

Safety Data Sheet

Colchicine

Division of Safety
National Institutes
of Health



WARNING!

THIS COMPOUND IS ACUTELY TOXIC AND TERATOGENIC. IT IS READILY ABSORBED THROUGH THE INTESTINAL TRACT AND TRANSPLACENTALLY. IT MAY CAUSE SEVERE IRRITATION OF MUCOUS MEMBRANES. AVOID FORMATION AND BREATHING OF AEROSOLS.

LABORATORY OPERATIONS SHOULD BE CONDUCTED IN A FUME HOOD, GLOVE BOX, OR VENTILATED CABINET.

AVOID SKIN CONTACT: IF EXPOSED, WASH WITH SOAP AND COLD WATER. AVOID WASHING WITH SOLVENTS AND EXPOSURE TO UV LIGHT. AVOID RUBBING OF SKIN OR INCREASING ITS TEMPERATURE.

FOR EYE EXPOSURE, IRRIGATE IMMEDIATELY WITH LARGE AMOUNTS OF WATER. FOR INGESTION, INDUCE VOMITING. DRINK MILK OR WATER. REFER FOR GASTRIC LAVAGE. FOR INHALATION, REMOVE VICTIM PROMPTLY TO CLEAN AIR. ADMINISTER RESCUE BREATHING IF NECESSARY. REFER TO PHYSICIAN AT ONCE.

IN CASE OF LABORATORY SPILL, WEAR PROTECTIVE CLOTHING DURING CLEAN UP. AVOID SKIN CONTACT OR BREATHING OF AEROSOLS. USE WATER TO DISSOLVE COMPOUND. USE ABSORBENT PAPER TO MOP UP SPILL. DISPOSE OF WASTE SOLUTIONS AND MATERIALS APPROPRIATELY.

A. Background

Colchicine is the major medicinally active alkaloid of Colchicum autumnale L., Liliaceae (autumn crocus, meadow saffron) as well as of many other species of the Liliaceae family. Depending on the method of purification, it is a pale yellow amorphous (scales,

Issued: 2/88

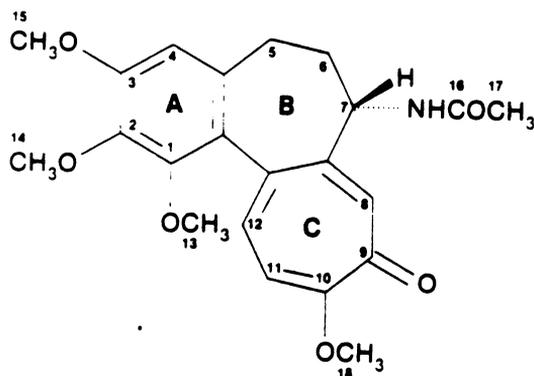
Prepared by the Environmental
Control and Research Program

powder) or crystalline compound, soluble in water, ethanol, and chloroform, and sensitive to UV light. It has been used for many centuries in the treatment of gout and more recently as a general anti-inflammatory agent and in the treatment of Familial Mediterranean Fever. Its chief toxic action is due to a specific binding to tubulin, the subunit protein of microtubules which are structures found in all eukaryotic cells where they participate in mitosis, cell shaping, secretion, motility, and other functions. This binding results in inhibition of tubulin polymerization and, therefore, of mitosis in the anaphase of the normal mitotic cycle.

The chemical and biological properties of colchicine have been reviewed extensively. Recent pertinent references include: Dustin, 1978; Wyatt et al., 1981; Malkinson, 1982; Wilson, 1986.

B. Chemical and Physical Data

1. Chemical Abstract Nos.: 64-86-8 for the biologically active (S) form; 54192-66-4 for the racemic form; 75520-89-7 for the R form.
2. Synonyms: Acetamide, N-(5,6,7,9,-tetrahydro-1,2,3,10-tetra-methoxy-9-oxobenzo[α]heptalen-7-yl)-, (S);^A N-acetyl trimethyl-colchicine acid methyl ether; benzo(α)heptalen-9(5H)-one, 7-acetamido-6,7-dihydro-1,2,3,10-tetramethoxy-.
3. Chemical Structure and Molecular Weight:



$C_{22}H_{25}NO_6$; 399.46

Related compounds (products of chemical, physical, or metabolic degradation)

- a. Colchicine: -OH instead of -OCH₃ at position 10.

