European Medicines Agency
Veterinary Medicines and Inspections

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COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

1-METHYL-2-PYRROLIDONE

SUMMARY REPORT (2)

1. 1-Methyl-2-pyrrolidone (also known as N-methyl-pyrrolidone, NMP and M-pyrol) is a widely used industrial solvent. It has been used as an excipient in topical pharmaceutical preparations in human medicine and in cosmetics. It is used as a solubilising agent in veterinary medicines intended for parenteral and topical application.

   Currently, 1-methyl-2-pyrrolidone is included in Annex II of Council Regulation (EEC) No. 2377/90 as follows:

Pharmacologically active substance(s)	Animal species	Other provisions
1-Methyl-2-pyrrolidone	Equidae	

   An application has now been submitted, which refers to the use of the substance as a solvent in a topical ectoparasiticide formulation for administration to sheep, corresponding to a dose of 13 mg/kg bw 1-methyl-2-pyrrolidone, and as a solvent in injectable antibacterial formulations for administration to cattle (equivalent to a single parenteral administration of up to 40 mg/kg bw of 1-methyl-2-pyrrolidone or 2 intramuscular or subcutaneous doses of 17 mg/kg bw of 1-methyl-2-pyrrolidone at 48 hour intervals), sheep (equivalent to a single parenteral dose of 40 µg/kg of 1-methyl-2-pyrrolidone) and pigs (equivalent to a single parenteral administration of up to 40 mg/kg bw of 1-methyl-2-pyrrolidone or 2 intramuscular or subcutaneous doses of 17 mg/kg bw of 1-methyl-2-pyrrolidone at 48 hour intervals).

   Study reports, which were previously supplied only as brief summaries, have now been made available.

2. No pharmacodynamic studies were provided. In single dose toxicity studies using oral gavage, signs of toxicity indicative of an effect on the central nervous system were observed at the lowest doses tested, 510 to 520 mg/kg bw. However no overt signs of toxicity were observed in 90-day repeated-dose toxicity studies in rats and dogs in which the substance was administered in the diet at concentrations equivalent to up to 250 mg/kg bw/day. It was concluded that pharmacodynamic effects would be observed only at very high dose levels and the absence of pharmacodynamic data was therefore justified.

3. Following administration of an oral dose of a mixture of 112 mg/kg bw ^{14}C-labelled-1-methyl-2-pyrrolidone and 75 mg/kg bw ^{14}C-labelled-2-pyrrolidone, in distilled water, C_{max} values of 57.1 µg/kg and 23.3 µg/kg were attained in male rats for the two substances respectively, approximately 2 hours after dosing. In female rats the C_{max} values were 70.6 µg/kg and 29.3 µg/kg respectively and were also obtained with a T_{max} value of 2 hours. Unmetabolised 1-methyl-2-pyrrolidone and 2-pyrrolidone accounted for more than 80% of the plasma radioactivity until 8

[1] The summary report was initially adopted in 1999. Following publication of additional relevant studies on carcinogenicity and developmental toxicity a review of the data was undertaken and this updated summary report published.

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hours post-dosing; however by 12 hours, almost the entire plasma radioactivity was in the form of polar metabolites. Within 24 hours of dosing 85 to 88% of the administered dose was recovered from the urine and 1 to 2% was recovered from the faeces. The oral bioavailability was close to 100%.

4. The experiment was repeated with the mixture, in isopropanol, applied topically to rats at doses equivalent to 2.5 mg/cm^2 of skin of ^{14}C-labelled-1-methyl-2-pyrrolidone and 1.67 mg/cm^2 of skin ^{14}C-labelled-2-pyrrolidone. The substances were applied under occlusive dressings which were held in place for up to 5 days. In males C_{max} values of 22.4 and 6.15 µg/ml were obtained for the 2 substances, 1 and 6 hours after the start of treatment. In females, C_{max} values of 30.9 µg/kg and 10.9 µg/kg were attained with T_{max} values of 2 hours for both substances. Within 5 days 68.9% and 77.8% of the administered radioactivity was recovered from the urine of males and females respectively. One to 2% of the applied dose was recovered from the faeces. From the occlusive dressing 11% of the dose was recovered. After 5 days, the amount remaining at the site of application was 2% in females and around 12% in males. Percutaneous absorption of the mixture over the 5 days was estimated to be 72% in males and 82% in females.

