

CHLORNAPHAZINE

Chlornaphazine was considered by previous IARC Working Groups in 1973 and 1987 ([IARC, 1974, 1987a](#)). Since that time, new data have become available, these have been incorporated into the *Monograph*, and taken into consideration in the present evaluation.

1. Exposure Data

1.1 Identification of the agent

Chem. Abstr. Serv. Reg. No.: 494-03-1

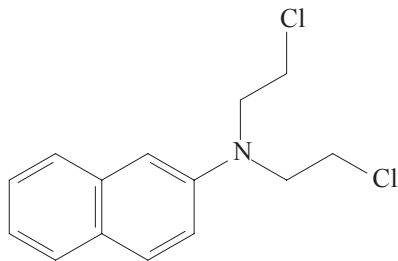
Chem. Abstr. Name: 2-Naphthalenamine, *N,N*-bis(2-chloroethyl)-

IUPAC Systematic Name: *N,N*-Bis(2-chloroethyl)naphthalen-2-amine

Synonyms: Bis(2-chloroethyl)-2-naphthylamine; chloronaphthine; di(2-chloroethyl)- β -naphthylamine; *N,N*-naphthylamine mustard; β -naphthylbis(β -chloroethyl)amine; β -naphthyl-di(2-chloroethyl)amine

Description: platelets ([O'Neil, 2006](#))

1.1.1 Structural and molecular formulae, and relative molecular mass



$C_{14}H_{15}Cl_2N$

Relative molecular mass: 268.2

1.2 Use of the agent

1.2.1 Indications

Chlornaphazine was used clinically in several countries as a chemotherapeutic agent for the treatment of Hodgkin lymphoma, as well as for the control of *polycythaemia vera* ([Thiede et al., 1964](#); [Videbaek, 1964a](#)).

The US National Toxicology Program ([NTP, 1980](#)) found no evidence that chlornaphazine had ever been produced or used commercially in the United States of America.

1.2.2 Dosage

No information (other than that given above) was available to the Working Group.

1.2.3 Trends in use

Chlornaphazine is not known to be used currently.

Table 3.1 Studies of cancer in experimental animals exposed to chlornaphazine

Species, strain (sex) Duration Reference	Route Dosing regimen, Animals/group at start	Incidence of tumours	Significance	Comments
Rat (strain & sex NR) Duration NR Koller (1953)	s.c. Injections of 40 mg over “several” months Initial number NR	Local sarcomas in 7 animals	NR	Purity NR; no control animals; very few details provided
Mouse, A/J (M, F) 39 wk Shimkin et al. (1966)	i.p. Injection in 200 µl 0.5% acacia of 0, 280, 1119, 4477 and 17910 µmol/kg bw (total dose) 3 injections/wk for 4 wk 360, 30, 30, 30, 30	Lung (adenomas and adenocarcinomas): 124/330, 12/30, 18/29, 25/29 and 25/25 Tumours per mouse: 0.48, 0.5, 0.9, 2.0 and 3.6	[p<0.01] (three highest doses; incidence)	Purity NR

bw, body weight; F, female; i.p., intraperitoneal; M, male; NR, not reported; s.c., subcutaneous; wk, week or weeks

2. Cancer in Humans

The previous evaluation of chlornaphazine was based on one report of three cases ([Videbaek, 1964b](#)), and one analytical study ([Thiede & Christensen, 1975](#)), described below.

Among 61 patients (34 men and 27 women) with *polycythaemia vera* treated with chlornaphazine in one Danish hospital department during 1954–62 and followed up until 1974, eight developed invasive carcinoma of the bladder, five developed papillary carcinoma grade II of the bladder, and eight had abnormal urinary cytology. [The Working Group noted that approximately 0.7 cases of bladder cancer and papillomas would have been expected using appropriate Danish incidence rates, giving a relative risk of about 20.] The invasive carcinomas were seen in four of five patients treated with a cumulative dose of 200 g or more, in two of 15 patients given 100–199 g, in one of ten patients given 50–99 g, and in one of 31 patients given less than 50 g ([Thiede & Christensen, 1975](#)). [The Working Group noted that no relative risk were reported.]

No additional relevant data were available to the Working Group.

3. Cancer in Experimental Animals

In one study, subcutaneous injection of rats with chlornaphazine induced local sarcomas; and in another, intraperitoneal injection of mice with chlornaphazine increased the incidence of combined benign and malignant lung tumours. ([IARC, 1974, 1987a; Table 3.1](#)).

No additional studies were available to the Working Group.

4. Other Relevant Data

The only data available on the metabolism of chlornaphazine was a study in rats administered chlornaphazine. Sulfate esters of 2-naphthylamine were excreted in the urine ([Boyland & Manson, 1963](#)).

