CHLORAMPHENICOL

This substance was considered by previous working groups, in October 1975 and March 1987 (IARC, 1976, 1987a,b). 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

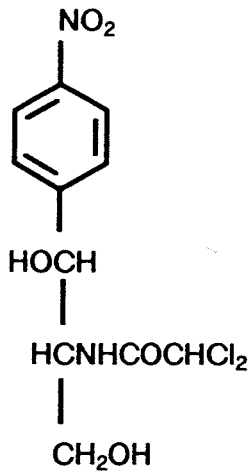
1.1 Synonyms

Chem. Abstr. Services Reg. No.: 56-75-7

Chem. Abstr. Name: Acetamide, 2,2-dichloro-*N*-[2-hydroxy-1-(hydroxymethyl)-2-(4-nitrophenyl)ethyl]-[R-(R*,R*)]-

Synonyms: 2,2-Dichloro-*N*-[(αR,βR)-β-hydroxy-α-hydroxymethyl-4-nitrophenethyl]acetamide; D-(-)-threo-2-dichloroacetamido-1-*para*-nitrophenyl-1,3-propanediol; D-threo-*N*-dichloroacetyl-1-*para*-nitrophenyl-2-amino-1,3-propanediol; D-threo-(-)-2,2-dichloro-*N*-[β-hydroxy-α-(hydroxymethyl)-*para*-nitrophenethyl]acetamide; D-threo-*N*-(1,1′-dihydroxy-1-*para*-nitrophenylisopropyl)dichloroacetamide; D-(-)-threo-*para*-nitrophenyl-1-dichloroacetamido-2-propanediol-(1,3)

1.2 Structural and molecular formulae and molecular weight



$C_{11}H_{12}Cl_2N_2O_5$ Mol. wt: 323.14

1.3 Chemical and physical properties of the pure substance

Data from Szulczewski and Eng (1975) and Al-Badr and El-Obeid (1986), unless otherwise specified

(*a*) *Description*: White to greyish-white or yellowish-white fine crystalline powder or fine crystals, needles or elongated plates. Of the four possible stereoisomers, only the αR,βR (or D-*threo*) form is active (Anon., 1979).

(*b*) *Melting-point*: 149-153°C (sublimes in high vacuum)

(*c*) *Optical rotation:* $[\alpha]_D^{27} = +18.6°$ (4.86% in ethanol)

(*d*) *Solubility*: 1:400 in water at 25°C; aqueous solutions are neutral; 1:6 in propylene glycol at 25°C; very soluble in methanol, ethanol, butanol, ethyl acetate, acetone; fairly soluble in diethyl ether (Windholz, 1983)

(*e*) *Spectroscopy data*: Ultraviolet, infrared, nuclear magnetic resonance and mass spectra have been reported.

(*f*) *Stability*: Stable in the solid state as a bulk drug and when present in solid dosage forms. Reasonable precautions taken to prevent excessive exposure to light or moisture are adequate to prevent significant decomposition over an extended period. In solution, chloramphenicol undergoes a number of degradative changes related to pH, temperature, photolysis and microbiological effects.

(*g*) *Reactivity*: The nitro group is readily reduced to the amine.

1.4 Technical products and impurities

Trade names: Ak-Chlor; Alcon Opulets Chloramphenicol; Amphicol; Antibiopto; Aquamycetin; Arcomicetina; Biomicin; Bioticaps; Cafenolo; Cébénicol; Chemicetina; Chemyzin; Chlomin; Chloramex; Chloramol; Chloratets; Chlorcol; Chlorofair; Chloromycetin; Chloroptic; Chlorsig; Cloramffen; Cloramplast; Clorbiotina; Clorfenicol Wolner; Clorofenicina; Cloromicetin; Cloromisol; Cloromoin; Cloroptic; Cutispray No. 4; Doctamicina; Econochlor; Espectro Medical; Farmicetina; Fenicol; Globenicol; Hortfenicol; I-Chlor; Iprobiot; Isopto Fenicol; Kamaver; Kemicetina; Kemicetine; Kloramfenikol Minims; Labamicol; Lennacol; Leukomycin; Levomicetina; Lomecitina; Micoclorina; Micodry; Minims Chloramphenicol; Mycetin; Mychel; Nevimycin; Normofenicol; Novochlorocap; Ocu-Chlor; Oftalent; Oleomycetin; Opclor; Ophtaphénicol; Ophthochlor; Paidomicetina; Pantofenicol; Pantovernil; Paraxin; Paraxin Succinat A; Pentamycetin; Plastodermo; Quemicetina; Ranphenicol; Rivomycine; Septicol; Sificetina; Sintomicetina; Sno Phenicol; Solnicol Ercé; Solu-Paraxin; Sopamycetin; Spersanicol; Succicaf; Synthomycetine; Thilocanfol; Tifomycine; Tramina; Troymycetin; Vernacetin

Many fixed combinations also contain chloramphenicol.