5. In another study, rats were given 3 daily oral doses of 400 mg/kg bw ^{14}C-labelled-1-methyl-2-pyrrolidone. In males, 76 to 81% of the dose was recovered in urine and 3.8 to 5.0% in faeces, within 120 hours of the last dose. In females, 71.5 to 79% was recovered from the urine and 3.3 to 5.1% from the faeces. Only 2.8% in males and 4.0% in females of the radioactivity in urine was unmetabolised 1-methyl-2-pyrrolidone. N-methyl-succinimide amounted to 2.5% and 2.2% of the radioactivity in urine from males and females. A major unidentified metabolite accounted for 76% and 78% of the radioactivity in male and female urine. This metabolite was also a major component of the radioactivity in faeces (20% and 28% in males and females). 1-Methyl-2-pyrrolidone accounted for 21.6% and 18.1% of the radioactivity in faeces from males and females respectively. Smaller amounts of N-methyl-succinimide were also present in faeces. 2-pyrrolidone was detected in the urine of one male rat (0.2% of radioactivity in sample) and in the faeces of one female (4.2% of radioactivity in sample). In rats killed 4 hours after dosing, 1-methyl-2-pyrrolidone was the major component of the residues in liver (50% and 67% of the radioactivity in males and females). Residues of N-methyl-succinimide were also found (8.3% and 9.8% of the radioactivity in liver from males and females).

6. In another study in which rats were given an intravenous injection of ^{14}C-labelled-1-methyl-2-pyrrolidone, the major metabolite in urine was identified as 5-hydroxy-1-methyl-2-pyrrolidone, accounting for approximately 68 to 69% of the radioactivity. Other studies showed that biliary excretion accounted for only 2% of the dose administered to bile duct-cannulated rats and that excretion of $^{14}CO_2$ in expired air represented only about 1% of the administered dose.

7. After oral administration to human males, unmetabolised 1-methyl-2-pyrrolidone was detected in urine only within one day of dosing. The major metabolite excreted in urine within the first 2 days of dosing, and accounting for 44% of the administered dose was 5-hydroxy-1-methyl-2-pyrrolidone; the elimination half-life of this metabolite was estimated to be 4 hours. N-methylsuccinimide and 2-hydroxy-N-methylsuccinimide were also found in human urine; the elimination half-lives of these metabolites were estimated to be 8 hours and 17 hours respectively.

8. Acute oral LD_{50} values for 1-methyl-2-pyrrolidone were in the range 3570 to 7650 mg/kg bw. In rats, signs of acute toxicity including decreased activity, ataxia, urinary incontinence and rales were observed at an oral dose of 510 mg/kg bw, the lowest dose level tested. In this study, deaths occurred at 2550 mg/kg bw and above. Instillation of 0.1 ml of 1-methyl-2-pyrrolidone into the conjunctival sac caused moderate eye irritation in rabbits. The substance was only a mild irritant to rabbit skin.

9. In a study in which groups of 25 male and 25 female Wistar rats were fed diets containing the equivalent of 0, 40, 100 or 250 mg/kg bw/day of 1-methyl-2-pyrrolidone for 90 days, body weight gain was significantly reduced in treated females but not males and the reduction was not dose-related. On occasions, food consumption was significantly reduced in treated females though again there was no dose-response relationship. Changes in urine values such as increased pH in males at 30 days (but not 90 days) and reduced specific gravity in females were also observed at the lowest dose level tested. However the urine effects were not dose related and did

not correlate with any pathological changes. Group mean absolute and relative thyroid weights were significantly increased in males in the 100 and 250 mg/kg bw/day. Based on the reduced body weight in females and the changes in urine values, it was considered that 40 mg/kg bw/day was a LOEL for the study.

10. Groups of 6 male and 6 female Beagle dogs were fed diets containing the equivalent of 0, 25, 79 or 250 mg/kg bw/day 1-methyl-2-pyrrolidone for 90 consecutive days. In the 250 mg/kg bw/day group, body weight gain of males and females was 54% and 37% that of the controls. At 79 and 250 mg/kg bw/day there were statistically significant increases in platelet counts in males. The increase appeared to correlate with a dose-related increase in megakaryocyte counts in the sternal bone marrow of males but the counts in all groups remained within the normal range for the laboratory. Also at these dose levels, there were significant reductions in serum cholesterol and total protein concentrations though these findings were of doubtful toxicological significance and did not correlate with any pathological findings. The NOEL was 25 mg/kg bw/day.

