Abbreviations

ANOVA	Analysis of variance
AUC	Area Under Curve
C_{max}	Maximum concentration
DRM	Doramectin
endectocide	Macrocyclic lactone antiparasitic against both (some) endoparasites and ectoparasites
epg	Eggs per gram of faeces
FEC	Faecal egg count
GABA	Gamma-amino butyric acid
IVM	Ivermectin
lpg	Larvae per gram of faeces
ML	Macrocyclic lactone
MXD	Moxidectin
po	*Per os*
sc	Subcutaneous
s.e.m.	Standard error of the mean
t_{max}	Time when maximum concentration is reached after drug administration

Introduction

Reindeer, the circumpolar cervid

The reindeer genus *Rangifer* comprises only one species, *R. tarandus* living in the northern hemisphere, both in the Palaearctic (Eurasian) and Nearctic (American) areas (Banfield, 1961). It inhabits most of the circumpolar land areas not covered by permanent ice. The southernmost reindeer (apart from those introduced to the southern hemisphere) graze in China (50 °N) and the northernmost on Svalbard, Greenland and arctic islands of Canada, even north of 80 °N. According to current systematics, there were 12 subspecies of *R. tarandus*, but two of them are now extinct (in Nieminen, 1994). There is not full agreement about the number of subspecies, other authors (e.g. Tyler & Røed, 1993) count 7 subspecies. The most important reasons for the evolution of the subspecies have apparently been the separation of the Asian and American continents and the repeated glacial periods (in Nieminen, 1994). The Nearctic wild reindeer is called caribou.

The semi-domesticated reindeer descends from the wild Eurasian mountain or tundra reindeer *R. t. tarandus*. There are still some 33 000 wild mountain reindeer in southern Norway, where they are important game animals (Skogland, 1994). As late as in 1970 it was estimated that there were also 22 000 wild reindeer on the Kola peninsula, but the number decreased to 2700 in 1984 (in Syroechkovskii, 1995). The semi-domesticated reindeer has probably also genes from the wild forest reindeer, *R. t. fennicus*, with which it readily cross-breeds. Some years ago, there were about 1 000 wild forest reindeer in Finland, partly in a close neighbourhood of the reindeer husbandry area (Kojola, 1995), but the population is growing. A relatively recent estimate of the population of this subspecies in Russian Karelia is 6 000 to 10 000 animals (in Nieminen, 1993a). The wild reindeer has always been a popular game animal wherever it shares habitat with humans. Reindeer hunt was practised in central Europe before the last Ice Age, and in Norway there is evidence of hunt 10 000 to 12 000 years ago.

The semi-domesticated reindeer

The reindeer has been crucial to the Saami and other northern peoples and cultures, enabling the settlement of the barren arctic and subarctic regions. The first report on European reindeer husbandry is obviously from AD 892, when the Norwegian chieftain Ottar informed King Alfred of England that he owned 600 reindeer, six of which were valuable decoy animals used to lure wild reindeer. Reindeer husbandry obviously developed from such hunt with decoy animals (in Vorren & Manker, 1976; Skjenneberg, 1984).

The contemporary estimate of the total *Rangifer* population of the world is nearly 8 million animals, half of them semi-domesticated (Staaland & Nieminen, 1993). About 20% of the semi-domesticated reindeer are in Fennoscandia (Finland, Sweden and Norway) and 75% in Russia, and the rest in North America and Greenland, with some thousand wild descendants of released semi-domesticated reindeer on Iceland, South Georgia (54°30'S, 37°0'W) and Kerguelen (48°15'S, 69°10'E). Small-scale reindeer herding is also practised in Scotland and Japan (in Nieminen, 1993b).

The main reindeer product is meat, but also hides possess a considerable income in Finland (Nieminen, 1992). In Russia reindeer are still important draught animals, and they are also milked and used in riding at some locations (Nieminen, 1995). Reindeer racing is becoming popular in Fennoscandia, so much so that doping tests have been introduced (Nieminen *et al.*, 1997). Velvet antlers constitute the major reindeer product in Alaska (Nieminen & Muhonen, 1996).

Reindeer calves are born mostly in May and early June with a body weight of 4-7 kg, and grow fast during the summer, commonly reaching body weight of 50 kg or more in September-October. Reindeer seldom deliver twins. In many areas, calves are ear-marked in midsummer. To do it, the flock must be rounded up. The next round-ups take place in autumn or winter, when animals are selected for breeding, and others are slaughtered. Those selected to live are often treated with antiparasitics (Kemppainen *et al.*, 1997).

Finnish co-operative reindeer husbandry

The Finnish reindeer husbandry organisation was founded in the 18th century. The basic unit, the reindeer herding co-operative, is called *paliskunta*, which name was first used in the beginning of the 19th century. Reindeer are owned by individual herders within a co-operative, but the pastures are common. The co-operatives are mostly separated from each other my means of fences. Presently there are 56 co-operatives, 40 in Lapland and 16 in the province of Oulu. The Finnish paliskunta has counterparts in Sweden, *sameby*, and in Norway, *reinbeitedistrikt*, or *siida*. The organisation structures differ, as in the Scandinavian countries the level of co-operation is lower, and reindeer

husbandry is limited to the indigenous Saami people. In Finland anybody (European Economic Area citizens) living within the reindeer husbandry area and being a member of the local co-operative has a legal right to own reindeer (Huttu-Hiltunen, 1993). In Finland, there are 6800 reindeer owners, and about 800 families live primarily on reindeer husbandry, but another 1000 get a considerable part of their living from reindeer (Anon., 1998). The reindeer husbandry area now comprises 115 000 square kilometres, or slightly over one third of the country.

The co-operative reindeer herding system has proved flexible and has continuously adapted new methods to intensify production. The total number of reindeer in Finland was 37 000 in 1845 (in Nieminen, 1993a). During the first half of the 1970's the number oscillated between 100 000 and 150 000. Because of the launch of new techniques, such as calf slaughter, winter supplementary feeding, and antiparasitic treatment, as well as the use of motorised herding, the amount increased rapidly, reaching 200 000 to 250 000 during the latter half of the 1980's. Between 1970 and 1976, the annual number of animals slaughtered averaged 38 000. It peaked in 1990-1991, when 160 000 reindeer were slaughtered. After that, both the overwintering population and the amount slaughtered have diminished. During 1996-1997, 202 000 reindeer were counted alive, 28 000 of which were calves. Eighty-eight thousand reindeer were slaughtered, whereof 61 000 calves (Anon., 1998). While calves contributed to less than one third of the slaughter reindeer in the early 1970's, the current proportion is about three fourths (Kemppainen *et al.*, 1997).

