10 females were given 0, 160, 320, 630, 1250 or 2500 ppm (equivalent to 15–240 mg/kg bw per day). Two male rats died in the highest-dose group; both male and female rats lost weight in a dose-dependent fashion. Poorly regenerative microcytic anaemia developed within two weeks, without observed changes in bone marrow. Moreover, increased kidney weight, tubular necrosis and loss of kidney function occurred after two weeks. Epithelial cell necrosis in kidney tubules was seen only at the highest dose in both sexes. Some mild changes in the liver were observed, such as weight increase. Demyelination in the medulla oblongata (brain) and spinal cord was found after 13 weeks in both males and females (Melnick *et al.*, 1994a).

In a concurrent study, B6C3F$_1$ mice were given to 0, 630, 1250, 2500, 5000 and 10 000 ppm [mg/L] in the drinking-water; exposures were equivalent to 100–1700 mg/kg bw per day for males and 140–1100 mg/kg bw per day for females. At the three higher dose levels, the mice lost weight and all males and females in the two highest-dose groups died before the end of the study. In both males and females, a dose-dependent increase in liver weight was observed after two weeks; the effect was present even at the lowest dose after 13 weeks in both males and females. Hepatocellular necrosis was found with doses ≥ 2500 ppm. Cytological changes in hepatocytes were found at all doses after 13 weeks. Kidney toxicity, including tubular necrosis, was seen

only in male mice after 13 weeks. In both males and females, degeneration of cardiac myocytes was seen at doses of 2500 ppm and above (Melnick *et al.*, 1994b).

In the same study (Melnick *et al.*, 1994a,b), the effects of dermal exposure were observed during a 13-week study. Groups of 10 male and 10 female rats received applications of 32–500 mg/kg bw on five days per week. At the highest dose, some rats died during the study period. Ulcerative skin lesions at the site of application developed, accompanied by inflammation, hyperkeratinosis and acanthosis of the epidermis. Microcytic anaemia also developed, similarly to that observed after oral exposure. Kidney toxicity, including tubular necrosis and mineralization, was observed, especially in females. Liver weights were increased in both males and females, but no histopathological changes were observed in the liver. Demyelination in the medulla oblongata (brain) and spinal cord also occurred. In mice, after skin application of doses of 80–1250 mg/kg bw on five days per week, the highest dose induced a decrease in body weight compared with controls. Skin toxicity was observed at the site of application and liver weight increased, but hepatocellular necrosis occurred only in male mice. Kidney toxicity, including tubular necrosis, and cardiac myocyte degeneration were found in both males and females.

Irritation of the eye and skin after application of pure (98%) diethanolamine was investigated in New Zealand White rabbits. After 72 h, irritation of the skin was moderate, whereas irritation of the eye was severe (Dutertre-Catella *et al*., 1982).

Diethanolamine has been shown to inhibit choline uptake into cultured Syrian hamster embryo (SHE) and Chinese hamster ovary cells and to inhibit the synthesis of phosphatidylcholine in in-vitro systems in a concentration-dependent, competitive and reversible manner (Lehman-McKeeman & Gamsky, 1999, 2000). Diethanolamine treatment caused a marked reduction in hepatic choline metabolite concentrations in mice following two weeks of dermal dosing. The most pronounced reduction was in the hepatic concentration of phosphocholine, the intracellular storage form of choline (Stott *et al.*, 2000). Moreover, the pattern by which choline metabolites were altered was similar to the pattern of change that has been observed following dietary choline deprivation in rodents (Pomfret *et al.*, 1990). Excess choline also prevented diethanolamine-induced inhibition of phosphatidylcholine synthesis and incorporation of diethanolamine into SHE cell phospholipids (Lehman-McKeeman & Gamsky, 2000).

4.3 Reproductive and developmental effects

4.3.1 *Humans*

No data were available to the Working Group.

4.3.2 *Experimental systems*

The reproductive and developmental toxicity of diethanolamine tested has been reviewed (Knaak *et al*., 1997).

Diethanolamine was administered by gavage to Sprague-Dawley rats on days 6–15 of gestation at dose levels of 0, 50, 200, 500, 800 or 1200 mg/kg bw per day. The rats were killed on day 20 and the uteri examined for number of implantation sites and for live and dead implantations. Rats receiving 500 mg/kg bw or higher doses either died or were in a moribund condition and were killed. Maternal body weight gain was reduced in the 200-mg/kg bw group, but none of the gestational parameters in the treated groups was significantly different from those of the controls (Environmental Health Research & Testing, 1990; cited by Knaak *et al.*, 1997).