Chloramphenicol is often formulated as the cinnamate, palmitate (1.7 g equivalent to 1.0 g chloramphenicol) or sodium succinate salt (US Pharmacopeial Convention, 1975; Reynolds, 1989). Preparations are available as capsules (50, 100 and 250 mg; USP grade contains 90-120% of the labelled amount of active ingredient), ear drops (solution in propylene glycol), eye drops (0.5% solution or sterile, dry mixture of chloramphenicol and suitable buffers containing 90-130% of the labelled amount of chloramphenicol; US Pharmacopeial Convention, Inc., 1975) and eye ointment (1% chloramphenicol; USP grade contains 90-130% of the labelled amount of active ingredient); and as the palmitate in a suspension for oral administration (USP 5 ml, 30 mg/ml, containing 90-120% of the labelled amount of active ingredient) and the succinate in vials of 1 g for injection (USP grade containing 90-115% of the labelled amount of active ingredient).

2. Production, Occurrence, Use and Analysis

2.1 Production and occurrence

Chloramphenicol is an antibiotic produced by *Streptomyces venezuelae* (Ehrlich *et al.*, 1947). The crystalline antibiotic substance was isolated by Bartz in 1948 (Goodman & Gilman, 1970), and, in 1949, its structural determination (Rebstock *et al.*, 1949) and chemical synthesis (Controulis *et al.*, 1949) were reported.

Chloramphenical can be synthesized by condensation of *para*-nitrobenzoyl chloride with ethyl malonate to give *para*-nitroacetophenone, followed by bromination in acetic acid to form *para*-nitro-α-bromoacetophenone, and reaction of this with hexamethylene tetramine, followed by hydrolysis to give *para*-nitro-α-aminoacetophenone; subsequent acetylation of the amine group and condensation with formaldehyde give a hydroxymethyl group *alpha* to the amine group. Treatment with aluminium isopropylate reduces the keto group to a secondary alcohol, and, after deacetylation, condensation of the amine group with methyl dichloroacetate gives chloramphenicol (Anon., 1969). Chemical syntheses of chloramphenicol usually include a resolution step to separate stereoisomers.

In Japan, production by a fermentation process has also been described. The process resulted from the discovery and isolation of a new strain of microbe and does not require separation of stereoisomers (Anon., 1972).

Chloramphenicol is synthesized in Brazil, China, Czechoslovakia, the Federal Republic of Germany, Hungary, Italy, India, Israel, Japan, Mexico, Romania, South Africa, Spain and the USSR and has also been produced in France, Switzerland, the UK and the USA. Commercial production of chloramphenicol in the USA was first

reported in 1948 (US Tariff Commission, 1949; Chemical Information Services, 1989-90).

In Sweden, 584 780 packages of chloramphenicol were sold in 1988 (Apoteksbolaget, 1988, 1989). In Finland, sales of chloramphenicol in 1987 were 0.01 defined daily doses per 1000 inhabitants (Finnish Committee on Drug Information and Statistics, 1988).

Chloramphenicol can be isolated from *Streptomyces venezuelae* in soil.

2.2 Use

Chloramphenicol is an antimicrobial agent recommended for serious infections in which the location of the infection, susceptibility of the pathogen or poor response to other therapy indicate restricted antimicrobial options. It has been used since the 1950s for a wide range of microbial infections, including typhoid fever and other forms of salmonellosis, and central nervous system, anaerobic and ocular infections (Bartlett, 1982; Sande & Mandell, 1985).

The usual dosage of chloramphenicol is 50 mg/kg daily in divided doses up to two to four weeks (Bartlett, 1982; Sande & Mandell, 1985). In certain indications, e.g. cystic fibrosis, treatment has been continued for years (Harley *et al.*, 1970).

An allowed daily intake (ADI) could not be set for chloramphenicol because of the dose-independence of chloramphenicol-induced aplastic anaemia (FAO/-WHO, 1969; FAO/WHO Expert Committee on Food Additives, 1988).

Chloramphenicol is believed to have been widely used as a veterinary antibiotic, despite legal controls in many countries, and there have been a few reports of residual amounts in various animal products (Allen, 1985). In countries in which its veterinary use is permitted, food regulations require withdrawal periods so as to avoid residues in the final product (FAO/WHO, 1969; FAO/WHO Expert Committee on Food Additives, 1988).