Carrying capacity of the Finnish reindeer pastures was clearly exceeded during several decades (Kojola & Helle, 1993; Kumpula *et al.*, 1997). It has been extended with increased supplementary feeding and pen-feeding where winter pastures are scarce (Helle & Kojola, 1993; Kemppainen *et al.*, 1997; Nieminen *et al.*, 1998). In addition, the increased slaughter of calves keeps the overwintering population low. To minimise parasite-induced damage to the condition of the animals, antiparasitic treatment is used. This may indirectly help in keeping the overwintering breeding stock as small as possible. About 80% of overwintering reindeer are treated yearly with ivermectin (Anon., 1993). Future challenges are in sustainability; balancing reindeer husbandry and its productivity needs with the carrying capacity of the pastures, not forgetting the other needs of the ground, e.g. conservation, forestry, agriculture and tourism.

PARASITE FAUNA OF THE REINDEER AND ANTIPARASITIC MEASURES

A parasite is a symbiont living on the cost of the other counterpart of the symbiosis, the host. Reindeer harbour a variety of different parasites (see Halvorsen, 1986). Although viruses, many bacteria and fungi are definitively parasitic, they are not handled with in this thesis. So, the parasites here are (invertebrate) animals living of the reindeer. Furthermore, those not practically controllable with current macrocyclic lactone (ML) endectocides are not discussed at all. ML endectocides have efficacy against nematodes and arthropods, which phyla contain many important reindeer parasites. It is worth specially noticing that ML endectocides do not have efficacy against cestodes, such as *Echinococcus* and *Moniezia* tapeworms, and trematodes, such as the *Paramphistomum* rumen fluke and liver flukes. The knowledge on the efficacy of ivermectin against reindeer parasite species is discussed in a later chapter (page 27), and because other ML endectocides are newer products, there is no former literature on the use of them in reindeer.

Losses estimated to be due to reindeer parasites (gain of treatment)

It is perhaps principally erroneous to discuss parasite-induced losses in reindeer, as the parasites certainly belong to the ecosystem the reindeer live in, almost like weather and vegetation, and are not so easily separable additions. It is therefore better to debate in terms of possible gains caused by antiparasitic treatment. In older literature, however, attempts to estimate the costs of parasitism were often made. Nordkvist (1967) estimated warbles and throat bots to consume 15-20% of the reindeer production income in Sweden, and Saval'ev (1968) approximated warbles alone to reduce the income of the Soviet reindeer husbandry by 25-30%. Thinking about such high losses of production, control measures might easily appear worthwhile. There is, however, very little scientific evidence that organophosphate treatments would have improved the survival or weight gain of reindeer, although several experiments showed a high degree of efficacy against warbles and throat bots (Nordkvist 1967; Klement'eva, 1975; Nieminen *et al.*, 1980; Persen *et al.*, 1982). In one experiment, weight loss during winter was higher in famphur treated calves than in untreated ones, but the

subsequent higher weight gain during summer compensated the winter weight loss, leading to slightly higher mean slaughter weights in treated animals the next autumn (Persen *et al.*, 1982). Parasite weight might at least partly have been responsible for the higher live weight of untreated animals in the spring. A single full-grown 3rd stage warble larva weighs 1.6 to 1.7 g (Nilssen, 1997a). Nordkvist (1967) calculated that a normal warble infection could make up a larval mass of about 500 g per reindeer. The probably higher value of intact hides from reindeer treated during the previous years might have increased the profitability of organophosphate treatment.

Later, using ivermectin, Nordkvist *et al.* (1984) showed significantly lower mean live weight loss (10.2 kg compared with 14.0 kg) in treated than in non-treated reindeer calves during winter. In another trial, a significant increase in mean live weight gain of about 3 kg was seen during the subsequent year in treated calves as compared to non-treated ones (Heggstad *et al.*, 1986).

In one trial, antiparasitic treatment with ivermectin increased antler symmetry, which was speculated to be related with reproductive success (Folstad *et al.*, 1996).

Summer treatment of reindeer calves with ivermectin or luxabendazole (broad-spectrum benzimidazole anthelmintic with efficacy against nematodes, cestodes and trematodes) has in two small trials increased the weight gain of reindeer calves before the slaughter season (Oksanen & Nieminen, 1995; Oksanen *et al.*, 1996). This indicates that subclinical parasitism may be a growth-limiting factor to reindeer calves, at least if the infection pressure is high.

Parasite species

Nematodes

Nematodes are commonly considered the most important parasites of domestic ruminants. In cattle, sheep and goats, gastrointestinal nematodes can cause even fatal disease or, more commonly, subclinical infection that leads to impaired production (Urquhart *et al.*, 1987). The most important gastrointestinal nematodes are those of the abomasum (*Ostertagia* spp., *Haemonchus* spp.) but also nematodes of the small intestine (*Trichostrongylus* spp., *Nematodirus* spp., *Cooperia* spp.) are regarded as important pathogens in some areas (Soulsby, 1982). The other important group of parasitic nematodes in domestic ruminants is the *Dictyocaulus* spp. lungworms. In farmed red deer (*Cervus elaphus*), *Dictyocaulus* lungworms are considered the most important parasites (Watson & Charleston, 1985), but also abomasal nematodes may cause clinical disease (Connan, 1991).

Brainworm

A lot of nematode species are known also from the reindeer, but most of them have usually been regarded as rather harmless. The most widely recognised pathogen is probably the brainworm *Elaphostrongylus rangiferi*, which is blamed for severe outbreaks of meningoencephalitis after warm and rainy summers (Handeland & Slettbakk, 1994). Reindeer brainworms have been studied extensively (e.g. Bakken & Sparboe, 1973; Halvorsen, 1986; Handeland & Norberg, 1992; Hemmingsen *et al.*, 1993; just to name a few). The life cycle of the brainworm is heteroxenous with snails as intermediate hosts and reindeer as definitive host. The reindeer brainworm can also infect moose (Stéen *et al.*, 1997), sheep and goats (Handeland, 1991; Handeland & Sparboe, 1991, Handeland & Skorping, 1992).

Gastro-intestinal nematodes

Reindeer are also known to harbour several species of abomasal and intestinal nematodes (Bye & Halvorsen, 1983; Bye, 1987; Bye *et al.*, 1987; Fruetel & Lankester, 1988; Korsholm & Olesen, 1993), but so far there is only little evidence of their clinical importance (Christensson & Rehbinder, 1975; Rehbinder & Christensson, 1977; Rehbinder & von Szokolay, 1978). However, Arneberg *et al.* (1996) clearly showed that abomasal nematodes depress food intake in reindeer during late winter. Reindeer calves, born mostly in May, pick up infective stages of gastro-intestinal parasites soon after their birth and harbour patent nematode infections as early as late June or early July (Oksanen *et al*,. 1990).