Diethanolamine was painted as an aqueous solution on the skin of CD rats on days 6–15 of gestation at dose levels of 0, 150, 500 and 1500 mg/kg bw per day. The two higher dose levels produced severe skin irritation. There was no effect of any treatments on fetal weight or on the incidence of external, visceral or skeletal abnormalities, but delayed ossification of the axial skeleton and distal appendages was observed in fetuses of the 1500-mg/kg bw group (Marty *et al.*, 1999).

Diethanolamine was applied as an aqueous solution to the skin of New Zealand White rabbits on days 6–18 of gestation at dose levels of 0, 35, 100 or 350 mg/kg bw per day. The highest dose level produced marked skin irritation. There was no effect of any treatments on development or on the incidence of external, visceral or skeletal abnormalities (Marty *et al.*, 1999).

In a 13-week subchronic study in male Fischer 344/N rats, testis and epididymis weights were decreased at diethanolamine doses of 1200 ppm or more in the drinking water (Melnick *et al.*, 1994a). Reduced sperm count and motility as well as degeneration of the seminiferous tubules were found at a dose of 2500 ppm.

Inhalation exposure of pregnant Wistar rats to 0.2 mg/m^3 diethanolamine aerosols for 6 h per day on days 6–15 of gestation caused an increased incidence of cervical ribs in the fetuses. No treatment-related malformations were observed (Gamer *et al.*, 1993, cited in Marty *et al.*, 1999).

4.4 Genetic and related effects

The genetic toxicity of diethanolamine has been reviewed by an expert panel for the cosmetic ingredient review (Beyer *et al.*, 1983) and by Knaak *et al.* (1997).

4.4.1 *Humans*

No data were available to the Working Group.

4.4.2 *Experimental systems* (see Table 8 for references)

Diethanolamine was not mutagenic to *Salmonella typhimurium* strains TA100, TA1535, TA1537, TA1538 or TA98 in three studies, or to *Escherichia coli* WP2 *uvrA* in a single study, in the presence or absence of exogenous metabolic activation. It did

Table 8. Genetic and related effects of diethanolamine

Test system	Result[a]		Dose (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
Salmonella typhimurium TA100, TA1535, TA1537, TA1538, reverse mutation	–	–	3333 µg/plate	Haworth *et al.* (1983)
Salmonella typhimurium TA100, TA1535, TA1537, TA98, reverse mutation	–	–	3333 µg/plate	National Toxicology Program (1999a)
Salmonella typhimurium TA100, TA1535, TA1537, TA1538, TA98, reverse mutation	–	–	4000 µg/plate	Dean *et al.* (1985)
Escherichia coli WP2/WP2*uvr*A, reverse mutation	–	–	4000 µg/plate	Dean *et al.* (1985)
Saccharomyces cerevisiae JD1, mitotic gene conversion in stationary and log-phase cultures	–	–	5000	Dean *et al.* (1985)
Gene mutation, mouse lymphoma L5178Y cells, *Tk* locus *in vitro*	–	–	330	National Toxicology Program (1999a)
Sister chromatid exchange, Chinese hamster ovary CHO cells *in vitro*	–	–	2176	Sorsa *et al.* (1988)
Sister chromatid exchange, Chinese hamster ovary CHO cells *in vitro*	–	–	1500	National Toxicology Program (1999a)
Chromosomal aberrations, Chinese hamster ovary CHO cells *in vitro*	–	–	3010	National Toxicology Program (1999a)
Chromosomal aberrations, rat liver RL cells *in vitro*	–	–	$0.5 \times GI_{50}$	Dean *et al.* (1985)
Cell transformation, Syrian hamster embryo cells (8-day treatment)	–	NT	500	Inoue *et al.* (1982)
Cell transformation, Syrian hamster embryo cells (24-h treatment)	+	NT	4500	Kerckaert *et al.* (1996)
Cell transformation, Syrian hamster embryo cells (7-day treatment)	+	NT	250	Kerckaert *et al.* (1996)
Cell transformation, Syrian hamster embryo cells (7-day treatment)	+[c]	NT	500	Lehman-McKeeman & Gamsky (2000)

Table 8 (contd)