2.3 Analysis

Methods for the analysis of chloramphenicol have been reviewed (Wenk *et al.*, 1984; Al-Badr & El-Obeid, 1986). The compound has been determined in serum by high-performance liquid chromatography (Ryan *et al.*, 1984; Sood *et al.*, 1987; Meatherall & Ford, 1988) and enzyme immunoassay (Schwartz *et al.*, 1988).

Chloramphenicol has been analysed in pharmaceutical preparations using microbiological turbidimetric and spectrophotometric assays (US Food and Drug Administration, 1988; US Pharmacopeial Convention, Inc., 1989).

Analytical methods for chloramphenicol residues in meat, milk and eggs have been reviewed (Allen, 1985). The methods include high-performance liquid chromatography (Schmidt *et al.*, 1985) and radioimmunoassay (Arnold *et al.*, 1984; Arnold & Somogyi, 1985; Hock & Liemann, 1985).

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

3.1 Carcinogenicity studies in animals

(a) *Oral administration*

Mouse: In a study reported in an abstract, groups of 50 male and 50 female BALB/c mice, six weeks of age, were administered chloramphenicol [purity unspecified] at 0, 500 or 2000 mg/l in drinking-water for 104 weeks, at which time all survivors were killed. The incidences of lymphomas in mice of each sex (combined) were 3% in controls, 6% in low-dose animals and 12% in high-dose animals ($p < 0.05$). The incidences of other types of tumour were similar in treated and control animals (Sanguineti *et al.*, 1983). [The Working Group noted the incomplete reporting of the study.]

As reported in the same abstract, groups of 50 male and 50 female C57Bl/6N mice, six weeks of age, were administered chloramphenicol [purity unspecified] at 0, 500 or 2000 mg/l in drinking-water for 104 weeks, at which time all survivors were killed. The incidences of lymphomas in mice of each sex (combined) were 8% in controls, 22% in low-dose animals ($p < 0.05$) and 23% in high-dose animals ($p < 0.01$). The incidences of malignant liver-cell tumours in mice of each sex (combined) were: control, 0; low-dose, 2/90; and high-dose, 11/91 ($p < 0.01$) (Sanguineti *et al.*, 1983). [The Working Group noted the incomplete reporting of the study.]

(b) *Intraperitoneal administration*

Mouse: Two groups of 45 male BALB/c × AF_1 mice, six to eight weeks of age, received four intraperitoneal injections of 0.25 ml acetone in distilled water. After a 20-week rest period, one group received daily intraperitoneal injections of chloramphenicol [purity unspecified] at 0.25 ml (2.5 mg) in 0.9% saline solution on five days per week for five weeks. The mice were killed on day 350. Controls received injections of saline solution only. No increase in the incidence of tumours was observed (Robin *et al.*, 1981). [The Working Group noted the short duration of treatment and observation.]

(c) *Administration with known carcinogens*

Mouse: Two groups of 45 male BALB/c × AF_1 mice, six to eight weeks of age, received intraperitoneal injections every two weeks of four doses of 0.5 mg busulphan (1,4-butanediol dimethanesulfonate) in 0.25 ml acetone. After a 20-week rest period (on day 183 of the experiment), one group received chloramphenicol [purity unspecified] at 2.5 mg on five days per week for five weeks. On day 350 of the experiment, all surviving mice were killed. The incidence of lymphomas was 13/37

in the combined treatment group compared with 4/35 in a group treated with busulphan alone (p = 0.02, Fisher's exact test) (Robin *et al.*, 1981). [The Working Group noted the short duration of the experiment.]

3.2 Other relevant data

(*a*) *Experimental systems*

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

In dogs, chloramphenicol was readily absorbed after oral administration of 50 mg/kg bw, giving plasma levels of 16.5 μg/ml 2 h after dosing (Watson, 1972, 1977a). Similar findings were made in rabbits (Cid *et al.*, 1983).

Five minutes after intravenous administration of ^{14}C-chloramphenicol to newborn pigs at 0.52 mg/kg bw, most tissues had higher levels of ^{14}C label than the blood; however, levels of chloramphenicol in bone marrow did not reach those noted in serum (Appelgren *et al.*, 1982).

Chloramphenicol and its metabolites were excreted in the urine of rats after oral dosing; up to 70% of an oral dose may be excreted in this way (Glazko *et al.*, 1949). About 0.4% of an intramuscular dose of 40 mg/kg to rats was detected in the bile within 4 h (Kunii *et al.*, 1983). In newborn pigs, most of an intravenous dose of chloramphenicol was excreted in the urine (Appelgren *et al.*, 1982). Following intravenous administration to goats, 69% of the dose was excreted in the urine within 12 h (Javed *et al.*, 1984).