The most important gastro-intestinal nematodes are those in the abomasum (Fruetel & Lancaster, 1988), but reindeer calves have also *Nematodirus* and/or *Nematodirella* nematodes of the small intestine (Bye, 1987; Oksanen *et al.*, 1990). The reindeer specific species are *Nematodirus tarandi* and *Nematodirella longissimespiculata*, but also other species primarily from other hosts may parasitise reindeer (Fruetel & Lankester, 1988). Other intestinal nematodes are *Capillaria* sp. (Christensson & Rehbinder, 1975; Rehbinder & Christensson, 1977; Nordkvist *et al.*, 1983, 1984) and *Trichuris* sp. (in caribou, Fruetel & Lancaster, 1988). The life cycles of intestinal nematodes are not well-known, but the transmission is probably direct. It is known that the eggs of *Nematodirus*

battus of lambs develop further and hatch only after winter, but eggs of other species of the genus may hatch during the summer they were produced (Urquhart *et al.*, 1987). Thus, *N. battus* from lambs produce eggs that become infective for the lambs of the subsequent year. It is not known whether *N. tarandi* follow a pattern similar to *N. battus* or not, but the short summer of the Arctic might make that strategy beneficial.

Pinworms of the genus *Skrjabinema* live in the caeca of ruminants. Females deposit eggs on the perianal skin, where they drop off and can be with faecal samples. The parasites are not considered pathogenic (Soulsby, 1982), but are occasionally observed in sheep and goats (Borgsteede and Dercksen, 1996). In one experiment, immature and adult *Skrjabinema ovis* were present in two ivermectin treated goats (DeVaney *et al.*, 1992). One species of the genus, *S. tarandi*, is known to occur in reindeer, also in Finland (S. Nikander, unpublished). Eggs of the genus are easily recognised because of their highly asymmetrical shape.

Abomasal nematodes

The most common abomasal nematode species is the reindeer specific *Ostertagia gruehneri* (Bye & Halvorsen, 1983; Bye, 1987; Nikander, 1988; Fruetel & Lancaster, 1988). Another reindeer specific species, *O. arctica,* is now considered the less common morphotype of *O. gruehneri* (Lichtenfels *et al.*, 1990). Moreover, many species that principally parasitise other cervids or domestic ruminants have been found in reindeer abomasum (Pryadko, 1976; Bye & Halvorsen, 1983; Fruetel & Lancaster, 1988; Korsholm & Olesen, 1993). The life cycle of *O. gruehneri* is obviously similar to that of other members of the genus. Seasonal inhibition, as known in *Ostertagia* spp. from domesticated ruminants in temperate areas (e.g. Michel *et al.*, 1974; Thomas & Waller, 1979) and also from deer (Connan, 1991, 1997; Belem *et al.*, 1993), has also been observed in reindeer (Nordkvist *et al.*, 1984). The long arctic winter obviously makes this strategy meaningful for parasite (and host) survival. It has been found that the abundance of abomasal nematodes in reindeer calves may be considerably lower than that of adult reindeer (Bye & Halvorsen, 1983; Bye, 1987), which is in discrepancy with what is known from domestic ruminants. The importance of milk as a source of nutrition to reindeer calves may explain this finding (see Nieminen, 1994). An interesting and surprising abomasal nematode species found in the wild polar Svalbard reindeer *Rangifer tarandus platyrhynchus* (Bye & Halvorsen, 1983; Bye *et al.*, 1987) is *Marshallagia marshalli*, the distribution of which is generally considered to be much more southern in domesticated ruminants (Soulsby, 1982; Barth, 1991).

Lungworm

Lungworm infection is common in reindeer and may cause serious disease (Kummeneje, 1977; Dau, 1981; Holmström *et al.*, 1989). The causative species was earlier identified as *Dictyocaulus viviparus*, that of bovines, but now the reindeer species is most often referred to as *D. eckerti* (Skrjabin *et al.*, 1971; Rahko *et al.*, 1992; Nikander & Saari, 1993).

Vector-transmitted nematodes

Besides the nematodes infecting reindeer orally, there are several known or suspected arthropod vector -transmitted nematode parasite species in reindeer. *Onchocerca tarsicola* was commonly detected (30%) in tibiotarsal or radiocarpal regions of limbs of 407 Finnish reindeer. The worms were most often found in flat swellings or nodules of connective tissue in membranes surrounding the tendons of the tibiotarsal and radiocarpal joints (Bylund *et al.*, 1981). The parasite is transmitted by simulids (Schulz-Key & Wenk, 1981). *Lappnema auris* is a nematode which induces the formation of large fibrotic nodules on the auricles of reindeer. Males of the parasite are unknown, and parthenogenetic reproduction is suspected (Bain & Nikander, 1983). The species has become rare, perhaps because of endectocide treatment (Nikander, 1992). Subcutaneous parasitic nodules in the muzzle of reindeer were thought perhaps to be caused by an *Onchocerca* nematode (Lisitzin, 1964). Both *O. tarsicola*, *E. rangiferi* and *Setaria tundrae* were found in visceral granulomas of Swedish reindeer (Rehbinder *et al.*, 1979; Rehbinder, 1990). In Alaska, *Setaria* of the reindeer has been identified as *Setaria yehi*. The parasite has been associated with subclinical chronic peritonitis (Dieterich & Luick, 1971).

Nematocidic treatment

Because the brainworm is considered a dangerous pathogen, several anthelmintics have been experimented against it. No efficacy was seen following treatment with chlorophos, ditrazine phosphate, phosphamide or tetramisole, while phenothiazine temporarily reduced their reproduction (Smirnov, 1976). In one experiment, reindeer infected with *E. rangiferi* were treated daily for 10 days with mebendazole given at 6

mg/kg bodyweight in feed. This treatment eliminated brainworm larval production for at least 43 days, but in another group of reindeer a single dose of mebendazole at 40 mg/kg bodyweight did not remove these larvae (Rehbinder *et al.*, 1981). In another trial, both mebendazole and fenbendazole at 6 mg/kg/day for 10 days had high efficacy against *E. rangiferi* (Nordkvist *et al.*, 1983). Oral tetramisolum at 10 mg/kg 2 or 3 times a year has been empirically observed to eliminate *Dictyocaulus* and *Trichostrongylus* species from reindeer herds (Kurkela & Kääntee, 1978).

Arthropods

Both insects, arachnids and pentatastomids include parasites of reindeer.