^AChemical Abstracts name, used for listings in 9th Decennial Index and subsequently; prior listings under "colchicine."

b. Trimethylcolchicinic acid: -OH instead of -OCH₃ at position 10; NH₂ instead of NHCOCH₃.

c. For structures of α -, β -, and γ -lumicolchicine see Wyatt et al., 1981.

Density: No data.

Optical rotation: $[\alpha]_D^{17} = -429^\circ$ in aqueous solution; $[\alpha]_D^{17} = -121^\circ$ in chloroform; for other conditions see Wyatt et al., 1981.

Absorption spectroscopy: Ultraviolet absorption maxima in many solvents have been tabulated; in most solvents there are four absorption maxima in the ranges of 340-355, 240-260, 234, and 199-204 nm. In aqueous solution the following values of λ_{\max} (log ϵ) are listed: 354(4.21); 246(4.50); 234(4.43); 199 (Roight and Leblanc, 1973). Extensive data for infrared, NMR, and mass spectra have been summarized (Wyatt et al., 1981). It is of interest that free colchicine shows little or no fluorescence but has marked fluorescence when bound to tubulin (Akai and Okuyama, 1975).

Volatility: No data; may be regarded as essentially non-volatile.

Solubility: At room temperature 1 g colchicine dissolves in 22 ml water, 220 ml ether, and 100 ml benzene. It is freely soluble in ethanol and chloroform but practically insoluble in petroleum ether.

Description: Pale yellow amorphous scales or powder, needles when crystallized from ethyl acetate. Forms two crystalline compounds with one or two molecules of chloroform which are stable unless heated to 60-70°C. Also forms di- and higher hydrates when crystallized from water. pKa = 12.35 at 20°C; pH of a 5% solution = 5.9.

Boiling point: No data; melting point: There is a considerable range in the literature which is probably due to uncertainties in purity and state of hydration. The melting point after drying at 105°C for 3 hours is 140-141.5°C; other values, which range as high as 155-157°C, are listed by Wyatt et al. (1981).

Stability: Colchicine in aqueous solution (and by implication in solid form) appears to be quite heat stable since such solutions may be autoclaved at 115°C or heated to 98-100°C for 30 minutes when protected from light (Smith et al., 1963). Colchicine darkens in solid form or in solution when exposed to sunlight or ultraviolet light with formation of α , β , and γ lumicolchicines. The β and γ forms are stereoisomers of a compound formed by bridging of the C ring between carbon atoms 8

and 12, and β -lumicolchicine is a head-to-head dimer of β -lumicolchicine (Chapman et al., 1963). Their structures are depicted in Wyatt et al. (1981). These photodegradation products are physiologically inactive, and care must be taken in the storage and analysis of colchicine to prevent exposure to sunlight. Colchicine in ethanolic solution in amber bottles may be stored at -15°C (Ertel and Wallace, 1970).

12. Chemical reactivity: Colchicine is demethylated to colchiceine with dilute acid, and further hydrolyzed with concentrated acid to trimethylcolchicinic acid (see B3 above) (Ertel and Wallace, 1970). Methods for their separation and identification have been described (Lacey and Brady, 1984). Similar hydrolyses are found in strongly alkaline solution ($\text{pH} > 13$). Reduction in presence of platinum oxide catalyst results in hydrogenation of the C ring, while permanganate oxidation destroys the B and C rings and results in trimethoxyphthalic acid. An in vitro system designed to mimic oxidative metabolism in liver microsomes ("Udenfriend system"), consisting of exposure to oxygen in the presence of ascorbic acid, EDTA, and ferrous or cupric ion, results in demethylation at O^2 , O^3 , and O^{10} and a compound in which the C ring is rearranged to a benzenoid structure (Schoenharting et al., 1973).
13. Flashpoint: No data.
14. Autoignition temperature: No data.
15. Explosive limits in air: No data.