Chloramphenicol was detected in the milk of goats and cattle after parenteral administration (Roy *et al.*, 1986); however, after oral administration [dose unspecified] to cattle, no chloramphenicol was detected in milk (De Corte-Baeten & Debackere, 1976).

In addition to free chloramphenicol and the glucuronide, the oxamic acid, alcohol, base, acetylarylamine and arylamine metabolites have been found in the urine of rats given intramuscular doses of ^{3}H-chloramphenicol (the 1R,2R-isomer). On the basis of recovered radioactivity, the major metabolites were assumed to be chloramphenicol base (~26%) and the acetylarylamine derivative (~20%) (Bories *et al.*, 1983).

In dogs, chloramphenicol base and chloramphenicol glucuronide conjugate were reported to be the major metabolites (Glazko *et al.*, 1950). Chloramphenicol, the glucuronide conjugate and the oxamic acid, acetylarylamine, arylamine and base derivatives were found in the urine of goats given intramuscular injections of chloramphenicol (Bories *et al.*, 1983).

The glucuronide is the main metabolic product in isolated rat hepatocytes exposed to chloramphenicol (Siliciano *et al.*, 1978). A study using perfused rat liver

and rat liver microsomes indicated that the arylamine derivative may undergo *N*-oxidation to form nitrosochloramphenicol (Ascherl *et al.*, 1985).

(ii) *Toxic effects*

The intravenous and intraperitoneal LD_{50}s for single doses of chloramphenicol in albino mice were 200 and 1320 mg/kg bw, respectively. The intravenous LD_{50} in rats was 170 mg/kg bw. Lethal amounts of chloramphenicol given orally or parenterally produced respiratory failure (Gruhzit *et al.*, 1949). In rats treated with chloramphenicol at 50 and 100 mg/kg bw, the lipid content of the liver increased and the activities of aspartate and alanine aminotransferases in serum were elevated (Mandal *et al.*, 1982).

After three groups of ten three-month-old Swiss mice were given daily intraperitoneal injections of chloramphenicol at 20, 40 or 100 mg/kg bw for three months, splenomegaly, hepatomegaly, lymph adenopathy and hypertrophy of the thymus occurred in a dose-dependent fashion (German & Loc, 1962).

Chloramphenicol caused decreased entry into S-phase in dividing bone-marrow cells of mice treated *in vivo* (Benes *et al.*, 1980). The drug had a deleterious effect on bone-marrow recovery in mice after X-irradiation (Benes *et al.*, 1980; Vacha *et al.*, 1981) and after busulfan treatment in one study (Morley *et al.*, 1976) but not another (Pazdernik & Corbett, 1980). Bone-marrow damage has been described in cats and dogs after 14-21 days' treatment with chloramphenicol (Penny *et al.*, 1967; Watson, 1977b; Watson & Middleton, 1978; Watson, 1980). Effects included vacuolation of the myeloid and erythroid precursors and bone-marrow hypoplasia in cats, and suppression of erythropoiesis and a reduced rate of granulocyte formation but not bone-marrow vacuolation in dogs.

Chloramphenicol caused dose-related inhibition of erythroid and granulocytic colony forming units obtained from LAF_1 mice (Yunis, 1977).

Chloramphenicol and nitrosochloramphenicol inhibited DNA synthesis in rat bone-marrow cells *in vitro*. This effect was reversible with chloramphenicol but not with the nitroso compound. Similarly, the nitroso compound but not chloramphenicol bound irreversibly to bone-marrow cells (Gross *et al.*, 1982). In another study *in vitro*, chloramphenicol and nitrosochloramphenicol had no effect on mouse haematopoietic precursor cells (Pazdernik & Corbett, 1979).

Several studies have demonstrated an effect of chloramphenicol on mitochondrial protein synthesis. *In vitro*, chloramphenicol inhibited mitochondrial protein synthesis in rat liver and rabbit bone marrow (Summ *et al.*, 1976; Abou-Khalil *et al.*, 1980). Nitrosochloramphenicol inhibited rat mitochondrial DNA polymerase *in vitro*, whereas the arylamine derivative and chloramphenicol itself did not (Lim *et al.*, 1984).