Insects

Insect parasites of reindeer, excluding harassment by blood-sucking insects, include lice and oestrid flies. Sucking lice, *Solenopotes tarandi,* were originally described in Sweden (Mjöberg, 1915) and are also known from Alaska (Weisser & Kim, 1973). Biting lice, *Damalinia tarandi*, were also described in Sweden (Mjöberg, 1916), and are also known from Finland (A. Oksanen, unpublished). The pathogenic effect of lice in reindeer is unknown.

There are two oestrid fly species (Diptera: Oestridae) parasitising the reindeer, the warble fly *Hypoderma tarandi* and the throat bot fly *Cephenemyia trompe*. The imagos of these flies lack mouth parts, and do not feed. Therefore, the entire nutritional needs are covered by parasitism during the larval stage (see Nilssen & Anderson, 1995b).

Warble

Larvae of *H. tarandi* are called warble fly larvae (e.g. Helle, 1980), subcutaneous gadfly larvae (Solopov, 1989), warble bots (Nilssen & Haugerud, 1995) and grub fly larvae (Nordkvist, 1967). Because of simplicity, and consistent with Dieterich & Craigmill (1990) and Vercruysse (1993), they are here called just warbles, even though this word can also refer to the whole papule formation, consisting both of the larva and host tissue reaction. In Latin, reindeer warble was earlier called *Oedemagena tarandi* (also in publications I and III), but the inclusion of the species in the genus *Hypoderma* is now generally accepted (Wood, 1987).

The life cycle of *H. tarandi* is very similar to that of other species of *Hypoderma* (e.g. *H. bovis* and *H. lineatum* of cattle). Female warble flies lay eggs on hairs of the host, especially on feet, during the summer (Saveljev, 1968; Anderson *et al.*, 1994). The larvae hatch, crawl down the hair and penetrate the skin (Karter *et al.*, 1992). They wander in the connective tissue, and reach the subcutaneous tissue of the back, where they mature to the 3rd instar (Breyev, 1971). During the winter, they perforate the skin and breath through the hole. In spring the mature larvae emerge, drop down, bury to the ground, where they pupate, and the imagos emerge about one month later (Nilssen, 1997b). The infection intensity in reindeer is often high; the average number (150-200) is some ten times higher than that of *H. bovis* and *H. lineatum* in cattle (Breyev, 1961).

Warbles are nearly ubiquitous in reindeer. Generally, just the northernmost Arctic herds, and those in the southern hemisphere, are unaffected. They are absent from Svalbard and Iceland (Skjenneberg & Slagsvold, 1968; Saval'ev, 1968; Leader-Williams, 1980; Wahburn *et al.*, 1980). In the barren ground caribou of the Canadian Beverly herd located south from 65°N, as many as 97 to 100% of animals sampled had warbles, but in the Peary caribou on the Canadian Parry Islands (75°N) only 14% were infected (Thomas & Kiliaan, 1990). A plausible explanation for the absence of warbles from the high Arctic regions is the cold climate. The free-living pupae require at 12 °C not less than 50 days to develop, while at 27 °C development could take less than 10 days (Nilssen, 1997b).

Nordkvist (1967) estimated that normally more than 95% of reindeer were infected in Sweden. In western Finnmark in northern Norway, 99.9% of 1305 reindeer hides were warbled (Folstad *et al.*, 1989). In Finland the prevalence and infection intensity of reindeer warbles were investigated in adult males, females and calves of six reindeer herding co-operatives (Helle, 1980). A general observation was that calves and males were more heavily infected than adult females, which is in agreement with the Norwegian results (Folstad *et al.*, 1989). In Finland, both prevalence and infection intensity were lowest in the southernmost co-operative located in the forest area, prevalence there in calves being from 42 to 63% and abundance (mean intensity) from 3 (s.e.m. 1) to 11 (4) during the three year study. In the northernmost co-operatives the prevalence was 87 to 100%. Abundance there varied between 23 (6) and 75 (6) larvae. Warbles were thus most common in the northernmost areas. It is possible that the flies find each other and the reindeer easier in the open terrain of the north (Helle, 1982).

Earlier, warbles were often removed mechanically by compressing them between the thumb and

forefinger in the spring. Bergman (1917) experimented with covering the back of reindeer with tar to suffocate warbles instead of the laborious compression. The results were promising, but the method never became widely used. Instead, the compression method was still utilised sporadically. Even though the procedure was laborious, Saval'ev (1968) considered it useful irrespective of other possible control measures. After compression, the warble holes could be covered with creolin emulsion (Saval'ev, 1968). Another control method of warbles and throat bots was resting the herd on wet swamps in early summertime in order to let the emerging larvae drown (Nordkvist, 1967).

Because of their specific attraction to light coloured reindeer, warble fly females were lured to land on unfolded white hides where they were easily killed, which was a task of youths (Saval'ev, 1968). Other prophylactic measures were driving the herd after calving at least 50 to 60 kilometres away from the place where the parasite larvae were shed, and not returning to the calving ground before mid September (Saval'ev, 1968). This kind of migration is considered natural to the reindeer (Folstad *et al.*, 1991). Hadwen (1926) noticed that Lapland reindeer had fewer warbles than those in Alaska, perhaps because the herds were constantly moving. He also mentioned to have seen dark sheds in Finnish Lapland that provided shelter to reindeer against all forms of insect harassment. Such a «*liemu*» shed can nowadays be seen at the *Siida* Saami museum in Inari. Also smokes have been used to repel insects during the warmest summer days (Saval'ev, 1968). On the other hand, carbon dioxide has been used to attract warble and throat bot flies, as well as blood-sucking insects for scientific purposes (Helle *et al.*, 1992; Anderson & Nilssen, 1996).

With the changing reindeer husbandry habits, defined chemical antiparasitics were adopted. In Russia, dichloro-diphenyl-trichloroethane (DDT) was sprayed together with hexachlorane against harassment by blood-sucking insects as well as warble and throat bot flies (Saval'ev, 1968). To treat a herd of 1000 reindeer, 12.5 kg of pure DDT and the same amount of hexachlorane was needed for one summer season. According to the author, carefully performed treatment increased the weight gain of the animals during the summer by 5 to 6 kg. The amount of warbles decreased also improving the quality of hides. Other insecticides were found effective as well; both chlorophos and pyrethrum (pyrethrin I) were found to act faster than DDT (Saval'ev, 1968).

If warbles become less abundant for example due to antiparasitic treatment, serological tests may be used in early detection of infected animals (see Monfray & Boulard, 1990).