Test system	Result[a]		Dose (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
Micronucleus formation, newt larvae (*Pleurodeles waltl*) blood cells *in vivo*	–		75 ppm; 12 d	Fernandez *et al.* (1993)
Micronucleus formation, newt larvae (*Pleurodeles waltl*) blood cells *in vivo*[d]	–		75 ppm; 12 d	L'Haridon *et al.* (1993)

[a] +, positive; –, negative; NT, not tested
[b] LED, lowest effective dose; HID, highest ineffective dose; in-vitro tests, µg/mL; in-vivo tests, mg/kg bw/day
[c] Negative in the presence of 30 mM choline
[d] In the presence of sodium nitrite or nitrate at pH 8.6 and 5
GI_{50}, concentration causing 50% growth inhibition

not induce gene conversion in *Saccharomyces cerevisiae* strain JD1 in the presence or absence of exogenous metabolic activation. Exposure of the larvae of the newt *Pleurodeles waltl* to diethanolamine did not induce micronuclei in their blood cells and this result remained unaffected by changing the pH or by the addition of sodium nitrite or nitrate.

Diethanolamine did not induce mutations in mouse lymphoma L5178Y cells at the *Tk* locus in the presence or absence of exogenous metabolic activation in one study. It did not induce sister chromatid exchanges in Chinese hamster ovary cells in two studies with or without exogenous metabolic activation. A single study using cultured rat liver cells found no induction of chromosomal aberrations and one study in Chinese hamster ovary cells also found no induction of chromosomal aberrations in either the presence or absence of exogenous metabolic activation.

In one study of cell transformation in the Syrian hamster embryo clonal assay, diethanolamine had no effect after an eight-day treatment. A much larger study revealed induction of cell transformation at a similar dose after a seven-day treatment and at a much higher dose after a 24-h treatment with diethanolamine.

A further seven-day treatment cell transformation study demonstrated a positive dose-related response to diethanolamine up to 500 μg/mL that was abolished by co-administration with 30 mM choline.

4.5 Mechanistic considerations

In mice, diethanolamine alters choline homeostasis in a manner resembling choline deficiency. Stott *et al.* (2000) showed that diethanolamine induced choline deficiency and depleted several choline-containing compounds in B6C3F_1 mice, while Lehman-McKeeman & Gamsky (1999, 2000) found that diethanolamine inhibited the uptake of choline into mammalian cells.

It is known that deprivation of choline in the diet of rodents predisposes to the appearance of hepatocellular carcinomas (Zeisel, 1996). Diethanolamine-induced choline deficiency thus provides a mechanism for the tumorigenesis noted in mice but not in rats.

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Diethanolamine is a viscous liquid widely used as a chemical intermediate and as a corrosion inhibitor and surface-active agent in various products including metal-working fluids, oils, fuels, paints, inks, cosmetic formulations and agricultural products. Occupational exposure may occur by inhalation and dermal contact, particularly in metal-machining occupations. No data were available on environmental exposure to

this substance. The general population may be exposed through contact with a variety of personal care products.

5.2 Human carcinogenicity data

Two cohort studies and two nested case–control studies looked at cancer mortality or incidence among workers using metalworking fluids with ethanolamines as additives, with or without sodium nitrite. Small excesses were observed for cancers at various sites, in particular the stomach, oesophagus and larynx. In most of these studies, only associations with use of soluble oils or synthetic fluids were presented and no results were given specifically in relation to diethanolamine exposure. It is difficult to draw conclusions regarding diethanolamine using data from studies of exposures to these complex mixtures.

5.3 Animal carcinogenicity data

Diethanolamine was tested for carcinogenicity by dermal application in one study in mice and in one study in rats. In the mouse study, there was a treatment-related increase in the incidences of both hepatocellular adenomas and carcinomas in both males and females, as well as an increase in the incidence of hepatoblastomas in males. There was also a marginal increase of renal tubule adenomas in males. In rats, no treatment-related increase in the incidence of tumours was seen in either males or females.

In a Tg.AC transgenic mouse model using similar doses to the first mouse study, there was no treatment-related increase in the incidence of skin tumours after skin application.

5.4 Other relevant data

Diethanolamine is metabolized by biosynthetic routes common to endogenous alkanolamines (ethanolamine and choline) and incorporated into phospholipids. It is excreted predominantly unchanged with a half-life of approximately one week in urine. In the absence of sodium nitrite, no conversion to *N*-nitrosodiethanolamine is observed. Diethanolamine competitively inhibits the cellular uptake of choline *in vitro* and hepatic changes in choline homeostasis, consistent with choline deficiency, are observed *in vivo*.

