AZIRIDINE

Data were last reviewed in IARC (1975) and the compound was classified in *IARC Monographs* Supplement 7 (1987).

1. Exposure Data

1.1 Chemical and physical data

1.1.1 *Nomenclature*

Chem. Abstr. Serv. Reg. No.: 151-56-4
Chem. Abstr. Name: Aziridine
IUPAC Systematic Name: Ethylenimine
Synonyms: Azacyclopropane; dimethylenimine; ethyleneimine

1.1.2 *Structural and molecular formulae and relative molecular mass*

C_2H_5N Relative molecular mass: 43.07

1.1.3 *Chemical and physical properties of the pure substance*

(*a*) *Description*: Clear, colourless oily liquid with an intense odour of ammonia (American Conference of Governmental Industrial Hygienists, 1991; Budavari, 1996; Verschueren, 1996)
(*b*) *Boiling-point*: 56°C (Lide, 1997)
(*c*) *Melting-point*: –77.9°C (Lide, 1997)
(*d*) *Solubility*: Miscible with water; very soluble in diethyl ether; soluble in ethanol; and slightly soluble in chloroform (Budavari, 1996; Lide, 1997)
(*e*) *Vapour pressure*: 21 kPa at 20°C; relative vapour density (air = 1), 1.5 (Verschueren, 1996)
(*f*) *Flash point*: –11°C, closed cup (American Conference of Governmental Industrial Hygienists, 1991)
(*g*) *Reactivity*: Polymerizes explosively in contact with silver, aluminium or acid (American Conference of Governmental Industrial Hygienists, 1991; Budavari, 1996)

(*h*) *Explosive limits*: Upper, 46%; lower, 3.6% by volume in air (American Conference of Governmental Industrial Hygienists, 1991)
(*i*) *Conversion factor*: $mg/m^3 = 1.76 \times ppm$

1.2 Production and use

Global production capacity for aziridine is more than 12 000 tonnes per year (Scherr *et al.*, 1995). Information available in 1995 indicated that it was produced in Germany and Japan (Chemical Information Services, 1995).

Aziridine is an intermediate and monomer in the preparation of cationic polymers, such as polyaziridine (polyethyleneimine). These polymers are used to improve wet strength of paper, in fuel-oil and lubricant refining, as flocculating agents and in protective coatings, in textile finishing and for adhesives, polymer stabilizers, and surfactants (Lewis, 1993; Scherr *et al.*, 1995).

1.3 Occurrence

1.3.1 *Occupational exposure*

According to the 1981–83 National Occupational Exposure Survey (NOES, 1997), approximately 1000 workers in the United States were potentially exposed to aziridine (see General Remarks). Occupational exposures to aziridine may occur in its production and in the preparation of polyaziridine polymers.

1.3.2 *Environmental occurrence*

No data on the environmental occurrence of aziridine were available to the Working Group.

1.4 Regulations and guidelines

The American Conference of Governmental Industrial Hygienists (ACGIH) (1997) has recommended 0.88 mg/m^3 as the 8-h time-weighted average threshold limit value, with a skin notation, for occupational exposures to aziridine in workplace air. Similar values have been used as standards or guidelines in many countries (International Labour Office, 1991). It is listed as an animal carcinogen in Germany (Deutsche Forschungsgemeinschaft, 1998).

No international guideline for aziridine in drinking-water has been established (WHO, 1993).

2. Studies of Cancer in Humans

No data were available to the Working Group.

3. Studies of Cancer in Experimental Animals

Aziridine has been tested for carcinogenicity in two strains of mice by oral administration, producing an increased incidence of liver-cell and pulmonary tumours. Subcutaneous injection of single doses in suckling mice produced an increased incidence of lung tumours in males. In one experiment in rats, aziridine increased the incidence of tumours at the injection site following its subcutaneous injection in oil (IARC, 1975).

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*

[^{14}C]Aziridine injected intraperitoneally into rats is widely distributed, with some accumulation of radioactivity in liver, intestines, spleen and kidney. About half of the radioactivity was excreted in urine, 3–5% was expired as carbon dioxide and 1–3% was expired otherwise, probably as aziridine (IARC, 1975).