Fire, Explosion, and Reactivity Hazard Data

1. Colchicine does not require special fire-fighting procedures or equipment and does not present unusual fire and explosion hazards.
2. Strong alkali, acid, and oxidants contribute to the instability of colchicine.
3. Colchicine is highly sensitive to exposure to visible or ultraviolet light. No other incompatibilities are known.
4. Colchicine does not require nonspark equipment.

Operational Procedures

The NIH Guidelines for the Laboratory Use of Chemical Carcinogens describe operational practices to be followed when potentially carcinogenic chemicals are used in NIH laboratories. The NIH Guidelines should be consulted to identify the proper use conditions required and specific controls to be implemented during normal and complex operations or manipulations involving colchicine.

It should be emphasized that this data sheet and the NIH Guidelines are intended as starting points for the implementation of good laboratory practices when using this compound. The practices and procedures described in the following sections pertain to the National Institutes of Health and may not be universally applicable to other institutions. Administrators and/or researchers at other institutions should modify the following items as needed to reflect their individual management system and current occupational and environmental regulations.

1. Chemical inactivation: No validated method reported.
2. Decontamination: Turn off equipment that could be affected by colchicine or the materials used for clean up. If there is an uncertainty regarding the procedures to be followed for decontamination, call the NIH Fire Department (dial 116) for assistance. Use absorbent paper to mop up spill. Wipe off surfaces with ethanol, then wash with copious quantities of water. Glassware should be rinsed in a hood with ethanol, followed by soap and water. Animal cages should be washed with water.
3. Disposal: No waste streams containing colchicine shall be disposed of in sinks or general refuse. Surplus colchicine or chemical waste streams contaminated with colchicine shall be handled as hazardous chemical waste and disposed of in accordance with the NIH chemical waste disposal system. Nonchemical waste (e.g., animal carcasses and bedding) containing colchicine shall be handled and packaged for incineration in accordance with the NIH medical-pathological waste disposal system. Potentially infectious waste (e.g., tissue cultures) containing colchicine shall be disinfected by heat using a standard autoclave treatment and packaged for incineration, as above. Burnable waste (e.g., absorbent bench top liners) minimally contaminated with colchicine shall be handled as potentially infectious waste and packaged for incineration, as above. Absorbent materials (e.g., associated with spill clean up) grossly contaminated shall be handled in accordance with the chemical waste disposal system. Radioactive waste containing colchicine shall be handled in accordance with the NIH radioactive waste disposal system.
4. Storage: Store solid colchicine and its solutions in dark-colored, tightly closed containers under refrigeration. Avoid exposure to light and moisture. Store working quantities of colchicine and its solutions below -10°C in amber bottles with caps and Teflon cap liners.

Monitoring and Measurement Procedures Including Direct Field Measurements and Sampling for Subsequent Laboratory Analysis

Note: Analytical procedures through 1980 have been covered in detail (Wyatt et al., 1981).

1. Sampling: For any analytical method, care must be taken to avoid exposure to sunlight or ultraviolet light. All authors stress the importance of carrying out urine collections, extractions, centrifugations, etc. in the dark, in glassware wrapped in aluminum foil, or in amber glassware. It is preferable to carry out these operations at low temperatures as rapidly as possible.
2. Analysis: Radioimmunoassay is a method of choice. Schermann et al. (1980) has described a procedure which is faster and more sensitive than those previously described (Boudene et al., 1976; Ertel et al., 1976). The limit of sensitivity is 70 pg per assay tube or 0.35 ng/ml. High performance liquid chromatography in various modifications is tabulated by Wyatt et al. (1981); a particularly rapid method, designed for relatively high levels as a guide in colchicine intoxication, has been described (Lhermite et al., 1985). Fluorimetry of a compound colchicine with isonicotinic hydrazide and gallium chloride has been applied to urine and plasma analysis (Bourdon and Galliot 1976). It has been mentioned (see B6) that the complex of colchicine with tubulin shows marked fluorescence (Akai and Okuyama, 1975) and this reaction has been used in the study of the mechanism of the colchicine-tubulin reaction.