Throat bot

Throat bots are also called nasal bots (Dieterich & Craigmill, 1990), nostril fly larvae (Helle, 1980), nose bot fly larvae (Nilssen & Haugerud, 1995) and nasal warble fly larvae (Saval'ev, 1968). Besides the scientific name *Cephenemyia trompe*, also an erratic form, *Cephenomyia trompe,* has been used (also in publications I-III). The confusion in the scientific name is based apparently on a 150 years old mistake (see Zumpt, 1965). After that, both names have been used, and the erroneous form *Cephenomyia* has been very common. Modeer (in 1786) is generally considered the author of the original description, but as Linné obviously knew the parasite already in 1722, some scientists have regarded him as the original author. The geographical distribution of throat bots follows rather closely that of warbles (Bennett & Sabrosky, 1962; Skjenneberg & Slagsvold, 1968).

Temporally, the life cycle of *C. trompe* resembles that of *H. tarandi*. The bots mature in tonsil pouches (Rehbinder & Nordkvist, 1983) during the spring, drop down to the ground, pupate and emerge as mature flies in the summer. The flies have mating places on prominent hill-tops. After mating, the female flies expel uterine fluid with larvae to the muzzle of reindeer (Anderson & Nilssen, 1990). The larvae invade the tonsil pouch, where the development is very slow in the beginning (Hadwen, 1926; Nilssen & Haugerud, 1995). Rapid development starts in the spring. Earlier, definitive diagnosis of throat bots required the slaughter of animals (e.g. Nilssen & Haugerud, 1995).

Before the commercial pharmaceuticals became available to reindeer herders, tobacco water was used for «deworming» throat bots. It was poured into the pharynx via the nostrils or mouth (Nieminen, 1989). Bots could also be removed manually by inserting a petroleum jelly lubricated hand into the mouth and pharynx of a well restrained animal. This task was entrusted to small-handed women or youths, and could only be carried out on adult reindeer (Saval'ev, 1968).

When throat bot flies were noticed to have specific mating places, attempts were made to kill the flies there by spraying the mating hilltops with hexachlorane (Saveljev, 1972). The method was never widely used, as main concern also in Russia was given to the treatment of parasitic stages with

organophosphates (Nepoklonov *et al.*, 1973). Later, it has been found that mating sites are far too numerous to be practical targets for control (Nilssen & Anderson, 1995a). The mating sites of *H. tarandi* are even more difficult to control in practice (Anderson *et al.*, 1994).

In the 1950's and 1960's, several systemically administered organophosphates were experimented with in Russia and some of them were found efficacious against reindeer warbles and throat bots (Savel'ev *et al.*, 1972; Nepoklonov *et al.*, 1973). Good efficacy of famophos, trichlorfon and fenthion against these parasites was reported also in Sweden (Nordkvist, 1967, 1980). In Finland, the organophosphates fenthion and famphur were taken into practice in the late 1970's (Mykkänen, 1978) and their good efficacy against warbles (Nieminen *et al.*, 1980) and throat bots made them popular in a short period until the ivermectin era began.

Arachnids

Arachnids can also give trouble to reindeer. Locally in Russia, reindeer are known to be parasitised by both sarcoptic and chorioptic mange mites (Saval'ev, 1968). *Sarcoptes scabiei* causes first small vesicles but later the affected skin may become covered by even a few centimetres thick scabs. Reindeer suffering from sarcoptic mange gradually lose their condition. During winter the weight loss is rapid, and the affected reindeer may perish (Saval'ev, 1968). The disease can be transmitted to humans, too. Once, the source of sarcoptic scabies in Taimyrian reindeer was traced to infected cattle (Mitskovich & Savel'ev, 1984).

Chorioptic mange mites cause local bald spots with no thick scabs and are not considered as serious pathogens as sarcoptic mange mites (Saval'ev, 1968). Rather apathogenic appearing chorioptic mites (*Chorioptes texanus*) are known from the ears of reindeer in Canada (Sweatman, 1958) and Finland (S. Nikander, unpublished). Apart from that, reindeer parasitic mites are not known from Fennoscandia.

As sarcoptic mange was considered an important reindeer health problem in Russia, means of chemotherapy were developed. In spring and summer hexachlorane and hexachlorane-creolin liniments were used, or if the situation was considered really serious the whole animals were dipped in solution containing the same medication. In winter, dipping of the reindeer would lead to chilling, so the animals were treated by fumigation. The reindeer was placed in an airtight chamber with a hole for the head. Inside the chamber, a cast iron stove was heated with timber. A tray filled with sulphur was placed on the stove to produce sulphur dioxide fumes. The treatment lasted for 40-45 minutes and was repeated one week later. Also the reindeer harnesses, saddles and accessories were fumigated. An important part of mange control was also the isolation of infested animals and herds (Saval'ev, 1968).

Pentastomids

Reindeer are parasitised by one member of the phylum; *Linguatula arctica* is morphologically close to the widespread (although not prevalent) *L. serrata* of dogs and other species of tropical carnivores. *L. arctica* is called «sinus worm» because it lives in the paranasal sinuses of reindeer, especially calves. The species and different aspects of life cycle, epidemiology, pathogenity, taxonomy and antiparasitic treatment of *L. arctica* have been described and reviewed by Haugerud (e.g. 1986, 1989; Haugerud *et al.*, 1993).

No interspecific covariation

In one study, there was no association between the reindeer brainworm and gastrointestinal nematode infection intensities measured as faecal larva and egg counts (Karter, 1993). Likewise, no interspecific covariation was found in intensities of the brainworm, abomasal nematodes, warble, throat bot, and sinus worm in 351 reindeer calves examined *post mortem* from herds where antiparasitic treatment had not been performed (Nilssen *et al.*, 1998). So, a high (or low) warble burden is not indicative of the size of the abomasal nematode burden in the individual. The study also indicates transmission, not immunity, to be the key factor for parasitic infection.

MACROCYCLIC LACTONE ENDECTOCIDES

There are already thousands of publications on the macrocyclic lactone (ML) endectocides. This review is highly selective to include just those considered pertinent to the introduction to the subject of this thesis.

History of the endectocides commercially available

Ivermectin

The experience with many insecticides, anthelmintics and antibacterial antibiotics shows that revolutionary new drugs may soon lose their efficacy as evolution produces pests resistant to the new drugs. However, the discovery of the extremely high antiparasitic properties of a new group of macrocyclic lactones produced by soil

actinomycetes opened a totally new era in the antiparasitic treatment of livestock in the late 1970's and early 1980's. The group was called avermectins (*a* - negation, *ver* - worms, *ect* - ectoparasites, *in* - pharmaceutical product) (Shoop *et al.*, 1995). The producing actinomycete was thereafter named as *Streptomyces avermitilis*. The first commercial application, launched in 1981, a semisynthetic derivative of avermectin B_1, is called 22,23-dihydroavermectin B_1, or ivermectin. It is a mixture containing not less than 80% of the component B_{1a} and not more than 20% of the component B_{1b}, both of which molecules have antiparasitic activity (Shoop *et al.*, 1995). Because of the very high commercial success of ivermectin (Ivomec®, MSD, now Merial), intense activity was triggered in the fields of chemistry, pharmacology and parasitology to find even more effective molecules, or at least commercially feasible ones.

