



COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

CHLORAMPHENICOL

SUMMARY REPORT

1. Chloramphenicol is a broad-spectrum antibiotic which is predominantly active against the main pathogenic gram negative bacteria occurring in a number of food producing animals.
2. Chloramphenicol is rapidly absorbed following oral or parenteral administration with maximum blood concentrations reached 1-5 hours after dosing. The substance is rapidly distributed throughout the organs and tissues. Residues of chloramphenicol and its metabolites are found in all edible tissues and in milk and eggs. Generally there are some inter-species differences in the metabolite profiles. For swine these are remarkably different compared to those of calves and poultry. But for muscle tissue, no metabolic differences occur. The major route of excretion in pigs and cattle is the one via the kidneys.
3. Single intravenous doses of chloramphenicol were moderately toxic to mice. No repeat-dose toxicity studies were available.
4. No adequate reproductive toxicity studies were available.
5. In teratogenicity studies in the rat and the rabbit chloramphenicol did not show teratogenic effects but caused a high incidence of foetal deaths even at the lowest dose levels tested.
6. Almost all *in vitro* mutagenicity assays carried out with chloramphenicol showed positive results. Chloramphenicol induced DNA fragmentation in both V79 cells and in rat hepatocytes. Positive results were also obtained in DNA repair assays in cultured human and rat hepatocytes. There was a significant increase in the frequency of 6-thioguanine resistant clones of V79 cells.

Chloramphenicol induced chromosomal aberrations in cultured human lymphocytes. Chloramphenicol increased sister chromatid exchanges in cultured human lymphocytes, in Chinese hamster V79 cells, and in bovine fibroblasts.
7. The available *in vivo* mutagenicity assays provided equivocal results. No increase of micronuclei was observed in rat bone marrow after administration of a single oral dose of 1250 mg/kg bw chloramphenicol to rats. Oral administration of 50 and 100 mg/kg bw chloramphenicol to mice induced chromosomal aberrations in mouse bone marrow cells.
8. Three metabolites of chloramphenicol : nitroso-chloramphenicol, dehydro-chloramphenicol and dehydro-chloramphenicol-base were also shown to be mutagenic in an *in vitro* assay.
9. Tests for the carcinogenicity of chloramphenicol in experimental animals were inadequate. In a study reported only as an abstract, chloramphenicol administered in the drinking water increased the incidence of lymphomas in two strains of mice and of hepatocellular carcinomas in one mouse strain.
10. Historical epidemiological data suggested that the treatment of humans with chloramphenicol was associated with the induction of blood dyscrasias, particularly aplastic anaemia. New epidemiological data relating to ophthalmic use of chloramphenicol in humans now suggests that this form of treatment is not associated with the induction of aplastic anaemia. However it was not possible to quantify the systemic exposure resulting from the ophthalmic use. Consequently, although the overall incidence of chloramphenicol-associated aplastic anaemia in humans was very low, it was not possible to identify a "threshold" level below which the effect would not occur.

11. It was concluded that no ADI could be estimated for chloramphenicol, because of :
 - the inability to identify a "threshold" level for the induction of aplastic anaemia in humans;
 - its genotoxicity in a number of *in vitro* and *in vivo* test systems;
 - the lack of an adequate carcinogenicity study;
 - the lack of a NOEL for foetotoxicity;
 - the lack of an adequate reproductive toxicity study.
12. Following administration of a single oral dose of ¹⁴C-radiolabelled chloramphenicol to calves, swine and poultry, the parent drug and the metabolites chloramphenicol-glucuronide, chloramphenicol base and hydroxyamphenicol were present in the tissues of all three species. Residues of some other metabolites, dehydro-chloramphenicol, nitrophenylaminopropanedione and nitroso-chloramphenicol were also found in liver, muscle and kidney of chickens which had been dosed orally with chloramphenicol.
13. However there were no radiolabelled depletion studies for residues in edible tissues of cattle or swine over an extended period. Consequently it was not possible to determine the concentration of the total residues during drug depletion. The percentage of the total residues, corresponding to the parent drug and its metabolites, during depletion could not be ascertained. It was concluded that there was insufficient information to confirm a "marker" residue.
14. No results for bound chloramphenicol residues, in any species, were available.
15. A number of analytical methods are available which are suitable for monitoring chloramphenicol residues as parent compound at concentrations of 1 µg/kg or 1 µg/litre.
16. It was concluded that no MRLs could be elaborated because :
 - no ADI could be estimated;
 - no information about residues of toxicological concern was available;
 - there was insufficient information to confirm a "marker" residue which would reflect total residues.
17. In order to establish an ADI and MRLs a considerable amount of further data would be required to address the points raised above. The CVMP is not aware of ongoing studies in progress to address these issues. The provision of Council Regulation (EEC) N° 2377/90 foreseen to extend the time period of provisional MRLs in order to allow for the completion of studies in progress cannot be applied.

It was therefore agreed that chloramphenicol should be included in Annex IV of Council Regulation (EEC) N° 2377/90.