4.2 Toxic effects

4.2.1 *Humans*

No data were available to the Working Group.

4.2.2 *Experimental systems*

Degenerative changes occur in many organs of rats after administration of aziridine by various routes, including inhalation (IARC, 1975). Acute renal papillary necrosis is produced in rats and dogs administered aziridine. At low doses in rats, there was necrosis of interstitial cells, thin limbs of the loops of Henlé and vasa recta, while collecting ducts were spared. At higher doses, there was total papillary necrosis (Ellis *et al*., 1973; Ellis & Price, 1975; Axelsen, 1978).

4.3 Reproductive and developmental effects

No data were available to the Working Group.

4.4 Genetic and related effects

4.4.1 *Humans*

No data were available to the Working Group.

4.4.2 *Experimental systems* (see Table 1 for references)

The mutagenicity of aziridine has been reviewed (Verschaeve & Kirsch-Volders, 1990). In particular, the many studies of the effects of aziridine on plants are referenced and discussed; these data are not addressed in the present review or in the accompanying table.

Aziridine induces gene mutations in *Salmonella typhimurium* and cultured Chinese hamster ovary CHO cells and sex-linked recessive lethal mutations in *Drosophila melanogaster*. It also induces gene conversion in *Saccharomyces cerevisiae* but not chromosomal loss in *D. melanogaster*. In cultured mammalian cell lines, it induces DNA strand breakage and chromosomal aberrations. Dominant lethal effects were induced in both *D. melanogaster* and mice. Adducts are formed between aziridine and [^{14}C]- or [^{3}H]-guanosine *in vitro* at pH 5–8, although the reaction rate was greater at pH values below 7. Two adducts were identified: imidazole-ring opened 7-alkylguanosine and 1-alkylguanosine, which accounted for 80% and 14% of all adduct radioactivity, respectively. At pH 6, intact 7-alkylation products were formed (Hemminki, 1984). The importance of ring-opening of the modified guanine (forming formamidopyrimidine residues) in mutagenesis has been investigated in CHO cells expressing the *E. coli fpg* gene, which encodes a DNA glycosylase that removes formamidopyrimidine residues (Cussac & Laval, 1996). At an aziridine concentration of 2 mM, the mutation frequency was reduced by at least 50% in the cells expressing *fpg*. In contrast, CHO cells transfected with rat *APDG* cDNA (encoding rat *N*3-methyladenine-DNA glycosylase, which removes both *N*3- and *N*7-alkylguanine residues) showed no reduction in mutation frequency when treated with aziridine. Thus, imidazole ring opening appears to be an important step in aziridine mutagenicity.

4.4.3 *Mechanistic consideration*

Based on the known chemical reactivity of aziridine and its ability to form adducts with DNA, sex-linked recessive lethal mutations in *Drosophila*, dominant lethal effects in *Drosophila* and mice, and gene mutation at the *hrpt* locus of CHO cells *in vitro*, it is probable that the biological effects of aziridine would be expressed in any mammalian species.

5. Summary of Data Reported and Evaluation[1]

5.1 Exposure data

Aziridine is a highly reactive and volatile chemical. Exposure to the compound may occur during its use as an intermediate and monomer in the production of cationic polymers.

---

[1] Summary (but not the evaluation) prepared by the Secretariat after the meeting.