Since the launch of ivermectin in 1981, until 1998, another five commercial ML endectocides have been introduced for use in production animals.

Abamectin

Abamectin, or avermectin B_1, was developed by the same medical company as ivermectin and is, interestingly, a natural fermentation product of *S. avermitilis*, and the direct raw material of ivermectin. Like ivermectin, also abamectin is a mixture containing not less than 80% of avermectin B_{1a} and not more than 20% of avermectin B_{1b}. Abamectin was registered in 1985 in Australia (Avomec®, MSD) for the treatment of various endo- and ectoparasites in cattle and is now also available in Europe (Enzec®, Janssen) (Heinze-Mutz *et al.*, 1993). The nematocidic and acaricidic activities of abamectin surpass its insecticidic activity (Shoop *et al.*, 1995). Abamectin is also used in crop protection (Dybas, 1989) which may be a cause of environmental concern as much as avermectin use in farm animals.

Moxidectin

The next endectocide to reach the market was a milbemycin derivative. The milbemycins (*milbe* - mite, *myc* - fungus, *in* - pharmaceutical product), like avermectins, are 16-membered macrocyclic lactones. They differ from the avermectins as they do not have the bisoleandrosyloxy substituent at the 13-position of the macrolide ring (McKellar, 1994). The milbemycins were already detected before the avermectins, but their full antiparasitic potential was not realised immediately. First they were aimed against mites in crop production (Shoop *et al.*, 1995). The actinomycete *Streptomyces cyaneogriseus* ssp. *noncyanogenus* produces a milbemycin called nemadectin (apparently *nema* - nematode, *ect* - ectoparasites; Zulalian *et al.*, 1994). Chemically modified nemadectin becomes moxidectin (the name from the *m*eth*oxi*me substitution of the carbon C23). Moxidectin is marketed (Cydectin®, American Cyanamid, now Fort Dodge) world-wide for domestic animal endectocide treatment.

Moxidectin is one hundred fold more lipophilic than ivermectin as measured by the standard octanol/water partitioning ratio. The lipophility of moxidectin causes that it is preferably stored in fat and this storage probably contributes to the much longer depletion half life measured in sheep than that of ivermectin (Hayes, 1994).

Moxidectin is more efficacious against nematodes in domestic ruminants than ivermectin, to the extent that ivermectin resistant nematodes may appear moxidectin sensitive (Pankavich *et al.*, 1992; Craig *et al.*, 1992; Pomroy & Whelan; 1993; Várady *et al.*, 1995) in spite of the probably similar mode of action and demonstrated cross-resistance (Shoop *et al.*, 1993; Le Jambre *et al.*, 1995). The long depletion half life causes that the persistent activity of moxidectin against nematode infections in domestic ruminants is longer (Taylor *et al.*, 1993; Hubert *et al.*, 1995). Injectable moxidectin at 200 µg/kg is reported to have high efficacy against cattle warbles (*Hypoderma lineatum*) (Scholl *et al.*, 1992), but there is also a report on poor efficacy of oral moxidectin at 400 µg/kg against third instar larvae of the equine bots *Gasterophilus* spp. (Xiao *et al.*, 1994). In one trial, injectable moxidectin had 96% efficacy against first instars of *Oestrus ovis*, but 100% against second and third instars (Puccini *et al.*, 1994). It appears that the anthelmintic properties of moxidectin are more pronounced than its insecticidal activity (Shoop *et al.*, 1995). Cattle dung has been less toxic against insects following moxidectin than following ivermectin treatment (Strong & Wall, 1994).

Doramectin

The fourth rival in the endectocide market is doramectin, 25-cyclohexyl-5-*O*-demethyl-25-de(1-methylpropyl) avermectin A_{1a}, produced by a mutant strain of *S. avermitilis*. The generic name obviously does not mean anything, but may give an impression of durability. In cattle doramectin has almost twice as long a half-life as 22,23-dihydroavermectin B_{1a}, the major component of ivermectin (Goudie *et al.*, 1993). Doramectin is marketed for sc injection (Dectomax®, Pfizer) in sesame oil with ethyl oleate solution which contributes to low tissue irritability (Wicks *et al.*,

1993; Nowakowski *et al.*, 1995). Doramectin is claimed to have an antiparasitic spectrum close to that of abamectin (Shoop *et al.*, 1995).

Eprinomectin

The latest endectocide was presented in 1996-97. Eprinomectin (Shoop *et al.*, 1996) comes from the same pharmaceutical company as ivermectin and abamectin, although the company is now called Merial. The generic name eprinomectin is perhaps based on the chemical name 4''-epi-acetylamino-4''-deoxy-avermectin B_1. To begin with, eprinomectin is only marketed as pour-on (Eprinex®, Merial). Eprinomectin is a racemic mixture of compounds which comprises not less than 90% of the component B_{1a} and not more than 10% of the component B_{1b}. Probably the most obvious practical advantage of the product is its zero milk and meat withdrawal (in the USA). The commercial formulation contains 0.5% of eprinomectin, and the rest is fractionated oils of natural sources.

Mode of action

The mode of action of the different ML endectocides is similar at any rate in that it is not totally understood (McKellar & Benchaoui, 1996). Efficacy has been demonstrated against nematodes and arthropods, with some exceptions, such as the nematode *Thelazia lacrymalis* and the mite *Ornithonyssus sylviarum* (Campbell & Benz, 1984). Later, ivermectin has been found efficacious against other species of *Thelazia* (Kennedy *et al.*, 1994). The efficacy of ivermectin against equine cyathostome larvae is low (Klei *et al.*, 1993), but that of moxidectin is significantly higher (Xiao *et al.*, 1994). In one study, no efficacy of even high doses of ivermectin was seen against various nematodes in domestic fowl (Oksanen & Nikander, 1989). Avermectin activity was explained to be caused by binding to GABA-mediated synapses (Bennett, 1986). In vertebrates, there are GABA mediated synapses only within the central nervous system. Recent evidence shows that avermectins also interact to a nematode specific glutamate-gated chlorine channel distinct from GABA-sensitive chloride channels, which is now considered the main mode of action (Turner & Schaeffer, 1989; Arena *et al.*, 1995). The chloride ion flux into neurones is the probable cause of the observed paralysis and death of the parasites. However, these may not be the only modes of action. Because of the closely similar chemical structure, antiparasitic spectrum and cross-resistance, it is likely that the mode of action of milbemycins is similar to that of avermectins (Shoop *et al.*, 1995). In nematodes, low concentrations of ML endectocides have been shown to paralyse pharyngeal pumping, which leads to starving due to the worm's inability to feed. Higher concentrations inhibit motility, which might lead to a faster expulsion because the parasite loses its ability to swim against the tide of digesta (Gill & Lacey, 1998). The expulsion of *Ostertagia circumcincta* takes longer than that of *Haemonchus contortus* or *Trichostrongylus colubriformis* in sheep, which has been interpreted to suggest that the main method of expulsion in the first-mentioned species would be the inhibition of feeding, while the latter species probably are expelled due to inhibition of motility (Gill & Lacey, 1998).