(iii) *Effects on reproduction and prenatal toxicity*

High oral doses of chloramphenicol of 500-2000 mg/kg to rats and mice and of 500 and 1000 mg/kg to rabbits produced high incidences of embryonic and fetal deaths and fetal growth retardation in all three species. Teratogenic effects—predominantly umbilical hernia—were observed only in rats. The pregnant animals showed no toxic sign, except that those given the highest dose gained significantly less weight than controls (Fritz & Hess, 1971).

Groups of eight pregnant albino mice were given chloramphenicol orally at 25, 50, 100, or 200 mg/kg bw in 10 ml distilled water over the third stage of pregnancy for seven days. Animals were allowed to give birth, and the young were tested for conditioned avoidance response, electroshock seizure threshold and performance in open-field tests. Dose-related effects were seen in all three elements of the test: progeny of chloramphenicol-treated dams had reduced learning ability, higher brain seizure threshold and poorer performance in the open-field test (Al-Hachim & Al-Baker, 1974).

Chloramphenicol was also investigated for its effects on avoidance learning in rats. Four groups of 15 pregnant Wistar rats each were treated as follows: chloramphenicol was given subcutaneously at 50 mg/kg bw on days 7-21 of gestation; chloramphenicol was given subcutaneously at 50 and 100 mg/kg bw to pups for the first three days after birth; and the fourth group served as controls. No adverse effect on pregnancy or postnatal weight gain was seen, but when the animals were 60 days old, they had significant impairment of avoidance learning (Bertolini & Poggioli, 1981).

(iv) *Genetic and related effects*

The genetic toxicology of chloramphenicol has been reviewed (Rosenkranz, 1988).

Chloramphenicol did not induce lysogenic phage in *Staphylococcus aureus* (Manthey *et al.*, 1975). It did not induce differential toxicity in *Escherichia coli* (Slater *et al.*, 1971; Shimizu & Rosenberg, 1973; Longnecker *et al.*, 1974; Venturini & Monti-Bragadin, 1978; Mitchell *et al.*, 1980; Leifer *et al.*, 1981), *Salmonella typhimurium* (Nader *et al.*, 1981; Pall & Hunter, 1985), *Proteus mirabilis* (Adler *et al.*, 1976) or *Bacillus subtilis* (Kada *et al.*, 1972; Suter & Jaeger, 1982), although a contradictory positive result was obtained in the *rec* assay with *E. coli* (Suter & Jaeger, 1982). Chloramphenicol gave negative results in the SOS chromotest in *E. coli* (Mamber *et al.*, 1986). It induced breaks in DNA of *E. coli* B/r and *S. typhimurium* TA1976 (Jackson *et al.*, 1977). It did not induce mutations in *E. coli* (Hemmerly & Demerec, 1955) and was not mutagenic in plate incorporation assays with *S. typhimurium* in the presence or absence of an exogenous metabolic system (Brem *et al.*, 1974; McCann *et al.*, 1975; Mortelmans *et al.*, 1986). In a liquid

pre-incubation assay, chloramphenicol did not induce reversions in *E. coli*; it did, however, induce forward mutations to azetidine-2-carboxylic acid resistance in the same bacterial strain. In the same assay system, chloramphenicol was weakly mutagenic to *S. typhimurium* TA98 in the presence or absence of an exogenous metabolic system (Mitchell *et al.*, 1980).

Chloramphenicol induced petite mutations in haploid strains of *Saccharomyces cerevisiae* (Weislogel & Butow, 1970; Williamson *et al.*, 1971) but not in diploid strains (Carnevali *et al.*, 1971).

Treatment of *Arabidopsis* seeds with chloramphenicol did not induce lethal mutations (Müller, 1965). Chloramphenicol induced chromosome breakage in root-tip meristem cells of germinating barley (Yoshida *et al.*, 1972) and *Vicia faba* seeds (Prasad, 1977). It did not induce micronuclei in pollen tetrads of *Tradescantia paludosa* (Ma *et al.*, 1984).

Chloramphenicol did not induce sex-linked recessive lethal mutations in *Drosophila melanogaster* treated either by injection (Clark, 1963) or by feeding (Nasrat *et al.*, 1977).

It inhibited DNA synthesis in human lymphoblastoid cell lines (Yunis *et al.*, 1973), in rat bone-marrow cells (Gross *et al.*, 1982) and in mouse Ehrlich ascites cells (Freeman *et al.*, 1977). DNA strand breaks were induced in human lymphocytes by chloramphenicol at 2.0 mM (Yunis *et al.*, 1987) but not at 0.8 mM in a human lymphoblastoid cell line, in human lymphocytes or in human bone-marrow cells (Isildar *et al.*, 1988). Chloramphenicol did not induce unscheduled DNA synthesis in Syrian hamster embryo cells in the presence or absence of an exogenous metabolic system (Suzuki, 1987).