Table 1. Genetic and related effects of aziridine

Test system	Result[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
SA0, *Salmonella typhimurium* TA100, reverse mutation	+	NT	5	McCann *et al*. (1975)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	+	NT	5	McCann *et al*. (1975)
SCG, *Saccharomyces cerevisiae* D4, gene conversion	+	NT	860	Zimmerman (1971)
DMX, *Drosophila melanogaster*, sex-linked recessive lethal mutations	+		NG	Shvartsman & Sharygina (1982)
DMX, *Drosophila melanogaster*, sex-linked recessive lethal mutations	+		NG	Shvartsman *et al*. (1985)
DMX, *Drosophila melanogaster*, sex-linked recessive lethal mutations	+		43 feed	Zijlstra & Vogel (1988)
DMN, *Drosophila melanogaster*, ring-X chromosome loss	–		43 feed	Zijlstra & Vogel (1988)
DML, *Drosophila melanogaster*, dominant lethal test	+		NG	Shvartsman & Sharygina (1982)
DML, *Drosophila melanogaster*, dominant lethal test	+		430 inj	Šrám (1970)
DIH, DNA single-strand breaks, HeLa S3 cells *in vitro*	+	NT	21	Painter (1978)
GCO, Gene mutation, Chinese hamster ovary CHO cells, various loci *in vitro*	+	NT	2	Gupta & Singh (1982)
GCO, Gene mutation, Chinese hamster ovary CHO cells, *hprt* locus *in vitro*	+	NT	21	Cussac & Laval (1996)
CIH, Chromosomal aberrations, human WI-36 cells and leukocytes *in vitro*	+	NT	4	Chang & Elequin (1967)
DLM, Dominant lethal test, male C57BL/6 mice	+		5 ip × 1	Dean *et al*. (1981)

[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; NG, not given; inj; injection; ip, intraperitoneal

5.2 Human carcinogenicity data

No data were available to the Working Group.

5.3 Animal carcinogenicity data

Aziridine was tested for carcinogenicity in mice by oral administration, producing an increased incidence of liver-cell and pulmonary tumours. Subcutaneous injection of single doses in suckling mice produced an increased incidence of lung tumours in males. In one experiment in rats it increased the incidence of tumours at the injection site following injection in oil.

5.4 Other relevant data

Aziridine produces genetic damage in bacteria, insects and mammalian cells in culture, as well as dominant lethal effects in mice. Opening of the aziridine ring appears to be an important metabolic step in its mutagenic action.

5.5 Evaluation

No epidemiological data relevant to the carcinogenicity of aziridine were available.

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

Overall evaluation

Aziridine is *possibly carcinogenic to humans (Group 2B)*.

In making the overall evaluation, the Working Group took into consideration that aziridine is a direct-acting alkylating agent which is mutagenic in a wide range of test systems and forms DNA adducts that are promutagenic.

6. References

American Conference of Governmental Industrial Hygienists (1991) *Documentation of the Threshold Limit Values and Biological Exposure Indices*, 6th Ed., Vol. 1, Cincinnati, OH, pp. 628–630

American Conference of Governmental Industrial Hygienists (1997) *1997 TLVs® and BEI®*, Cincinnati, OH, p. 24

Axelsen, R.A. (1978) Experimental renal papillary necrosis in the rat: the selective vulnerability of medullary structures to injury. *Virchows Arch. A. Pathol. Anat.,* **381,** 79–84

Budavari, S., ed. (1996) *The Merck Index*, 12th Ed., Whitehouse Station, NJ, Merck & Co., p. 648

Chang, T.H. & Elequin, F.T. (1967) Induction of chromosome aberrations in cultured human cells by ethylenimine and its relation to cell cycle. *Mutat. Res.,* **4,** 83–89

Chemical Information Services (1995) *Directory of World Chemical Producers 1995/96 Edition*, Dallas, TX

Cussac, C. & Laval, F. (1996) Reduction of the toxicity and mutagenicity of aziridine in mammalian cells harboring the *Escherichia coli fpg* gene. *Nucleic Acids Res.,* **24,** 1742–1746

Dean, B.J., Anderson, D. & Šrám, R.J. (1981) Mutagenicity of selected chemicals in the mammalian dominant lethal assay in comparative chemical mutagenesis. *Environ. Sci. Res.,* **24,** 487–538

Deutsche Forschungsgemeinschaft (1998) *List of MAK and BAT Values 1998* (Report No. 34), Weinheim, Wiley-VCH Publisher, p. 58

Ellis, B.G. & Price, R.G. (1975) Urinary enzyme excretion during renal papillary necrosis induced in rats with ethyleneimine. *Chem.-biol. Interact.,* **11**, 473–482

Ellis, B.G., Price, R.G. & Topham, J.C. (1973) The effect of papillary damage by ethyleneimine on kidney function and some urinary enzymes in the dog. *Chem.-biol. Interact.,* **7**, 131–141