Dosage and efficacy

The manufacturers' dose recommendations are based on dose titration trials with various parasite species. The susceptibility of different parasite species and their developmental stages vary a lot. The dose recommended is designed to be effective against the least susceptible target parasite species, in ruminants *Cooperia* or *Nematodirus* species. At the time of the introduction of ivermectin, 90% efficacy was considered very good and 80-90% moderately effective (Powers *et al.*, 1982). However, the endectocides themselves have changed the standards, currently a drug is regarded as highly effective if it has over 98% efficacy against the parasite species in question, effective if the efficacy is 90-98%, and moderately effective if 80-89% (Wood *et al.*, 1995). Against *Nematodirus helvetianus*, the efficacy of ML endectocides has been only moderate (Benz *et al.*, 1989), with the exception of moxidectin, which has high efficacy (Flochlay & Deroover, 1997). Before eprinomectin none of the drugs had established label claims against both adult and immature *Nematodirus* in cattle.

The recommended dose to domestic ruminants is the same 200 µg/kg for all the commercial endectocides for subcutaneous injection and oral administration, and 500 µg/kg for pour-on application. Eprinomectin is so far only marketed as a pour-on at 500 µg/kg for cattle.

For other animal species the dosage recommendations vary. The least dose widely used is that of oral ivermectin against canine heartworm microfilariae, given monthly at 6 µg/kg, while demodectic mange of dogs is treated with an oral dose of 600 µg/kg daily even for months (Ristic *et al.*, 1995) The latter is extra-label use, the manufacturer does not officially recommend

ivermectin at high doses for dogs and cats, at least partly because ivermectin can cause fatal intoxications in dogs, especially collies (Paul *et al.*, 1987). The standard dose in swine is 300 µg/kg against all ivermectin sensitive parasites (Sutherland, 1990).

In red deer (*Cervus elaphus*), the subcutaneously administered standard dose 200 µg/kg of ivermectin was found to give insufficient nematocidal efficacy, so the authors recommended doubling the dose (Andrews *et al.*, 1993). However, even the double dose 400 µg/kg did not give efficacy comparable with that of 200 µg/kg in cattle. The low efficacy was associated with pharmacokinetics; the peak concentration and AUC in red deer remained considerably lower than in cattle. It has been reported that pour-on eprinomectin at 500 µg/kg has high activity against strongyle parasites and lungworm in red deer (Gogolewski *et al.*, 1997).

Ivermectin has been observed to be extremely efficacious against cattle warbles, *Hypoderma lineatum*, close relatives of reindeer warbles. A high efficacy of injection was reported at a dose of 0.2 µg/kg - one thousandth of the recommended dose (Drummond, 1984). Ivermectin pour-on at 2 µg/kg has also been highly efficacious in the chemoprophylaxis of cattle warbles (*Hypoderma bovis* and *H. lineatum*) (Benakhla *et al.*, 1998).

Pharmacokinetics and route of application

Pharmacokinetics of ivermectin in domestic ruminants has been reviewed by Bennett (1986) and Steel (1993) and of various ML endectocides by McKellar & Benchaoui (1996). The ivermectin absorbed to the circulation is almost totally excreted in the bile. Because of lipophility of ivermectin, the volume of distribution is large, larger in sheep than in cattle (4.6 l/kg versus 1.9 l/kg) (Lo *et al.*, 1985). The larger distribution volume causes the plasma concentration to be intrinsically lower and the clearance rate more rapid in sheep than in cattle. The mean volume of distribution in cattle was also quite different for ivermectin (3.35 l/kg), doramectin (2.92 l/kg), and moxidectin (13.6 l/kg), respectively (Lanusse *et al.*, 1997). The large distribution volumes (especially that of moxidectin) are probably caused by distribution in adipose tissue. The distribution volumes vary a lot between different endectocides and animal species, thus affecting the plasma concentrations available for parasites.

A lot of commercial endectocide preparations have appeared to be used for different animal species, including man. For ruminants the main methods of application are subcutaneous injection, oral liquid, pour-on (topical percutaneous), and ruminal sustained-release bolus. Common to all these application methods is that as an endectocide the drug is designed to act systematically, so it is essential that the active ingredient is absorbed to the blood circulation, in any case to get maximum activity against parenteral parasites.

In one trial, the area under the plasma concentration-time curve (AUC) was 5718 (s.e.m. 1203) ng*h/ml following subcutaneous injection of ivermectin at 200 µg/kg to sheep, and 2039 (231) ng*h/ml following oral administration at the same dose (Marriner *et al.*, 1987). The difference here was 2.8-fold. The AUC in goats after similar oral administration was only 516 (81) ng*h/ml (Scott *et al.*, 1990). Following sc injection to goats, the AUC of ivermectin was 1440 (144) ng*h/ml (Alvinerie *et al.*, 1993). The AUC for ivermectin, doramectin, and moxidectin in cattle following similar sc administrations of commercial preparations was 10790 (1128), 15048 (744), and 5208 (384) ng*h/ml (Lanusse *et al.*, 1997). In sheep, the AUC following sc dosing of moxidectin (2696 (499) ng*h/ml) was slightly higher than following oral dosing (2373 (375) ng*h/ml) (Alvinerie *et al.*, 1998). Based on earlier efficacy studies, the authors concluded that there was a relationship between plasma concentration and moxidectin efficacy.

