TRICHLORMETHINE (TRIMUSTINE HYDROCHLORIDE)

This substance was considered by a previous Working Group, in April 1975, under the title trichlorotriethylamine hydrochloride (IARC, 1975). Since that time, new data have become available, and these have been incorporated into the monograph and taken into consideration in the present evaluation.

1. Chemical and Physical Data

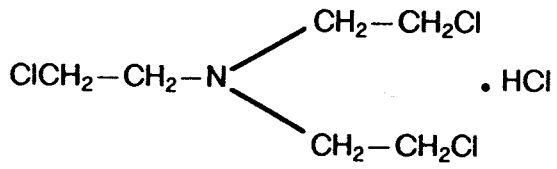
1.1 Synonyms

Chem. Abstr. Services Reg. No.: 817-09-4

Chem. Abstr. Name: Ethanamine-2-Chloro-*N*,*N*-bis(2-chloroethyl) hydrochloride

Synonyms: HN3[1]; HN3 hydrochloride NSC-30211; R-47; SK-100; tri(β-chloroethyl)amine hydrochloride; trichlorotriethylamine hydrochloride; 2,2′,2″-trichlorotriethylamine hydrochloride; trimustine[1]; tris(2-chloroethyl)-amine hydrochloride; tris(β-chloroethyl)amine hydrochloride; tris(2-chloroethyl)amine monohydrochloride; tris(β-chloroethyl)amine monohydrochloride; tris-*N*-lost; TS-160

1.2 Structural and molecular formulae and molecular weight



$C_6H_{12}Cl_3N.HCl$ Mol. wt: 241.0

[1]This name is also used for the free base, trichlorotriethylamine.

1.3 Chemical and physical properties of the pure substance

From Reynolds (1982) and Windholz (1983)

(*a*) *Description*: Crystals

(*b*) *Melting-point*: 130-131°C

(*c*) *Solubility*: Very soluble in water; soluble in ethanol

(*d*) *Stability*: Aqueous solutions deteriorate rapidly.

1.4 Technical products and impurities

Trade names: Lekamin; Sinalost; Trillekamin; Trimitan

2. Production, Occurrence, Use and Analysis

2.1 Production and occurrence

Trichlormethine can be prepared by treating triethanolamine with thionyl chloride (Ward, 1935). No current manufacturer is known.

Trichlormethine is not known to occur naturally.

2.2 Use and therapy

Trichlormethine is a cytostatic agent. It was first used in the treatment of Hodgkin's disease and leukaemias in 1946 (Goodman *et al.*, 1946) and subsequently for other neoplastic diseases (Bratzel *et al.*, 1963; Bundesverband der pharmazeutischen Industrie, 1969). It was recognized in the 1977 and 1982 editions of *Martindale. The Extra Pharmacopoeia*, but not in the 1989 edition (Wade, 1977; Reynolds, 1982, 1989).

2.3 Analysis

A colorimetric method in which 4-(4′-nitrobenzyl)pyridine is used as the analytical reagent has been used to analyse for various alkylating agents. Trichlormethine may also be determined by thin-layer chromatography (Epstein *et al.*, 1955; Petering & Van Giessen, 1963; Sawicki & Sawicki, 1969).

3. Biological Data Relevant to the Evaluation of Carcinogenic Risk to Humans

3.1 Carcinogenicity studies in animals

The Working Group was aware of a short letter (Griffin *et al.*, 1950) in which experiments were described with mice and rats injected subcutaneously with trichlormethine.

Subcutaneous administration

Mouse: A group of 20 mice [age, strain and sex unspecified] received weekly subcutaneous injections of trichlormethine [purity unspecified] at 1 mg/kg bw in aqueous solution for ten weeks, after which time only four mice were alive and treatment was terminated. At survival times of 548-567 days, one of the four mice had a lung adenoma, one had a lung carcinoma and one had a lung carcinoma and a spindle-cell sarcoma at the site of injection. In a control group of 40 untreated mice killed between 14 and 18 months of age, six animals had lung adenomas, two had hepatomas and three had enlarged lymph nodes (Boyland & Horning, 1949). [The Working Group noted the very small number of surviving animals.]

