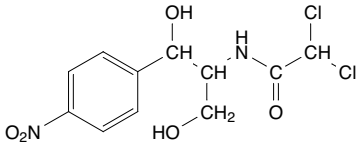
Chloramphenicol

CAS No. 56-75-7

Reasonably anticipated to be a human carcinogen

First listed in the *Tenth Report on Carcinogens* (2002)



Carcinogenicity

Chloramphenicol is *reasonably anticipated to be a human carcinogen*, based on limited evidence of carcinogenicity from studies in humans.

Cancer Studies in Humans

Numerous case reports have shown leukemia to occur after medical treatment for chloramphenicol-induced aplastic anemia, and three case reports have documented the occurrence of leukemia after chloramphenicol therapy in the absence of intervening aplastic anemia (IARC 1990). A case-control study in China found an increased risk of leukemia in children who had been treated with chloramphenicol; the risk increased significantly with increasing number of days the drug was taken (Shu *et al.* 1987, 1988). Two case-control studies found large but statistically nonsignificant increases in the risk of aplastic anemia associated with use of chloramphenicol in the six months before the onset of aplastic anemia (Issaragrisil *et al.* 1997, Laporte *et al.* 1998). However, two other case-control studies found no association between the use of chloramphenicol and the risk of leukemia in adults, suggesting that children may be a particularly susceptible subgroup (Zheng *et al.* 1993, Doody *et al.* 1996). One case-control study found an association between chloramphenicol use and increased risk of soft-tissue sarcoma (Zahm *et al.* 1989). Considered together, the many case reports implicating chloramphenicol as a cause of aplastic anemia, the evidence of a link between aplastic anemia and leukemia, and the increased risk of leukemia found in some case-control studies support the conclusion that chloramphenicol exposure is associated with an increased risk of cancer in humans.

Studies on Mechanisms of Carcinogenesis

Chloramphenicol inhibits protein synthesis in the mitochondria of mammalian cells (by binding to ribosomes), which accounts for the sensitivity of proliferating tissues, such as those that promote the formation of blood cells, to its toxicity. Anemia, including aplastic anemia, is a recognized hazard associated with chloramphenicol treatment in humans. In genotoxicity studies, chloramphenicol gave mainly negative results in bacterial systems and mixed results in mammalian systems. The most consistently positive results were observed for cytogenetic effects in mammalian cells, including DNA single-strand breaks and increased frequencies of sister chromatid exchange and chromosomal aberrations. Overall, chloramphenicol appears to be genotoxic (NTP 2000). Several studies have suggested that dehydrochloramphenicol, a chloramphenicol metabolite produced by intestinal bacteria, may be responsible for DNA damage and carcinogenicity (Isildar *et al.* 1988a,b, Jimenez *et al.* 1990, Kitamura *et al.* 1997). This metabolite can undergo nitroreduction in the bone marrow and has been shown to cause DNA single-strand breaks in bone-marrow cells. Mitochondrial abnormalities caused by chloramphenicol are similar to those observed in preleukemia, suggesting that mitochondrial DNA is involved in the pathogenesis of secondary leukemia.

Cancer Studies in Experimental Animals

No adequate studies of the carcinogenicity of chloramphenicol in experimental animals were identified. In male mice given chloramphenicol by intraperitoneal injection in combination with busulfan (the known human carcinogen 1,4-butanediol dimethanesulfonate), the incidence of lymphoma was significantly higher than in mice receiving either busulfan or chloramphenicol alone (Robin *et al.* 1981).

Properties

Chloramphenicol is a naturally occurring antibiotic derivative of dichloroacetic acid that is a white to grayish or yellowish-white fine crystalline powder at room temperature. It is soluble in water and very soluble in methanol, ethanol, butanol, ethyl acetate, chloroform, and acetone. It is fairly soluble in ether, but insoluble in benzene, petroleum ether, and vegetable oils (IARC 1990, HSDB 2009). It is stable under normal shipping and handling conditions (Akron 2009). The biologically active form of chloramphenicol is levorotatory (Chambers 2001). Physical and chemical properties of chloramphenicol are listed in the following table.

Property	Information
Molecular weight	323.1
Melting point	150°C to 152°C
Log K_{ow}	1.14
Water solubility	25 g/L at 25°C
Vapor pressure	1.7×10^{-12} mm Hg at 25°C

Source: HSDB 2009.

Use

Chloramphenicol is an antimicrobial agent with restricted use, because it causes blood abnormalities. It is used to combat serious infections for which other antibiotics are either ineffective or contraindicated. It can be used against gram-positive cocci and bacilli and gram-negative aerobic and anaerobic bacteria (Burnham *et al.* 2000). Chloramphenicol has been used since the 1950s to combat a wide range of microbial infections, including typhoid fever, meningitis, and certain infections of the central nervous system (IARC 1990). It currently is used in eye ointments and drops to treat superficial ocular infections involving the conjunctiva or cornea, in topical ointments or drops to treat the external ear or skin, in tablets for oral administration, and in intravenous suspensions to treat internal infections (FDA 2009, MedlinePlus 2009). Chloramphenicol has also been used in veterinary medicine as a highly effective and well-tolerated broad-spectrum antibiotic. Because of its tendency to cause blood abnormalities in humans, the U.S. Food and Drug Administration in 1997 banned its use in food-producing animals. Chloramphenicol continues to be used to treat both systemic and local infections in cats, dogs, and horses (FDA 1997, Brooks 2008).