Biological Effects (Animal and Human)

1. Absorption: Colchicine is absorbed from the gastrointestinal tract and presumably, because of its teratogenic effects, transplacentally. It does not penetrate the blood-brain barrier to any significant extent.
2. Distribution and pharmacokinetics: Very few data are available. Radioactivity due to ring-deuterated, parenteral colchicine in various species appears in considerable amounts in the liver within 3 hours (Bennett et al., 1981). The fact that mitosis is inhibited in all structures rich in microtubules (kidney, liver, spleen, brain, cilia, etc.) would indicate that colchicine is distributed to these sites as well.
3. Metabolism and excretion: Very little is known regarding the metabolism of colchicine but there are indications that an active metabolite may be formed. A comparison between the amounts of radioactivity in mouse brain after administration of ring A-4-³H and ring C-methoxy-³H colchicine (far higher activity after the latter) would indicate a certain amount of demethylation at the C¹⁰ site to colchiceine (Bennett et al., 1981). Demethylation also occurs in the A ring with formation

of glucuronides (Hunter and Klaassen, 1975). These in vivo results are mimicked in an in vitro system which simulates oxidative metabolism in liver microsomes (Schoenharting et al., 1973). In rats, 68% of-parenteral colchicine is excreted in the feces in 48 hours; 50% appears in the bile in 2 hours. There is considerable species variation, both in the rate of biliary excretion and the degree of conversion to biliary metabolites (Hunter and Klaassen, 1975).

Toxic effects: There is also a high degree of species variation in toxicity (as well as antimitotic activity) of colchicine: the intraperitoneal LD50s in the golden hamster, mongolian gerbil, Chinese hamster, mouse, and guinea pig are 470, 90, 7.3, 3.5, and 0.5 mg/kg, respectively (Fleischmann et al., 1962). The intravenous LD50 in the rat is 1.6 mg/kg (Rosenbloom and Ferguson, 1968). Ligation of the bile duct in mice and rats increases toxicity considerably (Klaassen, 1973), and intravenous toxicity in pregnant mice is almost three times higher than in nonpregnant ones (Beliles, 1972). Very similar results have been obtained in an in vitro study of the sensitivity of cell lines from various species (Gupta, 1985). These results indicate that a direct extrapolation of toxicity from animal studies to man is not possible.

The principal toxic action of colchicine appears to be its reaction with tubulin, a dimer of two proteins each of molecular weight 55,000. Each dimer has one colchicine-binding site (Garland, 1978). This binding results in prevention of assembly of microtubules. For a discussion of this reaction see Wilson (1986). It is noteworthy that tubulin polymerization of various species is inhibited with about the same sensitivity (Fitzgerald and Mayfield, 1976; Gupta, 1985) and thus cannot explain the species differences in toxicity and antimitotic activity in vivo.

Intravenous colchicine in mice (Rosenbloom and Ferguson, 1968) and rats (Singh et al., 1975) results in a decrease in circulating and concomitant increase in hepatic triglycerides, with formation of vesicles in the liver. These changes are completely reversible and disappear with the reappearance of microtubules.

Colchicine used to be considered a neurotoxin but it is now believed to be a nonspecific anti-inflammatory agent since significant neurological effects are produced only on intracerebral administration (Dasheiff and Ramirez, 1985). Similarly, eye effects (loss of pupillary reflex, temporary blindness) have been noted after intravitreal administration (Vaccarezza et al., 1973).

Toxic symptoms in man during clinical use of colchicine have been summarized (Arena and Drew, 1986). Early symptoms are characteristically delayed by 3-6 hours after even high doses. There may be severe abdominal pain, vomiting, and diarrhea followed by bloody stools due to hemorrhagic gastroenteritis. Shock may develop. Renal symptoms may include hematuria and, in extreme cases, renal failure. The fatal dose in man varies with the individual patient, and while ingestion of as little as 7 mg has been cited as being fatal, others may tolerate much higher doses.