The drug induced mutations at the *tk* locus of L5178Y mouse lymphoma cells in the presence and absence of an exogenous metabolic system (Mitchell *et al.*, 1988; Myhr & Caspary, 1988). It induced sister chromatid exchange in Syrian hamster embryo cells (Suzuki, 1987) but not in human leukocytes (Pant *et al.*, 1976). When human white blood cells were treated with low concentrations (10-40 μg/ml) of chloramphenicol, a concentration-dependent increase in the number of cells with chromosomal aberrations was observed (Mitus & Coleman, 1970). Chloramphenicol did not induce chromosomal aberrations in human lymphocytes (Jensen, 1972; Sasaki & Tonamura, 1973; Goh, 1979) or in human fibroblasts (Byarugaba *et al.*, 1975).

No morphological transformation was observed in Syrian hamster embryo cells after treatment with chloramphenicol at 100-1000 μg/ml (Suzuki, 1987). Chloramphenicol did not reproducibly enhance the transformation of Syrian hamster embryo cells by simian adenovirus SA7 (Hatch *et al.*, 1986).

Subcutaneous injections to C57Bl/10 mice of chloramphenicol at 320 mg/kg bw three times daily for three days led to inhibition of thymidine incorporation in bone-marrow cells (Benes *et al.*, 1980). Intramuscular injections of chloramphenicol (three times 1000 mg/kg bw) to Wistar rats did not induce chromosomal aberrations in bone-marrow cells (Jensen, 1972). At 50 mg/kg bw, the drug induced chromosomal aberrations in bone-marrow cells of mice [site of injection and number of animals tested unspecified] (Manna & Bardhan, 1972, 1977). Intramuscular injection of chloramphenicol at 50 mg/kg to Swiss albino mice [number of animals unspecified] induced chromosomal aberrations in mitotic and meiotic germ line cells (Roy & Manna, 1981).

Chloramphenicol did not induce dominant lethal mutations in mice when given twice at up to 15 000 mg/kg intraperitoneally (Epstein & Shafner, 1968; Ehling, 1971; Epstein *et al.*, 1972) but did when given at 500 mg/kg bw (Sram, 1972).

(*b*) *Humans*

(i) *Pharmacokinetics*

Chloramphenicol is readily absorbed from the gastrointestinal tract after oral administration of a crystalline powder of the active drug itself or a palmitate ester; the latter is hydrolysed in the small intestine to active chloramphenicol before absorption (Kauffman *et al.*, 1981). Esters of chloramphenicol—for example, the succinate—are converted to chloramphenicol *in vivo* (Salem *et al.*, 1981). Peak levels of 10-20 μg/ml appear 2-3 h after administration of chloramphenicol orally at 15 mg/kg bw (see Bartlett, 1982).

Chloramphenicol is also well absorbed by infants and neonates after oral administration. Serum (peak) concentrations of 20-24 μg/ml were noted after oral doses of 40 mg/kg bw to neonates. Infants given 26 mg/kg bw were found to have peak concentrations of 14 μg/ml (Mulhall *et al.*, 1983).

Chloramphenicol is distributed extensively in humans, regardless of its route of administration. The compound has been found in heart, lung, kidney, liver, spleen, pleural fluid, seminal fluid, ascitic fluid and saliva (Gray, 1955; Ambrose, 1984). It penetrates the blood-brain barrier, and its concentrations in cerebrospinal fluid can reach about 60% of that in plasma (Friedman *et al.*, 1979). The concentrations in brain tissue equal or even exceed those in plasma (Kramer *et al.*, 1969). Chloramphenicol easily crosses the placenta, and it is also excreted in breast milk (Havelka *et al.*, 1968).

Chloramphenicol has a half-time ranging from 1.6 to 4.6 h; using different techniques and in different adult patients, apparent volumes of distribution ranging from 0.2 to 3.1 l/kg have been measured (see Ambrose, 1984). The half-time is considerably longer in neonates (Rajchgot *et al.*, 1983): in one- to eight-day-old

infants the half-life ranged from 10 to over 48 h, and in 11-day- to eight-week-old infants the range was 5-16 h (Glazer *et al.*, 1980).

Six hours after an intravenous dose of 500 mg chloramphenicol succinate, the blood level was 4.5 μg/ml (2.8-6.9 μg/ml) in patients with chloramphenicol-induced bone-marrow depression, while in the control group the mean level was 1.2 μg/ml (0-2.3 μg/ml). Such findings suggest that patients susceptible to the effects of chloramphenicol on bone marrow may clear the drug from the blood more slowly than those who are not susceptible (Suhrland & Weisberger, 1969).