11. A GLP-compliant 3-generation reproduction study, with 2 litters per generation, was carried out in Sprague-Dawley rats. Groups of 30 males and 30 females were fed diets containing the equivalent of 0, 50, 160 or 500 mg/kg bw/day. Treatment commenced 10 weeks prior to mating and continued throughout gestation and lactation. At 500 mg/kg bw/day, parental body weight gain and food consumption were reduced. Also at this dose level, during breeding of the F2a and F2b litters, the male fertility index and the female fecundity index were significantly reduced. Growth rate and survival of the offspring were significantly reduced in all litters in the 500 mg/kg bw/day group. The effects observed at 160 mg/kg bw/day were limited to occasional significant reductions in parental food consumption and a significant reduction in the female fecundity index. It was noted that for the previous assessment of the CVMP only a brief abstract of this study was available and so it had not been possible to derive a NOEL at that time. However it was now concluded that the NOEL was 50 mg/kg bw/day.

12. Teratogenicity was observed following oral administration of 990 mg/kg bw/day to pregnant rats from days 6 to 15 of gestation (dilatation of the ventricles, undescended testes, hydrocephalus, ansarca). Also at this dose level, the incidence of resorptions was increased and foetal weight and length were reduced. There was no evidence of teratogenicity or foetotoxicity at the lower dose level of 330 mg/kg bw/day. No information was provided concerning the potential effects on the dams. No conclusion could be drawn regarding an overall NOEL for the study.

13. In a GLP-compliant study, groups of 20 female New Zealand White rabbits were given daily oral gavage doses of 0, 55, 175 or 540 mg/kg bw/day of 1-methyl-2-pyrrolidone from days 6 to 18 of gestation. Maternal toxicity was observed at 175 and 540 mg/kg bw/day with a significant reduction in maternal body weight gain in both groups. Also at 540 mg/kg bw/day, post-implantation loss was significantly increased, one dam aborted and another resorbed the entire litter. There was a corresponding reduction in the number of live foetuses in the 540 mg/kg bw/day group. The incidence of malformed foetuses was increased in the 540 mg/kg bw/day group; the malformations included malformed skull bones, bulbnous aortic arch, pulmonary trunk stenosis, ductus arteriosus stenosis and interventricular septal defect. The study report was not available for the previous assessment and so it had not been possible to derive any NOELs for the study at that time. However it was now concluded that the NOEL for both teratogenicity and foetotoxicity was 175 mg/kg bw/day. The NOEL for maternal toxicity was 55 mg/kg bw/day.

14. In a teratogenicity study in mice using oral dosing, teratogenicity was observed following administration of 2626 mg/kg bw/day to the dams from days 11 to 15 of gestation. There was no evidence of teratogenicity at the lower dose of 1046 mg/kg bw/day but foetotoxicity (increased resorption rate) was observed at this dose. The study was inadequately conducted and the dosing regime did not comply with OECD guidelines. No conclusions were drawn regarding a NOEL.

15. A study published in 2002 reports the results of a developmental toxicity study in Sprague-Dawley rats after oral administration of 1-methyl-2-pyrollidone at doses of 0, 125, 250, 500, and 700 mg/kg/day, by gavage on gestational days 6 through 20. Significant decreases in maternal body weight gain and food consumption during treatment, and a reduction in absolute body weight gain were observed at 500 and 750 mg/kg. The incidence of resorptions per litter was significantly higher than control at 500 and 750 mg/kg. Examination of the foetuses revealed treatment-related malformations including imperforate anus and absence of tail, anasarca, and

malformations of the great vessels and of cervical arches. The incidence of malformed foetuses per litter, and of litters with malformed foetuses was significantly increased at 500 and 750 mg/kg. At 250 mg/kg, one foetus showed malformations similar to those recorded at higher doses. There was a dose related decrease in ossification of skull bones, and of sternebra at 500 and 750 mg/kg. In summary, the no-observed-adverse-effect level (NOAEL) for maternal and developmental toxicity was 250 and 125 mg/kg/day, respectively.