Rat: Groups of ten male and ten female random-bred SPF Wistar rats, two months of age, received daily subcutaneous injections of trichlormethine [purity unspecified] at 0.1 or 0.25 mg/kg bw or weekly subcutaneous injections of 1 mg/kg bw in water for six months and were observed for one year after termination of treatment. Total doses were approximately 16.5, 40-42 and 24 mg/kg bw in the three treated groups, respectively. A control group of ten male and ten female rats received injections of 0.3 ml water only for six months. Survival was decreased in males receiving daily injections of trichlormethine. The incidences of sarcomas (mostly spindle-cell type) at the injection site were: males — low daily, 7/10 [$p < 0.0015$]; high daily, 8/10 [$p = 0.0004$]; weekly, 5/10 [$p = 0.016$]; females — low daily, 7/10 [$p < 0.0015$]; high daily, 7/9 [$p = 0.0007$]; weekly, 4/10 [$p = 0.04$]. In the group receiving 0.25 mg/kg bw daily, three males and one female had a mucus-secreting intestinal adenocarcinoma. Tumours were not seen in controls (Sýkora *et al.*, 1981).

3.2 Other relevant data

(*a*) *Experimental systems*

(i) *Absorption, distribution, excretion and metabolism*

No data were available to the Working Group.

(ii) *Toxic effects*

The LD_{50}s for mice, rats, rabbits and dogs after dermal application of trichlormethine were 7, 4.9, 19 and 1 mg/kg bw, respectively. After subcutaneous injections in saline, the LD_{50} for mice was 2.0 mg/kg bw. The LD_{50}s after intravenous injections were 0.7 mg/kg for rats and 2.5 mg/kg bw for rabbits (Anslow *et al.*, 1947).

Trichlormethine caused vomiting, anorexia and blood-containing faeces in dogs a few hours after a single intravenous injection of 1 mg/kg bw. Coma preceded death caused by anoxia as a consequence of peripheral circulatory failure (Houck *et al.*, 1947).

Decreased peripheral lymphocyte counts were observed in rabbits injected intravenously (Friederici, 1955) and in mice injected subcutaneously (Boyland & Horning, 1949) with trichlormethine.

This compound caused cross-links in membrane proteins and haemoglobin in human erythrocytes *in vitro* (Wildenauer & Weger, 1979; Ankel *et al.*, 1986); it alkylated nucleic acids *in vitro* (Szinicz *et al.*, 1981).

(iii) *Effects on reproduction and prenatal toxicity*

No data were available to the Working Group.

(iv) *Genetic and related effects*

Trichlormethine inhibited DNA synthesis and induced mutations at the *hprt* locus of Chinese hamster V79 cells (Slamenova *et al.*, 1983). It induced chromosomal aberrations in transplanted Walker rat carcinoma cells (Boyland *et al.*, 1948) and transplanted Ehrlich and Krebs tumour cells (Koller, 1969) following intraperitoneal injection into animals carrying these cells. [The Working Group noted that these early papers on transplanted tumour cells did not permit detailed evaluation.] A single intraperitoneal treatment with trichlormethine at 5 mg/kg induced dominant lethal mutations in mice (Sýkora & Gandalovicova, 1978).

(*b*) *Humans*

(i) *Pharmacokinetics*

No data were available to the Working Group.

(ii) *Adverse effects*

Lymphopenia, granulocytopenia, thrombocytopenia, anaemia, nausea and vomiting and thrombophlebitis in the vein receiving the infusion were reported after use of trichlormethine (Goodman *et al.*, 1946).

(iii) *Effects on reproduction and prenatal toxicity*

No data were available to the Working Group.

(iv) *Genetic and related effects*

No data were available to the Working Group.

3.3 Case reports and epidemiological studies of carcinogenicity to humans

No data were available to the Working Group.

4. Summary of Data Reported and Evaluation

4.1 Exposure data

Trichlormethine is a cytostatic agent that has been used since 1946 for the treatment of leukaemia and lymphoma.

4.2 Experimental carcinogenicity data

Trichlormethine was tested for carcinogenicity by subcutaneous injection in mice and rats. The study in mice was inadequate for evaluation. In rats, trichlormethine induced a high incidence of sarcomas (mostly spindle-cell type) in animals of each sex at the site of subcutaneous injection, as well as a few intestinal adenocarcinomas; neither tumour type was seen in controls.

4.3 Human carcinogenicity data

No data were available to the Working Group.

4.4 Other relevant data

In single studies, trichlormethine induced dominant lethal mutations in mice and gene mutations in Chinese hamster cells. (See Appendix 1.)

4.5 Evaluation[1]

There is *sufficient evidence* for the carcinogenicity of trichlormethine in experimental animals.

No data were available from studies in humans on the carcinogenicity of trichlormethine.

Overall evaluation

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

5. References

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[1]For description of the italicized terms, see Preamble, pp. 26–29.

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