No data on reproductive and developmental effects in humans were available.

Oral or dermal exposure of rats to diethanolamine during organogenesis was not associated with any sign of developmental toxicity, while inhalation exposure to diethanolamine aerosols caused signs of developmental toxicity. Dermal exposure of rabbits during organogenesis caused no sign of developmental toxicity.

Testicular effects have been found after exposure of rats to diethanolamine in the drinking water.

No data on genetic and related effects of diethanolamine in humans were available to the Working Group.

Diethanolamine induced cell transformation in Syrian hamster embryo cells *in vitro* in two studies but not in another. It did not induce gene mutations, sister chromatid exchanges or chromosomal aberrations. Diethanolamine did not induce micronucleus formation in larval newt blood cells in either the absence or presence of sodium nitrite or nitrate. It was without effect on gene conversion in yeast and was not mutagenic in bacteria.

The limited data available to the Working Group do not indicate that diethanolamine is genotoxic.

5.5 Evaluation

There is *inadequate evidence* in humans for the carcinogenicity of diethanolamine.

There is *limited evidence* in experimental animals for the carcinogenicity of diethanolamine.

Overall evaluation

Diethanolamine is *not classifiable as to its carcinogenicity to humans (Group 3)*[1].

6. References

American Conference of Governmental Industrial Hygienists (1999) *TLVs and other Occupational Exposure Values—1999* [CD-ROM], Cincinnati, OH, ACGIH®

Artom, C., Cornatzer, W.E. & Crowder, M. (1949) The action of an analogue of ethanolamine (diethanolamine) on the formation of liver phospholipides. *J. biol. Chem.*, 180, 495–503

Artom, C., Lofland, H.B. & Oates, J.A., Jr (1958) In vivo incorporation of diethanolamine into liver lipides. *J. biol. Chem.*, **233**, 833–837

Barbee, S.J. & Hartung, R. (1979a) The effect of diethanolamine on hepatic and renal phospholipid metabolism in the rat. *Toxicol. appl. Pharmacol.*, **47**, 421–430

Barbee, S.J. & Hartung, R. (1979b) Diethanolamine-induced alteration of hepatic mitochondrial function and structure. *Toxicol. appl. Pharmacol.*, **47**, 431–440

Beyer, K.H., Bergfeld, W.F., Berndt W.O., Boutwell, R.K., Carlton, W.W., Hoffmann, D.K., Schroeter, A.L. (1983) Final report on safety assessment of triethanolamine, diethanolamine, and monoethanolamine. *J. Am. Coll. Toxicol.*, **2**, 183–235

[1] Dr Mirer dissociated himself from the conclusions of the Working Group.

Blum, K., Huizenga, C.G., Ryback, R.S., Johnson, D.K. & Geller, I. (1972) Toxicity of diethanolamine in mice. *Toxicol. appl. Pharmacol.*, **22**, 175–185

Bollmeier, A.F. (1992) Alkanolamines. In: Kroschwitz, J.I. & Howe-Grant, M., eds, *Kirk-Othmer Encyclopedia of Chemical Technology*, 4th Ed., Vol. 2, New York, John Wiley, pp. 1–20

Budavari, S., ed. (1998) *The Merck Index*, 12th Ed., Version 12:2 [CD-ROM],Whitehouse Station, NJ, Merck & Co.

Chemical Information Services (1999) *Directory of World Chemical Producers (Version 99.1.0)*, Dallas, TX [CD-ROM]

Chou, H.J. (1998) Determination of diethanolamine and *N*-nitrosodiethanolamine in fatty acid diethanolamides. Drugs, Cosmetics, Forensic Sciences. *J. AOAC Internat.*, **81**, 943–947

Dean, B.J., Brooks, T.M., Hodson-Walker, G. & Hutson, D.H. (1985) Genetic toxicology testing of 41 industrial chemicals. *Mutat. Res.*, **153**, 57–77

Dow Chemical Company (1998a) *Sales Specification: Diethanolamine*, Midland, MI

Dow Chemical Company (1998b) *The Specifier's Guide to Buying and Applying Ethanolamines*, Midland, MI

Dow Chemical Company (1999) *Material Safety Data Sheet: Diethanolamine*, Midland, MI

