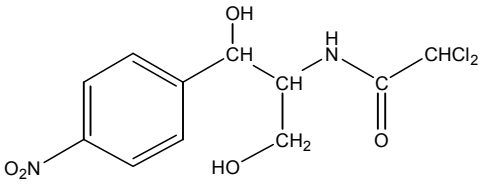
CHLORAMPHENICOL
CAS No. 56-75-7

First listed in the *First Annual Report on Carcinogens*, delisted from *the Second Annual Report on Carcinogens* because human data considered inadequate to list at that time, relisted in *Tenth Report on Carcinogens*



CARCINOGENICITY

Chloramphenicol is *reasonably anticipated to be a human carcinogen*, based on limited evidence of carcinogenicity from studies in humans. Numerous case reports have shown leukemia to occur after medical treatment for chloramphenicol-induced aplastic anemia (IARC 1990). Three case reports have documented the occurrence of leukemia after chloramphenicol therapy in the absence of intervening aplastic anemia (IARC 1990). In a case-control study in China, Shu *et al.* (1987, 1988) found elevated risks of childhood leukemia, which increased significantly with the number of days chloramphenicol was taken. Two case-control studies (Issaragrisil *et al.* 1997, Laporte *et al.* 1998) found high, but nonsignificant, increases in the risk of aplastic anemia associated with the use of chloramphenicol in the six months before onset of aplastic anemia. However, two case-control studies (Zheng *et al*. 1993, Doody *et al.* 1996) found no association between the use of chloramphenicol and the risk of adult leukemia, suggesting that children may be a particularly susceptible subgroup. One report (Zahm *et al.* 1989) found an association between chloramphenicol use and increased risk of soft-tissue sarcoma. 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 cancer risk in humans.

Chloramphenicol administered to mice was reported in an abstract to increase the incidence of lymphoma in two strains and liver tumors in one strain (Sanguineti *et al.* 1983). However, because this study was incompletely reported, the findings are considered insufficient to establish a definitive link between chloramphenicol exposure and cancer in experimental animals.

ADDITIONAL INFORMATION RELEVANT TO CARCINOGENESIS OR POSSIBLE MECHANISMS OF CARCINOGENESIS

The incidence of lymphoma was significantly higher in male mice given chloramphenicol intraperitoneally in combination with busulfan than in other groups of mice receiving either busulfan or chloramphenicol alone (Robin *et al*. 1981).

Chloramphenicol blocks protein synthesis in bacteria by binding to the 50S subunit of the 70S ribosome. Ribosomes in the mitochondria of mammalian cells also are affected, which accounts for the sensitivity of proliferating tissues, such as those that promote the formation of

blood cells, to the toxicity of chloramphenicol. Anemias, including aplastic anemia, are a recognized hazard associated with chloramphenicol treatment in humans.

Several studies (Isildar *et al.* 1988 a,b, Jimenez *et al.* 1990, Kitamura *et al.* 1997) show that dehydrochloramphenicol, a chloramphenicol metabolite produced by intestinal bacteria, may be responsible for DNA damage and carcinogenicity. This metabolite can undergo nitro-reduction in the bone marrow, where it causes DNA single-strand breaks. Mitochondrial abnormalities induced by chloramphenicol are similar to those observed in pre-leukemia, suggesting that mitochondrial DNA is involved in the pathogenesis of leukemia.

The available data on genotoxicity of chloramphenicol show 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 a genotoxin.

PROPERTIES

Chloramphenicol exists as white to grayish-white or yellowish-white fine crystalline powder, needles, or elongated plates, with a melting point of 150.5°C to 151.5°C. It sublimes in high vacuum and is sensitive to light. The nitro group is readily reduced to the amine group. Of the four possible stereoisomers, only the αR, βR (or D-*threo*) form is active (IARC 1990).

Chloramphenicol is soluble in water, chloroform, and ether, and very soluble in propylene glycol, 50% acetamide, methanol, ethanol, butanol, ethyl acetate, and acetone. It is insoluble in benzene, petroleum ether, and vegetable oils.