Production

Chloramphenicol is produced naturally by the bacterium *Streptomyces venezuelae*. It may be produced by chemical synthesis followed by a step to isolate stereoisomers. A fermentation process also has been described that does not require separation of stereoisomers (IARC 1990). Chloramphenicol was first produced in the United States in 1948 (IARC 1990). Annual U.S. production was estimated to exceed 908 kg (2,000 lb) in 1977 and 1979 (HSDB 2009). In 2009, chloramphenicol was produced by 16 manufacturers worldwide, including 11 in India, 1 in China, 2 in East Asia, and 2 in Europe (SRI 2009). U.S.

imports of chloramphenicol were estimated at 8,150 kg (17,970 lb) in 1977 and 8,200 kg (18,080 lb) in 1979 (HSDB 2009). Since 1989, annual imports of chloramphenicol and its derivatives have remained at or below 16,000 kg (35,000 lb), averaging 8,000 kg (18,000 lb) from 1989 to 2004. Over the same period, annual U.S. exports of chloramphenicol were less than 53,000 kg (117,000 lb) except in 1993, when 1.9 million kilograms (4 million pounds) were exported. No exports were reported for 1998 or 2000 (USITC 2009). In 2002, less than 10,000 lb of chloramphenicol (U.S. production plus imports) was reported under the U.S. Environmental Protection Agency's Toxic Substances Control Act Inventory Update Rule; no inventory update reports for chloramphenicol were filed before 2002 (EPA 2004).

Exposure

The primary routes of human exposure to chloramphenicol are oral and dermal, through its use as a drug. Exposure also may occur through inhalation, dermal contact, ingestion, or contact with contaminated water or soil (HSDB 2009). For adults, a typical dosage of chloramphenicol is 50 to 100 mg/kg of body weight per day, divided into four oral or intravenous doses (MedlinePlus 2009). Chloramphenicol also is used in ophthalmic ointments, solutions, and drops. It usually is taken for two to five days or until the infection is diminished. For many infections, continued treatment with chloramphenicol after the infection has resolved is suggested, for periods ranging from 48 hours for eye infections to 8 to 10 days for typhoid fever. No information was found on the number of prescriptions currently written for chloramphenicol in the United States. Children, especially newborns and young infants, metabolize chloramphenicol much more slowly than do adults. Pediatric doses must be lower so as to avoid gray-baby syndrome; this syndrome is characterized by cardiovascular collapse in infants, apparently caused by accumulation of active, unconjugated chloramphenicol in the serum, resulting from low inactivation through glucuronide conjugation in the liver (Chambers 2001). Initial dosages are 25 mg/kg of body weight every 24 hours for infants under one week old, 25 mg/kg every 12 hours for infants aged one to four weeks, and 50 mg/kg every 6 hours for children weighing less than about 25 kg (55 lb) (Sills and Boenning 1999).

Chloramphenicol can be detected in blood serum, plasma, cerebrospinal fluid, and urine. It is rapidly absorbed from the gastrointestinal tract and is distributed extensively through the human body, regardless of administration route. It has been found in the heart, lung, kidney, liver, spleen, pleural fluid, seminal fluid, ascitic fluid, and saliva. Upon metabolism, chloramphenicol yields D-*threo*-2-amino-1-(*p*-nitrophenyl)-1,3-propanediol and chloramphenicol-β-D-glucuronide (IARC 1990). Following degradation of chloramphenicol by intestinal bacteria via amidolysis, 18 metabolites were observed, the major ones being 2-amino-1-(*p*-nitrophenyl)-1,3-propanediol and its *p*-aminophenyl reduction by-product (HSDB 2009). Approximately 90% of chloramphenicol is excreted in urine, mostly as metabolites, including conjugated derivatives; only 15% is excreted as the parent compound (IARC 1990). The half-life of chloramphenicol in adult humans ranges from 1.6 to 4.6 hours. Peak levels appear two to three hours after oral administration of chloramphenicol. In adults given eight 1-g doses, once every six hours, the average peak serum level was 11.2 µg/mL one hour after the first dose and 18.4 µg/mL after the fifth dose. Mean serum levels ranged from 8 to 14 µg/mL over the 48-hour period (Burnham *et al.* 2000). In infants, chloramphenicol's half-life is much longer, ranging from 10 to more than 48 hours in infants aged one to eight days and from 5 to 16 hours in infants aged eleven days to eight weeks (IARC 1990).

Chloramphenicol is released to the environment and may be found in various waste streams as a result of its use as a medicinal and research antimicrobial agent. Chloramphenicol may also be isolated from *S. venezuelae* in the soil (HSDB 2009). If released to air, chloramphenicol will exist primarily as an aerosol and will be removed mainly through dry deposition. Chloramphenicol in the atmosphere reacts with photochemically produced hydroxyl radicals, with a half-life of 12 hours. If released to water, chloramphenicol will be essentially nonvolatile. Adsorption to sediment and bioconcentration in aquatic organisms are not expected to be important processes. If released to soil, chloramphenicol is expected to have high mobility. It is not expected to evaporate from either dry or wet soils. Various studies indicate that chloramphenicol may biodegrade in soil and water. It was found to degrade in adapted activated waste sludge (HSDB 2009).

Occupational exposure during the manufacture of chloramphenicol may occur through inhalation, dermal contact, or ingestion (HSDB 2009). Medical and veterinary personnel who administer drugs containing chloramphenicol also may be exposed (Burnham *et al.* 2000, Brooks 2008).

Regulations

Food and Drug Administration (FDA)

Chloramphenicol is a prescription drug subject to specific labeling requirements.
Extra-label use of chloramphenicol in food-producing animals is prohibited.
Chloramphenicol in ophthalmic and topical dosage form and in tablet form must not be used in animals producing meat, eggs, or milk.

Guidelines

National Institute for Occupational Safety and Health (NIOSH)

A comprehensive set of guidelines has been established to prevent occupational exposures to hazardous drugs in health-care settings.

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