Dutertre-Catella, H., Lich, N.P., Huyen, V.N. & Truhaut, R. (1982) Comparative study of skin and eye irritation by ethanolamines (mono, di, tri and poly). *Arch. mal. prof.*, **43**, 455–460

Eisen, E.A., Tolbert, P.E., Monson, R.R. & Smith, T.J. (1992) Mortality studies of machining fluid exposure in the automobile industry. I: A standardized mortality ratio analysis. *Am. J. ind. Med*., **22**, 809–824

Eisen, E.A., Tolbert, P.E., Hallock, M.F., Monson, R.R., Smith, T.J. & Woskie, S.R. (1994) Mortality studies of machining fluid exposure in the automobile industry. III: A case–control study of larynx cancer. *Am. J. ind. Med*., **26**, 185–202

Eller, P.M., ed. (1994) *NIOSH Manual of Analytical Methods* (DHHS (NIOSH) Publ. No. 94-113), 4th Ed., Cincinnati, OH, National Institute for Occupational Safety and Health [Method 3509]

Environment Canada (1995) *National Pollutant Release Inventory (NPRI) Summary Report 1995. Canada Environment Protection Act*, Ontario, p. 14

Environmental Protection Agency (1996) *1994 Toxics Release Inventory* (EPA 745-R-96-002), Washington DC, Office of Pollution Prevention and Toxics, p. 244

Fernandez, M., L'Haridon, J., Gauthier, L. & Zoll-Moreux, C. (1993) Amphibian micronucleus test(s): a simple and reliable method for evaluating in vivo effects of freshwater pollutants and radiations. Initial assessment. *Mutat. Res.*, **292**, 83–99

Fernando, L.A. (1995) Spectrophotometric determination of ethanolamines in lubricating emulsions©. *J. Soc. Tribol. Lubric. Engin.*, **51**, 701–704

Food and Drug Administration (1999) Food and drugs. *US Code Fed. Regul.*, **Title 21**, Parts 175.105, 176.170, 176.180, pp. 7, 138–165, 186–211

Fukui, M., Konishi, H., Ohta, K. & Tanaka, K. (1992) Ion-exclusion chromatography with UV detection for the determination of alkanolamines in cosmetics using water-glycerine as an eluent. *Bunseki Kagatu*, **41**, T27–T31

Gamer, A.O., Hellwig, J. & Hildebrand, B. (1993) *Study of the Prenatal Toxicity of Diethanolamin in Rats after Inhalation*, Project No. 31R0233/90010). BASF Aktiengesellschaft, Ludwigshafen, Germany

Gillner, M. & Loeper, I. (1995) Health effects of selected chemicals. 3. Diethanolamine. *Nord*, **28**, 52–75

Hammer, H., Körnig, W., Weber, T. & Kieczka, H. (1987) Ethanolamines and propanolamines. In: Gerhartz, W., Yamamoto, Y.S., Kaudy, L., Rounsaville, J.F. & Schulz, G., eds, *Ullmann's Encyclopedia of Industrial Chemistry*, 5th rev. Ed., Vol. A10, New York, VCH Publishers, pp. 1–19

Hartung, R., Rigas, L.K. & Cornish, H.H. (1970). Acute and chronic toxicity of diethanolamine (Abstract). *Toxicol. appl. Pharmacol.*, **17**, 308

Haworth, S., Lawlor, T., Mortelmans, K., Speck, W. & Zeiger, E. (1983) Salmonella mutagenicity test results for 250 chemicals. *Environ. mol. Mutag.*, **5** (Suppl. 1), 3–142

Hedenstedt, A. (1978) Mutagenicity screening of industrial chemicals: seven aliphatic amine and one amide tested in the Salmonella/microsome assay. *Mutat. Res.*, **53**, 198–199

IARC (1987a) *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans*, Suppl. 7, *Overall Evaluations of Carcinogenicity: An Update of* IARC Monographs *Volumes 1 to 42*, Lyon, IARC*Press*, pp. 120–122

IARC (1987b) *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans*, Suppl. 7, *Overall Evaluations of Carcinogenicity: An Update of* IARC Monographs *Volumes 1 to 42*, Lyon, IARC*Press*, pp. 174–175

IARC (1994) *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans,* Vol. 60, *Some Industrial Chemicals*, Lyon, IARC*Press*, pp. 73–159

IARC (1999) *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans*, Vol. 71, *Re-evaluation of Some Organic Chemicals, Hydrazine and Hydrogen Peroxide*, Lyon, IARC*Press*, pp. 109–225