USE

Chloramphenicol is an antimicrobial agent with restricted use, because it causes blood dyscrasia. 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 (DFC 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 to treat superficial ocular infections involving the conjunctiva or cornea, in topical ointments to treat the external ear or skin, in various tablets for oral administration, and in intravenous suspensions to treat internal infections (PDR 2000). Chloramphenicol also has been used in veterinary medicine as a highly effective and well-tolerated broad-spectrum antibiotic. Because of its tendency to cause blood dyscrasia in humans, the U.S. Food and Drug Administration (FDA) now prohibits its use in food-producing animals. Chloramphenicol continues to be used to treat both systemic and local infections in cats, dogs, and horses (MVM 1998).

An average adult human dose of chloramphenicol is 25 to 100 mg/kg body weight (b.w.) per day, divided into four oral or intravenous doses. Chloramphenicol also is used in ophthalmic preparations, including ointments, solutions, and drops. Dosing usually continues for two to five days or until the infection is diminished. After the infection has resolved, continued treatment with chloramphenicol is suggested for many infections, 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 (DFC 2000). Initial doses are 25 mg/kg b.w. 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).

PRODUCTION

Chloramphenicol is produced naturally by *Streptomyces venezuelae*. It now is produced by chemical synthesis followed by a step to isolate stereoisomers. A fermentation process has been described that does not require separation of stereoisomers (IARC 1990).

The first commercial production of chloramphenicol in the United States was reported in 1948. U.S. production of chloramphenicol was estimated to exceed 908 kg (2,002 lb) in 1977 and 1979. U.S. imports for these years were estimated at 8,150 kg (17,970 lb) and 8,200 kg (18,080 lb), respectively (HSDB 2000). Current production levels for either veterinary or human use were not found in the literature.

EXPOSURE

Chloramphenicol may be released to the environment and may be found in various waste streams because of its use as a medicinal and research antimicrobial agent. Chloramphenicol also may be isolated from *Streptomyces venezuelae* in the soil (HSDB 2000). If released into the atmosphere, chloramphenicol will exist primarily as an aerosol. Atmospheric chloramphenicol will be removed mainly through dry deposition. Because chloramphenicol reacts with photochemically produced hydroxyl radicals, its atmospheric half-life of is 12 hours. If released into water, chloramphenicol will be essentially nonvolatile. Adsorption to sediment and bioconcentration in aquatic organisms are not expected to be important processes. If released into soil, chloramphenicol is expected to have high soil mobility. It is not expected to evaporate from either dry or wet soils (HSDB 2000).

Various biodegradation studies indicate that chloramphenicol may biodegrade in soil and water. Chloramphenicol was found to degrade in adapted, activated waste sludge. It also was degraded by intestinal bacteria via amidolysis; 18 metabolites were observed, the major metabolites being 2-amino-1-(*p*-nitrophenyl)-1,3-propanediol and its *p*-aminophenyl reduction by-product (HSDB 2000).

Human exposure to chloramphenicol is primarily by the oral or topical route through its use as a drug. Exposure also may occur through inhalation, dermal contact, ingestion, or contact with contaminated water or soil (HSDB 2000). Occupational exposure during the manufacture of chloramphenicol may occur through inhalation, dermal contact, or ingestion (HSDB 2000). Medical and veterinary personnel who use drugs containing chloramphenicol may be exposed (MVM 1998, DFC 2000). No exposure data were found in the literature. Because of potentially harmful effects to humans, chloramphenicol was banned by the FDA in 1997 from use in food-producing animals (FDA 1997). No data on levels of chloramphenicol in food products were found in the literature.

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. Approximately 90% of chloramphenicol is excreted in urine, mostly as metabolites, including conjugated derivatives; only 15% is excreted as the parent compound (HSDB 2000).

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, one 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 (DFC 2000). In infants, chloramphenicolís 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 11 days to eight weeks.

REGULATIONS

The FDA regulates manufacturers, packers, and distributors to ensure proper labeling, certification, and usage requirements for any drug containing chloramphenicol. The FDA also describes specifications and conditions of use for chloramphenicol tablets, capsules, suspensions, ointments, and solutions for dogs and cats, and requires that chloramphenicol not be used in any food-producing animals.

The American Conference of Governmental Industrial Hygienists recommends a workplace exposure limit of 0.5 mg/m^3 as an 8-hour time-weighted average. The Occupational Safety and Health Administration regulates chloramphenicol under the Hazard Communication Standard and as a chemical hazard in laboratories. Regulations are summarized in Volume II, Table 32.

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