5. Carcinogenic effects: None has been reported. Because of the general effect of colchicine on rapidly dividing cells, it has been speculated that it might also find application as an anticarcinogen; however, there is no mention in the literature of the last 20 years of an actual use in this role, probably because of its high toxicity and the reversibility of its antimitotic effect.
6. Mutagenic and teratogenic effects: Colchicine is not mutagenic in Drosophila (Valencia et al., 1985) or Salmonella (Mortelmans et al., 1986). It is, however, highly teratogenic in the hamster (Ferm, 1963) and mouse (Seidenberg and Becker, 1987).

Emergency Treatment

For further information see Arena and Drew (1986), Dreisbach and Robertson (1987).

1. Skin and eye exposure: For skin exposure, remove contaminated clothing and wash skin with soap and water. Skin should not be rinsed with organic solvents or scanned with UV light. Avoid rubbing of skin or increasing its temperature. For eye exposure, irrigate immediately with copious quantities of running water for at least 15 minutes. Obtain ophthalmological evaluation.
2. Ingestion: Drink plenty of water or milk. Administer activated charcoal. Induce vomiting. Refer for gastric lavage.
3. Inhalation: Remove victim promptly to clean air. Administer rescue breathing if necessary.
4. Refer to physician at once. Consider treatment for pulmonary irritation, shock, and/or abdominal pain.

References

- Akai, T. and T.O. Okuyama. 1975. Fluorometric assay of tubulin-colchicine complex. *Anal Biochem* 69:443-450.
- Arena, J.M. and R.H. Drew (eds). 1986. *Poisoning*, 5th ed. Page 338. Charles C. Thomas, Springfield, IL.

- Beliles, R.P. 1972. The influence of pregnancy on the acute toxicity of various compounds in mice. *Toxicol Appl Pharmacol* 23:537-540.
- Bennett, E.L., M.H. Alberti, and J.F. Flood. 1981. Uptake of [3 H] colchicine into brain and liver of mouse, rat and chick. *Pharmacol Biochem Behav* 14:863-869.
- Boudene, C., F. Duprey, and C. Bohuon. 1975. Radioimmunoassay of colchicine. *Biochem J* 151:413-415.
- Bourdon R. and M Galliot. 1976. Dosage de la colchicine dans les liquides biologiques [Assay of colchicine in biological fluids] *Ann Biol Clin* 34:393-401.
- Chapman, O.L., H.G. Smith, and R.W. King. 1963. The structure of α -lumicolchicine: Some examples of diamagnetic shielding by the carbon-oxygen bond. *J Am Chem Soc* 85:806-812.
- Dasheiff, R.M. and L. Ramirez. 1985. The effects of colchicine in mammalian brain from rodents to rhesus monkeys. *Brain Res Revs* 10:47-67.
- Dreisbach, R.H. and W.O. Robertson. 1987. *Handbook of Poisoning*, 12th ed. Appleton and Lange, Norwalk, CT.
- Dustin, P. 1978. *Microtubules*. Springer-Verlag, New York, NY.
- Ertel, N.H. and S.L. Wallace. 1970. Purification of colchicine, its photoisomer(s), and some congeners by paper and thin-layer chromatography. *Biochem Med* 4:181-192.
- Ertel, N.H., J.C. Mittler, S. Akgun, and S.L. Wallace. 1976. Radioimmunoassay for colchicine in plasma and urine. *Science* 193:233-235.
- Ferm, V.H. 1963. Colchicine teratogenesis in hamster embryos. *Proc Soc Exp Biol Med* 112:775-778.
- Fitzgerald, T.J. and D.G. Mayfield. 1976. Effect of colchicine on polymerization of tubulin from rats, mice, hamsters and guinea pigs. *Experientia* 32:83-84.
- Fleischmann, W., O.Q. Russell, and S.K. Fleischmann. 1962. LD50 and minimal effective antimitotic dose of colchicine in various rodents. *Med Exp* 6:101-104.
- Garland, D.L. 1978. Kinetics and mechanism of colchicine binding to tubulin: Evidence for ligand-induced conformational change. *Biochemistry* 17:4266-4272.
- Gupta, R.S. 1985. Species-specific differences in toxicity of antimitotic agents toward cultured mammalian cells. *J Natl Cancer Inst* 74:159-164.
- Hunter, A.L. and C.D. Klaassen. 1975. Biliary excretion of colchicine. *J Pharmacol Exp Ther* 192:605-617.
- Klaassen, C.D. 1973. Comparison of the toxicity of chemicals in newborn rats to bile duct-ligated and sham-operated rats and mice. *Toxicol Appl Pharmacol* 24:37-44.
- Lacey, E. and R.L. Brady. 1984. Separation of colchicine and related hydrolysis and photodecomposition products by high-performance liquid chromatography, using copper ion complexation. *J Chromatogr* 315:233-241.