Inoue, K., Sunakawa, T., Okamoto, K. & Tanaka, Y. (1982) Mutagenicity tests and in vitro transformation assays on triethanolamine. *Mutat. Res.*, **101**, 305–313

Järvholm, B. & Lavenius, B. (1987) Mortality and cancer morbidity in workers exposed to cutting fluids. *Arch. environ. Health*, **42**, 361–366

Järvholm, B., Lillienberg, L., Sallsten, G., Thiringer, G. & Axelson, O. (1981) Cancer morbidity among men exposed to oil mist in the metal industry. *J. occup. Med.*, **23**, 333–337

Kenyon, E.M., Hammond, S.K., Shatkin, J., Woskie, S.R., Hallock, M.F. & Smith, T.J. (1993) Ethanolamine exposures of workers using machining fluids in the automotive parts manufacturing industry. *Appl. occup. environ. Hyg.*, **8**, 655–661

Kerckaert, G.A., Brauninger, R., LeBoeuf, R.A. & Isfort, R.J. (1996) Use of Syrian hamster embryo cell transformation assay for carcinogenicity prediction of chemicals currently being tested by the National Toxicology Program in rodent bioassays. *Environ. Health Perspect.*, **104** (Suppl. 5), 1075–1084

Knaak, J.B., Leung, H.-W., Stott, W.T., Busch, J. & Bilsky, J. (1997) Toxicology of mono-, di-, and triethanolamine. *Rev. environ. Contam. Toxicol.*, **149**, 1–86

Konishi, Y., Yokose, Y., Mori, Y., Yamasaki, H., Yamamoto, K., Nakajima, A. & Denda, A. (1987) Lung carcinogenesis by *N*-nitrosobis(2-hydroxypropyl)amine-related compounds and their formation in rats. In: Bartsch, H., O'Neill, I.K. & Schulte-Hermann, R., eds, *Relevance of N-nitroso Compounds to Human Cancer: Exposures and Mechanisms* (IARC Scientific Publications No. 84), Lyon, IARC*Press*, pp. 250–252

L'Haridon, J., Fernandez, M., Ferrier, V. & Bellan, J. (1993) Evaluation of the genotxicity of N-nitrosoatrazine, *N*-nitrosodiethanolamine and their precursors *in vivo* using the newt micronucleus test. *Water Res.*, **27**, 855–862

Lehman-McKeeman, L.D. & Gamsky, E.A. (1999) Diethanolamine inhibits choline uptake and phosphatidylcholine synthesis in Chinese hamster ovary cells. *Biochem. biophys. Res. Comm.*, **262**, 600–604

Lehman-McKeeman, L.D. & Gamsky, E.A. (2000) Choline supplementation inhibits diethanolamine-induced morphological transformation in Syrian hamster embryo cells: evidence for a carcinogenic mechanism. *Toxicol. Sci.*, **55**, 303–310

Levin, J.O., Andersson, K. & Hallgren, C. (1994) Exposure to low molecular polyamines during road paving. *Ann. occup. Hyg.*, **38**, 257–264

Lide, D.R. & Milne, G.W.A. (1996) *Properties of Organic Compounds*, Version 5.0 [CD-ROM], Boca Raton, FL, CRC Press

Loveday, K.S., Lugo, M.H., Resnick, M.A., Anderson, B.E. & Zeiger, E. (1989) Chromosome aberrations and sister chromatid exchanges in Chinese hamster ovary cells in vitro. II. Results with 20 chemicals. *Environ. mol. Mutag.*, **13**, 60–94

Marty, M.S., Neeper-Bradley, T.L., Neptun, D.A. & Carney, E.W. (1999) Developmental toxicity of diethanolamine applied cutaneously to CD rats and New Zealand White rabbits. *Regul. Toxicol. Pharmacol.*, **30**, 169–181

Mathews, J.M., Garner, C.E. & Matthews, H.B. (1995) Metabolism, bioaccumulation, and incorporation of diethanolamine into phospholipids. *Chem. Res. Toxicol*., **8**, 625–633

Mathews, J.M., Garner, C.E., Black, S.L. & Matthews, H.B. (1997) Diethanolamine absorption, metabolism and disposition in rat and mouse following oral, intravenous and dermal administration. *Xenobiotica*, **27**, 733–746