16. The complete reports of a range of GLP-compliant mutagenicity assays were provided. Negative results were obtained in two separate *in vitro* assays for gene mutation in *Salmonella typhimurium* strains TA 97, TA102 and TA104 in both the presence and absence of metabolic activation. Both studies used concentrations of 1-methyl-2-pyrrolidone in the range 667 to 10 000 µg/plate. A third *in vitro* assay using *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538 and concentrations of 1-methyl-2-pyrrolidone in the range 100 to 5 000 µg/plate also gave negative results. In an *in vitro* assay, 1-methyl-2-pyrrolidone did not cause gene mutation at the TK locus of mouse lymphoma L5178Y cells. An *in vitro* unscheduled DNA synthesis assay in rat primary hepatocytes also gave negative results.

17. According to a published report, 1-methyl-2-pyrrolidone induced aneuploidy in *Saccharomyces cerevisae* strain D61.M. In the same study, positive results were also obtained for the metabolite 2-pyrrolidone but not for succinimide. According to another published report, cold shock was necessary to obtain a positive response with 1-methyl-2-pyrrolidone in this assay.

18. To investigate the potential for 1-methyl-2-pyrrolidone to induce numerical aberrations *in vivo*, a GLP-compliant micronucleus test was carried out in which groups of 5 male and 5 female mice were given a single oral dose of 0, 950 or 1900 mg/kg bw 1-methyl-2-pyrrolidone and killed 24 hours after dosing. Further groups were given 3800 mg/kg bw and killed 16, 24 or 48 hours after dosing. 1000 polychromatic erythrocytes from each animal were scored and evaluated for small micronuclei (indicative of clastogens) and large micronuclei (indicative of aneugens). 1-Methyl-2-pyrrolidone did not increase the frequency of polychromatic erythrocytes containing either small or large micronuclei. In another *in vivo* study, Chinese hamsters were given an oral dose of 0, 1900 or 3800 mg/kg bw 1-methyl-2-pyrrolidone. Bone marrow cells were harvested at metaphase 24 hours after dosing at 1900 mg/kg bw and 24 and 48 hours after dosing at 3800 mg/kg bw. There was no increase in the number of mitoses containing either structural chromosomal aberrations or numerical chromosomal aberrations. It was concluded that 1-methyl-2-pyrrolidone was not genotoxic.

19. According to a published report, groups of 120 male and 120 female Charles River CD rats were exposed to atmospheres containing 0.04 mg/l or 0.4 mg/l of 1-methyl-2-pyrrolidone, 6 hours per day, 5 days per week, for up to 2 years. Control groups of 120 males and 120 female rats were exposed to air only. Groups of 10 male and 10 female rats from each dose group were killed after 1, 3, 6, 12 and 18 months of exposure; the surviving rats were killed after 2 years. Both sexes exposed to the top dose of 0.4 mg/l produced dark yellow urine. In males exposed to 0.4 mg/l, body weight gain was reduced at termination and haematocrit counts and serum alkaline phosphatase concentrations were elevated at 18 months. A complete histopathological examination was carried out on the control and 0.4 mg/l groups only; there were no treatment-related changes. There was no evidence of carcinogenicity.

20. A study published in 2001 reports the results of a two-year feeding study in rats and an 18-month feeding study in mice conducted to evaluate the potential chronic toxicity and oncogenicity of 1-methyl-2-pyrollidone in Crl:CD (SD)BR rats and B6C3F1/crlBR mice. Groups of 62 male and female rats were administered diets containing 0, 1600 mg/kg feed (66.4 to 87.8 mg/kg bw for males and females respectively), 5000 mg/kg feed (207 to 283 mg/kg bw), or 15000 mg/kg feed (678 to 939 mg/kg bw) of 1-methyl-2-pyrollidone for approximately 2 years. Groups of 50 male and female mice were administered diets containing 1-methyl-2-pyrollidone at 0, 600 mg/kg feed (corresponding to 90 and 115 mg/kg bw for males and females respectively), 1200 mg/kg (173 - 221 mg/kg bw), or 7200 mg/kg (1100 - 1400 mg/kg bw) for approximately 18 months. Over the course of the rat study, test substance related decreases in body weight and weight gain occurred at the high dose concentration of 15000 mg/kg feed in males and females. In males only, a toxicologically significant progressive nephropathy occurred at a feed concentration of 15000 mg/kg feed. There was no evidence of carcinogenicity. A NOAEL of approximately 207 mg/kg

bw (5000 mg/kg feed) was established. In male and female mice absolute and relative liver weights were increased at 7200 mg/kg feed, and at 1200 mg/kg feed in males only. These changes are considered to be related to the number of animals with liver tumours and/or centrilobular hepatocellular hypertrophy. The incidence of adenomas and carcinomas was 24% and 26% respectively, for male mice and was above historical control levels. For females, only incidences of hepatocellular adenoma were above historical control values, but not those for hepatocellular carcinoma. These tumours are common in B6C3F1 mice and occurred only at high, hepatotoxic doses and were therefore regarded to be of limited relevance. The NOAEL for chronic toxicity in mice was 600 mg/kg feed, corresponding to approximately 90 mg/kg bw in males based on a modest increase of relative liver weights. The NOAEL for females was 1200 mg/kg feed corresponding to approximately 221 mg/kg bw.