Chloramphenicol is excreted primarily in the urine (90%); up to 15% is excreted as the parent compound and the remainder as metabolites, including conjugated derivatives (Yunis, 1973; Burke *et al.*, 1980; Ambrose, 1984). Glomerular excretion is thought to be the major mechanism of excretion (Glazko *et al.*, 1949).

Approximately 48% of the chloramphenicol excreted in urine within 8 h of an oral dosing was the glucuronide conjugate; only 6% was excreted as the parent compound and 4% as the base derivative (Nagakawa *et al.*, 1975; Baselt, 1982; Bories *et al.*, 1983). The alcohol derivative has been detected in the urine of neonates (Dill *et al.*, 1960).

Human liver microsomes have been shown to reduce the nitro group of chloramphenicol (Salem *et al.*, 1981).

Chloramphenicol arylamide is formed by intestinal bacterial reduction of the NO_2 group to NH_2, which is acetylated and excreted in urine (Meissner & Smith, 1979). Oxamic acid (formed by oxidative dechlorination of the side chain) was identified as a major metabolite in one human volunteer (Corpet & Bories, 1987).

(ii) *Adverse effects*

The most important adverse effects of chloramphenicol involve the haematopoietic system (as reviewed by the FAO/WHO Expert Committee on Food Additives, 1988). Potentially fatal toxicity may develop in neonates exposed to excessive doses of chloramphenicol (Sande & Mandell, 1985). This so-called 'grey baby syndrome' may also occur in older children and in adults receiving doses resulting in serum concentrations of 40-200 μg/ml (see Bartlett, 1982). Other adverse effects include hypersensitivity reactions, gastrointestinal complaints and neurological complications after long-term treatment. Chloramphenicol can also precipitate haemolytic anaemia in subjects with glucose-6-phosphate dehydrogenase deficiency (Robertson *et al.*, 1968).

Dose-dependent, reversible bone-marrow suppression affects primarily the erythroid series and occurs regularly when plasma concentrations of chloramphenicol are 25 μg/ml or higher (Scott *et al.*, 1965; Yunis & Adamson, 1977). Another haematological side-effect is rare, unpredictable, non-dose-related

aplastic anaemia, which often appears after the drug has been discontinued (Best, 1967).

The metabolite (or metabolites) responsible for the induction of aplastic anaemia in human beings is unknown, but nitrosochloramphenicol has been implicated (Nagai & Kanamuru, 1978; Yunis, 1988): it is known to be toxic to human bone-marrow cells *in vitro* and, moreover, is more toxic than chloramphenicol itself (Yunis *et al.*, 1980a,b). Metabolites of chloramphenicol, such as dehydrochloramphenicol, produced by intestinal bacteria, are more than 20-fold more cytotoxic than the parent drug (Yunis, 1988).

There have been many case reports of the occurrence of aplastic anaemia following administration of chloramphenicol by various routes (Rosenthal & Blackman, 1965; Nagao & Mauer, 1969; Carpenter, 1975; Yunis, 1978; Abrams *et al.*, 1980; Silver & Zuckerman, 1980; Flach, 1982; Fraunfelder *et al.*, 1982; Plaut & Best, 1982; Issaragrisil & Piankijagum, 1985; Korting & Kifle, 1985; Elberg & Hansen, 1986; von Muhlendahl, 1987). In many of these cases, large doses had been taken repeatedly over periods of many years before the onset of symptoms of aplastic anaemia. Case-control studies have also suggested an association between chloramphenicol use and aplastic anaemia (for review, see FAO/WHO Expert Committee on Food Additives, 1988). A widely discussed causal association between topical application of chloramphenicol eye-drops and aplastic anaemia (Wade, 1972; Carptenter, 1975; Fraunfelder *et al.*, 1982) has not been established.

(iii) *Effects on reproduction and prenatal toxicity*

In the Collaborative Perinatal Project, in which drug intake and pregnancy outcome were studied in a series of 50 282 women in 1959-65, 98 women had been exposed to choramphenicol during the first trimester of pregnancy. There were eight malformed children in the exposed group, giving a nonsignificant standardized relative risk (RR) of 1.17. A total of 348 women had had exposure at any time during pregnancy with no evidence of an increase in the incidence of congenital malformations (Heinonen *et al.*, 1977).

No adverse effect was reported in the children of 22 patients treated at various stages of pregnancy with chloramphenicol (Cunningham *et al.*, 1973).

(iv) *Genetic and related effects*

No adequate study was available to the Working Group.