In the previous *IARC Monograph* ([IARC, 1987b](#)), it was reported that chlornaphazine exhibits mutagenic/genotoxic activity in various experimental systems. Chlornaphazine induced chromosomal aberrations in Chinese hamster cells, mutations in mouse lymphoma cells, and unscheduled DNA synthesis in rat hepatocytes *in vitro*. A single study of cell transformation

in virus-infected Syrian hamster embryo cells was inconclusive. Chlornaphazine induced sex-linked recessive lethal mutations and chromosomal aberrations in *Drosophila*.

In a subsequent study, chlornaphazine was shown to induce chromosomal aberrations in Chinese hamster lung cells, micronuclei in the bone-marrow cells of mice and rats, and to be mutagenic to *Salmonella typhimurium*, with and without, a metabolic activating system (Ashby *et al.*, 1988). After intraperitoneal administration, chlornaphazine induced dominant lethal mutations in mouse germ cells (Barnett & Lewis, 2003).

No data were available on the genetic and related effects of chlornaphazine in humans.

Chlornaphazine is a bifunctional alkylating agent with mutagenic/genotoxic activity. In addition, the presence of sulfate esters of 2-naphthylamine as intermediates in the metabolism of chlornaphazine in rats is consistent with the production of 2-naphthylamine, and the increased incidence of bladder tumours in humans (IARC, 2010, and Volume 100F, IARC, 2012).

5. Evaluation

There is *sufficient evidence* in humans for the carcinogenicity of chlornaphazine. Chlornaphazine causes cancer of the urinary bladder.

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

Chlornaphazine is *carcinogenic to humans* (Group 1).

References

- Ashby J, Loquet C, Ishidate M Jr *et al.* (1988). Mutagenicity to bacteria, cultured cells, and rodents of the human carcinogen chlornaphazine. *Environ Mol Mutagen*, 12: 365–374. PMID:3056719
- Barnett LB & Lewis SE (2003). Chlornaphazine and chlornambucil induce dominant lethal mutations in male mice. *Mutat Res*, 543: 145–154. doi:10.1016/S1383-5742(03)00012-7 PMID:12644184
- Boyland E, Manson D (1963). *Metabolism of 2-naphthylamine and its derivatives*. In: *A R Brit Emp Cancer Campaign for Research*, 41. Institute of Cancer Research, pp. 69–70.
- IARC. (1974). Some aromatic amines, hydrazine and related substances, N-nitroso compounds and miscellaneous alkylating agents. *IARC Monogr Eval Carcinog Risk Chem Man*, 4: 1–286.
- IARC (1987a). Overall evaluations of carcinogenicity: an updating of IARC Monographs volumes 1 to 42. *IARC Monogr Eval Carcinog Risks Hum Suppl*, 7: 1–440. PMID:3482203
- IARC (1987b). Genetic and related effects: An updating of selected IARC monographs from Volumes 1 to 42. *IARC Monogr Eval Carcinog Risks Hum Suppl*, 6: 1–729. PMID:3504843
- IARC (2010). Aromatic amines, organic dyes, and related exposures. *IARC Monogr Eval Carcinog Risks Hum*, 99: 1–704..
- IARC (2012). Chemical agents and related occupations. *IARC Monogr Eval Carcinog Risks Hum*, 100F:
- Koller PC (1953). Dicentric chromosomes in a rat tumour induced by an aromatic nitrogen mustard. *Heredity*, 6: 181–196.
- NTP (1980). *First Annual Report on Carcinogens*, Vol. 2. Department of Health and Human Services, pp. 66–67.
- O’Neil MJ, editor (2006). *The Merck Index*, 14th ed. Whitehouse Station, NJ: Merck & Co., Inc., pp. 349–350.
- Shimkin MB, Weisburger JH, Weisburger EK *et al.* (1966). Bioassay of 29 Alkylating Chemicals by the Pulmonary-Tumor Response in Strain A Mice. *J Natl Cancer Inst*, 36: 915–935.
- Thiede T, Chievitz E, Christensen BC (1964). Chlornaphazin as a bladder carcinogen. *Acta Med Scand*, 175: 721–725. doi:10.1111/j.0954-6820.1964.tb00628.x PMID:14171978
- Thiede T & Christensen BC (1975). Bladder tumors induced by chlornaphazine treatment. *Ugeskr Laeger*, 137: 661–666. PMID:1145787
- Videbaek A (1964a). Chlornaphazin (Erysan®) may induce cancer of the urinary bladder. *Acta Med Scand*, 176: 45–50. doi:10.1111/j.0954-6820.1964.tb00643.x PMID:14194189
- Videbaek A (1964b). Bladder cancer developing during treatment with chlornaphazin (erysan). *Ugeskr Laeger*, 126: 62–66. PMID:14118452