Maurer, W., Hohaus, E. & Schubert, B. (1996) [Analysis of alkanolamines in cosmetics and pharmaceutics]. *Parfü.m. Kosmet.*, **77**, 262–266 (in German)

Melnick, R.L. & Tomaszewski, K.E. (1990) Diethanolamine. In: Buhler, D.R. & Reed, D.J., eds, *Ethel Browning's Toxicity and Metabolism of Industrial Solvents*, Vol. II, *Nitrogen and Phosphorus Solvents*, Elsevier, Amsterdam, pp. 401–410

Melnick, R.L., Mahler, J., Bucher, J.R., Thompson, M., Hejtmancik, M., Ryan, M.J. and Mezza, L.E. (1994a) Toxicity of diethanolamine: 1. Drinking water and topical application exposures in F344 rats. *J. appl. Toxicol*., **14**, 1–9

Melnick, R.L., Mahler, J., Bucher, J.R., Hejtmancik, M., Singer, A. & Persing, R.L. (1994b) Toxicity of diethanolamine: 2. Drinking water and topical application exposures in B6C3F1 mice. *J. appl. Toxicol*., **14**, 11–19

Myhr, B.C., Bowers, L.R. & Caspary, W.J. (1986) Results from the testing of coded chemicals in the L5178Y $TK^{+/-}$ mouse lymphoma mutagenesis assay. *Environ. mol. Mutagen.*, **7** (Suppl. 3), 58

National Library of Medicine (1999*) Registry of Toxic Effects of Chemical Substances (RTECS) Database*, Bethesda, MD [Record No. 35205]

National Toxicology Program (1992) *Toxicity Studies of Diethanolamine (CAS No. 111-42-2) Administered Topically and in Drinking Water to F344/N Rats and B6C3F$_1$ Mice* (Tech. Rep. Ser. No. 20; NIH Publication No. 92-3343), Department of Health and Human Services, Research Triangle Park, NC

National Toxicology Program (1999a) *Toxicology and Carcinogenesis Studies of Diethanolamine (CAS No. 111-42-2) in F344/N Rats and B6C3F$_1$ Mice (Dermal Studies)* (Tech. Rep. Ser. No. 478; NIH Publ. No. 99-3968), Research Triangle, NC [This report has not been peer-reviewed]

National Toxicology Program (1999b) *Toxicology and Carcinogenesis Studies of Coconut Oil Acid Diethanolamine Condensate (CAS No. 68603-42-9) in F344/N Rats and B6C3F$_1$ Mice (Dermal Studies)* (Tech. Rep. Ser. No. 479; NIH Publication No. 99-3969), Department of Health and Human Services, Research Triangle Park, NC [draft]

National Toxicology Program (1999c) *Toxicology and Carcinogenesis Studies of Lauric Acid Diethanolamine Condensate in F344/N Rats and B6C3F$_1$ Mice (Dermal Studies)* (Tech. Rep. Ser. No. 480; NIH Publication No. 99-3970), Research Triangle Park, NC

National Toxicology Program (1999d) *Toxicology and Carcinogenesis Studies of Oleic Acid Diethanolamine Condensate in F344/N Rats and B6C3F$_1$ Mice (Dermal Studies)* (Tech. Rep. Ser. No. 481; NIH Publication No. 99-3971), Research Triangle Park, NC

National Toxicology Program (1999e) *Toxicology and Carcinogenesis Studies of Triethanolamine (CAS No. 102-71-6) in F344/N Rats and B6C3F$_1$ Mice (Dermal Studies)* (Tech. Rep. Ser. No. 449; NIH Publication No. 00-3365), Department of Health and Human Services, Research Triangle Park, NC

NOES (1999) *National Occupational Exposure Survey 1981–83*. Unpublished data as of July 1999. Cincinnati, OH, Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health

Partanen, T. & Boffetta, P. (1994) Cancer risk in asphalt workers and roofers: review and meta-analysis of epidemiologic studies. *Am. J. ind. Med.*, **26**, 721–740

Pfeiffer, W., Breuer, D., Blome, H., Deininger, C., Hahn, J.-U., Kleine, H., Nies, E., Pflaumbaum, W., Stockmann, R., Willer, G. & Sonnenschein, G. (1996) *Kühlschmierstoffe* [*Cutting Oils*], Sankt Augustin, Hauptverband der gewerblichen Berufsgenossenschaften, Germany (BIA-Report 7/96) (in German)