3.3 Case reports and epidemiological studies

Numerous case reports have been published of leukaemia occurring following chloramphenicol-induced aplastic anaemia (Edwards, 1969; Seaman, 1969; Goh, 1971; Cohen & Huang, 1973; Meyer & Boxer, 1973; Hellriegel & Gross, 1974; Modan *et al.*, 1975; IARC, 1976; Ellims *et al.*, 1979; Witschel, 1986; IARC, 1987a); three case

reports have been published of leukaemia following chloramphenicol therapy in the absence of interceding aplastic anaemia (Humphries, 1968; Popa & Iordacheanu, 1975; Aboul-Enein *et al.*, 1977).

Shu *et al.* (1987) reported a case-control study of 309 childhood leukaemia cases (under 15 years) notified to a population-based cancer registry in Shanghai, China, during 1974-86, and 618 age- and sex-matched population controls. Information was obtained from parents or guardians for lifetime use of selected drugs, including prescribed chloramphenicol and syntomycin (a racemic mixture of D- and L-chloramphenicol). The risk for all types of leukaemia combined showed a marked increase with accumulated use of chloramphenicol, yielding RRs of 1.7 (95% confidence interval, 1.2-2.5), 2.8 (1.5-5.1) and 9.7 (3.9-24.1) for one to five days', six to ten days' and more than ten days' treatment, respectively. The association was present in a subgroup in which first use had occurred more than five years prior to diagnosis and in one in which last use had been more than two years before diagnosis. Significant trends in risk with dose were observed both for acute lymphocytic leukaemia (56% of cases) and for acute nonlymphocytic leukaemia (30%). An association with leukaemia was also seen for use of syntomycin (RR, 1.9; 1.1-3.2). [The Working Group noted that interview was undertaken up to ten years after diagnosis, which adds to the possibility of differential recall between the parents of cases and controls. Little information was available with regard to use of other antibiotics, making it difficult to evaluate the possibility of bias.]

4. Summary of Data Reported and Evaluation

4.1 Exposure data

Chloramphenicol has been used widely as an antibiotic since the 1950s. Veterinary use of chloramphenicol has resulted in the occurrence of residues in animal-derived food.

4.2 Experimental carcinogenicity data

No adequate study was available to evaluate the carcinogenicity of chloramphenicol to experimental animals.

Intraperitoneal administration of chloramphenicol to mice enhanced the incidence of lymphomas induced by 1,4-butanediol dimethanesulfonate.

4.3 Human carcinogenicity data

Many case reports have described an unusual succession of leukaemia following chloramphenicol-induced aplastic anaemia and bone-marrow

depression. Additional evidence for the association between use of chloramphenicol and leukaemia has come from a single large case-control study in China, which demonstrated a relationship with duration of exposure.

4.4 Other relevant data

Use of chloramphenicol during the first trimester of pregnancy has not been associated with an increase in the incidence of congenital malformations. Chloramphenicol caused embryo- and fetolethality in mice, rats and rabbits.

In humans, chloramphenicol causes aplastic anaemia. In both humans and animals administered chloramphenicol, reversible suppression of the bone marrow is frequent whenever the drug reaches relatively high plasma concentrations.

Chloramphenicol induced chromosomal aberrations in bone-marrow cells of mice but not of rats treated *in vivo*. It induced chromosomal aberrations in meiotic cells of male mice. Contradictory results were obtained in dominant lethal tests in mice. In human cells, chloramphenicol did not induce sister chromatid exchange or chromosomal aberrations but gave contradictory results for DNA damage. It induced sister chromatid exchange in Syrian hamster cells. Chloramphenicol induced gene mutations in mouse lymphoma cells but did not induce DNA damage in hamster cells. Chloramphenicol did not induce sex-linked recessive lethal mutations in *Drosophila*. It induced chromosomal aberrations in plants. In haploid yeast, chloramphenicol induced petite mutations. In most studies, chloramphenicol was not mutagenic to and did not cause DNA damage in *Salmonella typhimurium* or *Escherichia coli* and did not induce DNA damage in *Proteus mirabilis* or *Bacillus subtilis*. (See Appendix 1.)

4.5 Evaluation[1]

There is *limited evidence* for the carcinogenicity of chloramphenicol in humans.

There is *inadequate evidence* for the carcinogenicity of chloramphenicol in experimental animals.

In making the overall evaluation, the Working Group also took note of the following information. Chloramphenicol induces aplastic anaemia, and this condition is related to the occurrence of leukaemia.

Overall evaluation

Chloramphenicol *is probably carcinogenic to humans (Group 2A)*.

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

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