As the NOAELs from chronic toxicity studies were 207 mg/kg bw (rats) and 90 mg/kg bw (male mice) and the maximum theoretical daily intake of 1-methyl-2-pyrollidone is 10 mg/day, margins of exposure of approximately 1250 and 540 respectively can be estimated.

21. No data concerning potential skin sensitisation were provided. However negative results were claimed in some brief published reports describing experiments in guinea pigs and humans. Because of the widespread use of 1-methyl-2-pyrrolidone in industry, it was considered that any potential for skin sensitisation in humans would have become apparent. No further data were required.

22. Healthy male human volunteers were exposed for 8 hours per day, for 4 days, in a chamber containing atmospheric concentrations of 0, 10, 25 and 50 mg/m^3 of 1-methyl-2-pyrrolidone. There were no symptoms of toxicity and no effects on pulmonary function, haematology or clinical chemistry parameters. 1-Methyl-2-pyrrolidone has been widely used as an industrial solvent. Like many solvents, it removes the protective layer of fat when it comes into contact with skin and cases of dermatitis have been reported following occupational exposure. The other reported side effects include headache and eye irritation. Some Member States have set limits for human occupational exposure. In Germany, an Occupational Exposure Limit (OEL) of 80 mg/m^3 has been set. In the UK, an occupational exposure standard (OES) of 412 mg/m^3 over an 8-hour time reference has been set.

23. An ADI of 0.25 mg/kg bw was established by applying a safety factor of 100 to the NOEL of 25 mg/kg bw/day which was established in the 90-day repeated dose toxicity study in dogs.

24. The European Food Safety Authority (EFSA) (2005) established an ADI of 1.0 mg/kg or 60 mg per person based on a NOAEL of 90 mg/kg in male mice from the chronic toxicity study referred to in paragraph 20. The US Environmental Protection Agency (EPA) (June, 2006) found 1-methyl-2-pyrollidone to be non-carcinogenic and non-mutagenic in the majority of studies. Both EFSA and the EPA evaluated the published chronic toxicity study in rats and mice (see paragraph 20) and the published oral developmental toxicity study in rats (see paragraph 15).

25. Male and female crossbred cattle were given two intramuscular injections of 16.7 mg/kg bw of 1-methyl-2-pyrrolidone, 48 hours apart. The 1-methyl-2-pyrrolidone was uniformly ^{14}C-labelled in the ring and was formulated as a commercial antimicrobial preparation. The cattle were slaughtered (3 per time-point) at 12 hours, 5, 15 and 30 days after the second dose. Mean total residues in kidney depleted from 17 215 µg equivalents/kg at 12 hours to 1192 µg equivalents/kg at 5 days and 568 µg equivalents/kg at 15 days. Mean total residues in liver depleted from 15 493 µg equivalents/kg at 12 hours to 1984 µg equivalents/kg at 5 days and 920 µg equivalents/kg at 15 days. Mean total residues in peri-renal fat depleted from 6140 µg equivalents/kg at 12 hours to 1043 µg equivalents/kg at 5 days and 884 µg equivalents/kg at 15 days. Mean total residues in loin muscle depleted from 12 045 µg equivalents/kg at 12 hours to 590 µg equivalents/kg at 5 days and 440 µg equivalents/kg at 15 days. Mean total residues at the last injection site depleted from 14 242 µg equivalents/kg at 12 hours to 837 µg equivalents/kg at 5 days and 618 µg equivalents/kg at 15 days.