Gupta, R.S. & Singh, B. (1982) Mutagenic responses of five independent genetic loci in CHO cells to a variety of mutagens. Development and characteristics of a mutagen screening system based on selection for multiple drug-resistant markers. *Mutat. Res.,* **94**, 449–466

Hemminki, K. (1984) Reactions of ethyleneimine with guanosine and deoxyguanosine. *Chem.-biol. Interact.,* **48,** 249–260

IARC (1975) *IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man*, Vol. 9, *Some Aziridines, N-, S- & O-Mustards and Selenium*, Lyon, pp. 37–46

IARC (1987) *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Suppl. 7, *Overall Evaluations of Carcinogenicity: An Updating of* IARC Monographs *Volumes 1 to 42*, Lyon, p. 58

International Labour Office (1991) *Occupational Exposure Limits for Airborne Toxic Substances*, 3rd Ed. (Occupational Safety and Health Series No. 37), Geneva, pp. 36–37

Lewis, R.J., Jr (1993) *Hawley's Condensed Chemical Dictionary*, 12th Ed., New York, Van Nostrand Reinhold, pp. 490–491

Lide, D.R., ed. (1997) *CRC Handbook of Chemistry and Physics*, 78th Ed., Boca Raton, FL, CRC Press, p. 3-16

McCann, J., Choi, E., Yamasaki, E. & Ames, B.N. (1975) Detection of carcinogens as mutagens in the *Salmonella*/microsome test: assay of 300 chemicals. *Proc. natl Acad. Sci. USA,* **72,** 5135–5139

NOES (1997) *National Occupational Exposure Survey 1981–83*, Unpublished data as of November 1997, Cincinnati, OH, United States Department of Health and Human Services, Public Health Service, National Institute for Occupational Safety and Health

Painter, R.B. (1978) Inhibition of DNA replicon initiation by 4-nitroquinoline 1-oxide, adriamycin, and ethyleneimine. *Cancer Res.,* **38,** 4445–4449

Scherr, G., Steuerle, U. & Fikentscher, R. (1995) Imines, cyclic. In: Kroschwitz, J.I. & Howe-Grant, M., eds, *Kirk-Othmer Encyclopedia of Chemical Technology*, 4th Ed., Vol. 14, New York, John Wiley, pp. 2–40

Shvartsman, P.Y., Bondarenko, L.V. & Romashkina, T.B. (1985) Differential cell mutability during oogenesis and exposure to ethyleneimine and ethylmethane sulfonate in different *Drosophila melanogaster* lines. *Genetika*, **21**, 958–963 (in Russian)

Shvartsman, P.Y. & Sharygina, N.V. (1982) Study of the mechanism of inactivation and mutagenesis under the effect of ethylenimine in the germ cells of *Drosophila*. 8. Protective action of formaldehyde and acetic acid. *Soviet Genetics,* **18**, 718–726 (in Russian)

Šrám, R.J. (1970) The effect of storage on the frequency of dominant lethals in *Drosophila melanogaster*. *Mol. gen. Genet.,* **106,** 286–288

United States National Library of Medicine (1998*) Hazardous Substances Data Bank (HSDB)*, Bethesda, MD [Record No. 540]

Verschaeve, L. & Kirsch-Volders, M. (1990) Mutagenicity of ethyleneimine. *Mutat. Res.,* **238,** 39–55

Verschueren, K. (1996) *Handbook of Environmental Data on Organic Chemicals*, 3rd Ed., New York, Van Nostrand Reinhold, pp. 975–976

WHO (1993) *Guidelines for Drinking Water Quality*, 2nd Ed., Vol. 1, *Recommendations*, Geneva

Zijlstra, J.A. & Vogel, E.W. (1988) The ratio of induced recessive lethals to ring-X loss has prognostic value in terms of functionality of chemical mutagens in *Drosophila melanogaster*. *Mutat. Res.,* **201,** 27–38

Zimmermann, F.K. (1971) Induction of mitotic gene conversion by mutagens. *Mutat. Res.*, **11**, 327–337