Pietsch, J., Schmidt, W., Sacher, F., Brauch, H.-J. & Worch, E. (1997) Liquid chromatographic determination of polar organic nitrogen compounds and their behaviour during drinking water treatment. *Vom Wasser*, **88**, 119–135

Piipari, R., Tuppurainen, M., Tuomi, T., Mäntylä, L., Henriks-Eckerman, M.-L., Keskinen, H. & Nordman, H. (1998) Diethanolamine-induced occupational asthma: a case report. *Clin. exp. Allergy*, **28**, 358–362

Pomfret, E.A., daCosta, K.A. & Zeisel, S.H. (1990) Effects of choline deficiency and methotrexate treatment upon rat liver. *J. Nutr. Biochem.*, **1**, 533–541

Preussmann, R., Spiegelhalder, B., Eisenbrand, G., Würtele, G. & Hofmann, I. (1981) Urinary excretion of *N*-nitrosodiethanolamine in rats following its epicutaneous and intratracheal administration and its formation *in vivo* following skin application of diethanolamine. *Cancer Lett.*, **13**, 227–231

Sadtler Research Laboratories (1980) *Sadtler Standard Spectra*, 1980 Cumulative Index (Molecular Formula Index), Philadelphia, PA, p. 51

Schubert, B.A., Hohaus, E., Dengel, H.S., Riepe, W. & Maurer, W. (1996) Determination of alkanolamines in water-miscible cooling lubricants by capillary zone electrophoresis. *Gefahrst. Reinhalt. Luft*, **56**, 393–399

Sollenberg, J. (1997) Isotachophoretic determination of ethanolamines in metalworking fluids and in air samples from workrooms. *Proc. Control Quality*, **10**, 313–317

Sorsa, M., Pyy, L., Salomaa, S., Nylund, L. & Yager, J.W. (1988) Biological and environmental monitoring of occupational exposure to cyclophosphamide in industry and hospitals. *Mutat. Res.*, **204**, 465–479

Spalding, J.W., French, J.E., Stasiewicz, S., Furefi-Machacek, M., Conner, F., Tice, R.R. & Tennant, R.W. (2000) Responses of transgenic mouse lines p53± and Tg·AC to agents tested in conventional carcinogenicity bioassays. *Toxicol. Sci.*, **53**, 213–223

Stott, W.T., Bartels, M.J., Brzak, K.A., Mar, M.-H., Markham, D.A., Thornton, C.M. & Zeisel, S.H. (2000) Potential mechanisms of tumorigenic action of diethanolamine in mice. *Toxicol. Lett.*, **114**, 67–75

Sullivan, P.A., Eisen, E.A., Woskie, S.R., Kriebel, D., Wegman, D.H., Hallock, M.F., Hammond, S.K., Tolbert, P.E., Smith, T.J. & Monson, R.R. (1998) Mortality studies of metalworking fluid exposure in the automobile industry: VI. A case–control study of esophageal cancer. *Am. J. ind. Med.*, **34**, 36–48

Sun, J.D., Beskitt, J.L., Tallant, M.J. & Frantz, S.W. (1996) In vitro skin penetration of monoethanolamine and diethanolamine using excised skin from rats, mice, rabbits, and humans. *J. Toxicol.- cut. ocular Toxicol.*, **15**, 131–146

Tolbert, P.E., Eisen, E.A., Pothier, L.J., Monson, R.R., Hallock, M.F. & Smith, T.J. (1992) Mortality studies of machining fluid exposure in the automobile industry. II. Risks associated with specific fluid types. *Scand. J. Work Environ. Health*, **18**, 351–360

Verschueren, K. (1996) *Handbook of Environmental Data on Organic Chemicals*, 3rd Ed., New York, Van Nostrand Reinhold, pp. 753–756

Waechter, J.M., Bormett, G.A. & Stewart, H.S. (1995) *Diethanolamine: Pharmacokinetics in Sprague-Dawley Rats Following Dermal or Intravenous Administration*, Midland, MI, Dow Chemical Company

Yordy, J.R. & Alexander, M. (1981) Formation of N-nitrosodiethanolamine from diethanolamine in lake water and sewage. *J. environ. Qual.*, **10**, 266–270

Zeisel, S.H. (1996) Choline. A nutrient that is involved in the regulation of cell proliferation, cell death and cell transformation. In: Hebver & Kritchevsky, eds, *Dietary Fats, Lipids, Hormones and Tumorigenesis*, New York, Plenum Press, pp. 131–141