26. Male and female cattle were given a single intramuscular injection of 41.32 mg/kg bw of 1-methyl-2-pyrrolidone. The 1-methyl-2-pyrrolidone was ^{14}C-labelled in the carbonyl carbon and was formulated as a commercial antimicrobial preparation. Over 70% of the administered dose was excreted in urine and less than 10% in faeces. The majority of the excreted material was

eliminated within 2 days of dosing. The cattle were killed (1 male and 1 female per time-point) at 1, 4 and 21 days after dosing. Mean total residues in liver depleted from 23 430 µg equivalents/kg, one day after dosing, 4860 µg equivalents 4 days after dosing, to 780 µg equivalents/kg, 21 days after dosing. Over the same time period, mean total residues in kidney depleted from 28 040 µg equivalents/kg to 3420 µg equivalents/kg to 420 µg equivalents/kg and in fat depleted from 2420 µg equivalents/kg to 250 µg equivalents/kg to 200 µg equivalents/kg. Mean total residues in muscle depleted from 19 930 µg equivalents/kg, one day after dosing, to 1670 µg/ equivalents/kg 4 days after dosing to 350 µg equivalents/kg, 21 days after dosing and residues at the injection site depleted from 20 140 µg equivalents/kg to 1650 µg equivalents/kg to 260 µg equivalents/kg. More than 90% of the residues in liver samples taken one day after dosing were extractable with methanol alone but proteolytic enzymes were required to release the residues at later time points. In liver samples taken 1 day after dosing 46% of the residues consisted of N-methylsuccinimide; around 15% consisted of succinimide and 6 to 9% was 2-pyrrolidone.

27. Male and female crossbred pigs were given a single intramuscular injection of 41.32 mg/kg bw of 1-methyl-2-pyrrolidone. The 1-methyl-2-pyrrolidone was ^{14}C-labelled in the carbonyl carbon and was formulated as a commercial antimicrobial preparation. The pigs were killed (1 male and 1 female per time-point) at 1, 4 and 21 days after dosing. Mean total residues in liver depleted from 21 800 µg equivalents/kg, one day after dosing, to 136 µg equivalents/kg, 21 days after dosing. Over the same time period, mean total residues in kidney depleted from 26 600 µg equivalents/kg to 52 µg equivalents/kg and in fat depleted from 5200 µg equivalents/kg to 71 µg equivalents/kg. Mean total residues in muscle depleted from 18 300 µg equivalents/kg, one day after dosing, to 69 µg equivalents/kg, 21 days after dosing and residues at the injection site depleted from 18 200 µg equivalents/kg to 70 µg equivalents/kg. In liver samples taken 1 day after dosing 12 to 15% of the residues consisted of N-methylsuccinimide; around 62 to 66% consisted of succinimide.

28. No proposal for a routine analytical method for the determination of residues of 1-methyl-2-pyrrolidone in tissues was provided.

29. In all the species studied (rats, humans, cattle and pigs), and regardless of the route of administration (oral, topical, parenteral), 1-methyl-2-pyrrolidone was rapidly metabolised and excreted, mostly in the urine as metabolites. In rats, 12 hours after dosing, the residues in plasma consisted mostly of polar metabolites. Up to approximately 4% of the total residues excreted in the urine of all species consisted of unmetabolised 1-methyl-2-pyrrolidone, but the substance was normally detectable only in urine samples taken up to one day after dosing. Although residues of unmetabolised 1-methyl-2-pyrrolidone were found in rat liver 4 hours after dosing, the substance was not detectable in the liver of cattle or pigs one day after dosing. The metabolites identified in urine and liver included 2-pyrrolidone, which is already included in Annex II of Council Regulation (EEC) No. 2377/90. No residue depletion data were provided for milk. However, the substance was used as a solvent in injectable antibacterial formulations for cattle, and ectoparasiticide formulations for topical administration to sheep, for which withdrawal periods for milk had been established in respect to the active ingredient of the medicinal product.

Conclusions and recommendation

Having considered that:

- an ADI of 0.25 mg/kg bw (i.e. 15 mg/person) has been established for 1-methyl-2-pyrrolidone,
- 1-methyl-2-pyrrolidone is rapidly and extensively metabolised and excreted,
- one day after the end of treatment, the amount of total residues derived from edible tissues of pigs and cattle represents approximately 66% of the ADI,
- the current use of 1-methyl-2-pyrrolidone in food producing species is not likely to result in residues in milk at concentrations of concern to the consumer;

the Committee for Veterinary Medicinal Products concludes that there is no need to establish MRLs for 1-methyl-2-pyrrolidone and recommends the amendment of the current entry in Annex II of Council Regulation (EEC) No 2377/90 in accordance with the following table:

Pharmacologically active substance(s)	Animal species	Other provisions
1-Methyl-2-pyrrolidone	All food producing species	