- Chermite, M., J.L. Bernier, D. Mathieu, M. Mathieu-Nolf, F. Erb, and P. Roussel. 1985. Colchicine quantitation by high performance liquid chromatography in human plasma and urine. *J Chromatogr* 342:416-423.
- Malkinson, F.D. 1982. Colchicine: New uses for an old, old drug. *Arch Dermatol* 118:453-457.
- Mortelmans, K., S. Haworth, T. Lawlor, W. Speck, B. Tainer, and E. Zeiger. 1986. Salmonella mutagenicity tests. II. Results from the testing of 270 chemicals. *Environ Mutagen* 8 (Suppl 7):1-119.
- Roight, H. and R.M. Leblanc. 1973. Processus photophysiques dans le molécule de colchicine [Photophysical reactions of the colchicine molecule]. *Can J Chem* 51:2821-2827.
- Rosenbloom, S.J. and F.C. Ferguson. 1968. Fatty change in organs of the rat treated with colchicine. *Toxicol Appl Pharmacol* 13:50-61.
- Schermann, J.M., L. Boudet, R. Pontikis, N.-H. Nam, and E. Fournier. 1980. A sensitive radioimmunoassay for colchicine. *J Pharm Pharmacol* 32:800-802.
- Schoenharting, M., P. Pfaender, A. Riecker, and G. Siebert. 1973. Metabolic transformation of colchicine. I. The oxidative formation of products from colchicine in the Udenfriend system. *Hoppe-Seyler's Zeitschr Physiol Chem* 354:421-436.
- Seidenberg, J.M. and R.A. Becker. 1987. A summary of results of 55 chemicals screened for developmental toxicity in mice. *Teratogenesis Carcinog Mutagen* 7:17-28.
- Singh, A., Y. LeMarchand, L. Orci, and B. Jeanrenaud. 1975. Colchicine administration to mice: A metabolic and ultrastructural study. *Eur J Clin Invest* 5:495-505.
- Smith, G., J.M. Bullivant, and P.H. Cox. 1963. Sterilisation of colchicine injection. *J Pharm Pharmacol* 15:92T-96T.
- Vaccarezza, O.L., E. Pasqualini, and J.P. Saavedra. 1973. Retinal alterations induced by intravitreal colchicine. *Virchow's Arch B* 12:159-167.
- Valencia, R., J.M. Mason, R.C. Woodruff, and S. Zimmering. 1985. Chemical mutagenesis testing in Drosophila. III. Results of 48 coded compounds tested for the National Toxicology Program. *Environ Mutagen* 7:325:348.
- Wilson, L. 1986. Microtubules as targets for drug and toxic chemical action: The mechanisms of action of colchicine and vinblastine. in *The Cytoskeleton: A Target for Toxic Agents*. Pages 37-52 Clarkson, T.W., P.R. Sager, and T.L.M. Syversen (eds). Plenum Press, NY.
- Wyatt, D.K., L.T. Grady, and S. Sun. Colchicine. in *Analytic Profiles of Drug Substances*. Pages 139-182, Vol. 10 Florey, K. (ed). Academic Press, NY.