Plasma concentration (Alvinerie *et al.*, 1998), and more specifically AUC, is perhaps the best explanating factor of the level of endectocidic efficacy of a given endectocide in a given animal species. This interpretation cannot, however, be expanded between different ML endectocides (Table 1) because of their different intrinsic antiparasitic efficacies. Neither is the efficacy against intestinal nematodes fully explainable with AUC as these parasites also may encounter the proportion of orally given drug that is not absorbed (McKellar *et al.*, 1991). On the other hand, ivermectin was not detected at all in abomasal fluid of sheep after sc injection at 200 or even 2000 µg/kg (Bogan & McKellar, 1988).

In the world endectocide literature there were 4436 papers listed until mid November 1998 in CAB abstracts only (CAB International, Wallingford, Oxon, UK). Most of them report excellent antiparasitic efficacy of one or more methods of endectocide application. Some papers also describe trials comparing the efficacy of two or more of the drugs. Relatively few, by contrast, compare the efficacy following various methods of application of the same drug in ruminants.

Table 1. Some plasma pharmacokinetic parameters of ML endectocides in different ruminants

Species	Drug	Dose (mg/kg)	n	Cmax (ng/ml)	tmax (h)	AUC (ng*h/ml)	Reference
Cattle	IVM	0.2 sc	5	54.6	35	10 790	Toutain *et al.* (1988)
Cattle	IVM	0.2 sc	4	42.8	96	11 016	Lanusse *et al.* (1997)
Cattle	IVM	0.2 sc	4	48.2	72		Herd *et al.* (1996)
Sheep	IVM	0.2 sc	5	30.8	60	5718	Marriner *et al.* (1987)
Goat	IVM	0.2 sc	5	6.12	68	1440	Alvinerie *et al.* (1993)
Red deer	IVM	0.2 sc	4	15.8	20		Mackintosh *et al.* (1985)
Red deer	IVM	0.2 sc	10	15.3	28		Andrews *et al.*. (1993)
Red deer	IVM	0.4 sc	10	28.3	28		Andrews *et al.* (1993)
Sheep	IVM	0.2 po	5	22.0	16	2039	Marriner *et al.* (1987)
Goat	IVM	0.2 po	6	16.0	<24	516	Scott *et al.* (1990)
Cattle	IVM	0.5 topic	4	28.3	48		Herd *et al.* (1996)
Goat	IVM	0.5 topic	6	4.00	48	317	Scott *et al.* (1990)
Cattle	IVM	SR [a]	4	10.2	924		Herd *et al.* (1996)
Cattle	DRM	0.2 sc	20	27.8	72-144	11 400	Nowakowski *et al.* (1995)
Cattle	DRM	0.2 sc	4	37.5	144	15 048	Lanusse *et al.* (1997)
Cattle	MXD	0.2 sc	3	75.0	4-6		Miller *et al.* (1994)
Cattle	MXD	0.2 sc	4	39.4	7.7	5208	Lanusse *et al.* (1997)
Sheep	MXD	0.2 sc	5	8.3	21	2696	Alvinerie *et al.* (1998)
Sheep	MXD	0.2 po	5	28.1	5.3	2373	Alvinerie *et al.* (1998)

IVM ivermectin, DRM doramectin, MXD moxidectin

[a] Sustained release bolus, contains 1.72 g of ivermectin and is designed to release 12.7 mg daily for 135 days.

The small number of direct comparisons of different application methods in domestic ruminants (sheep) indicate a higher efficacy of subcutaneous compared with oral application (McKellar *et al.*, 1988a; Zajac *et al.*, 1992). Subcutaneously applicated ivermectin had a persistent efficacy of at least 10 days against *Haemonchus contortus, Trichostrongylus vitrinus* and *Cooperia curticei*, but orally administered ivermectin showed no persistent efficacy (Borgsteede, 1993). A persistent efficacy lasting for one week was also seen for *Ostertagia circumcincta* (Grimshaw *et al.*, 1997). There is a 35 day persistent efficacy against *O. circumcincta* and *H. contortus* of both orally and subcutaneously administered moxidectin in sheep, and a high persistent efficacy of sc administration against *Trichostrongylus colubriformis* 21 days after treatment but no efficacy 21 days after oral treatment (Kerbouef *et al.*, 1995). Persistent efficacy is well-known from cattle treated sc with endectocides (e.g. Barth 1983; Armour *et al.*, 1985; Vercruysse *et al.*, 1997; Meeus *et al.*, 1997; Ranjan *et al.*, 1997). In one trial, injectable moxidectin was rather effective against first instars of the ovine nasal bot *Oestrus ovis*, but oral drench was not (Dorchies *et al.*, 1996). Both the therapeutic and persistent efficacy of ivermectin injection against *O. ovis* were higher than those of oral ivermectin (Dorchies *et al.*, 1997). The greater efficacy of sc injected endectocides is related to pharmacokinetics; the bioavailability of ruminally

administered ivermectin was only 25%, whereas that of subcutaneously injected ivermectin was 100% (Prichard *et al.*, 1985). The initial explanation to the low utilisation of orally administered drug was that it was probably metabolised in the rumen, but later evidence indicates that ivermectin is bound to the particles of the digesta (Andrew & Halley, 1996). Anyhow, the low bioavailability remains a widely accepted fact.

In mountain sheep (*Ovis canadensis*), injectable ivermectin at 200 µg/kg offered an effective means of treating lungworm (*Protostrongylus* species) infection (Miller *et al.*, 1987), but orally administered ivermectin at approximately 400 µg/kg was ineffective (Easterly *et al.*, 1992).

There are also reports showing that oral application of ivermectin had superior anthelmintic efficacy when compared with subcutaneous injection. One was in goats and another in dromedary camels. In goats, the report describes a faecal egg count reduction test showing 94% efficacy of ivermectin injection at 200 µg/kg, compared with 100% efficacy for ivermectin oral formulation, obviously at the same dose rate. No details were given on the group sizes. It was discussed that *Trichostrongylus* spp. might have been the predominant nematodes in the goats (Pearson & Rutherford, 1988). In dromedary camels, trichostrongylid egg counts were reduced by 100% when ivermectin was administered orally and by > 88% when given subcutaneously, both at the dose of 200 µg/kg. Egg counts of *Trichuris* sp. were reduced by > 85% with oral administration, but increased following subcutaneous treatment (Boyce *et al.*, 1984). In both these cases the parasites in question appear to have been intestinal nematodes which may be affected also by the unabsorbed fraction of orally given ivermectin.

Topical pour-on administration of ivermectin to cattle at a dose of 500 µg/kg has been shown to cause high antiparasitic therapeutic and persistent activity (Alva-Valdes *et al.*, 1986; Yazwinski *et al.*, 1994; Williams & Broussard, 1995). Pharmacokinetic studies, however, show that the maximum plasma concentration and the AUC following such a treatment are smaller than those following subcutaneous administration despite the 2.5-fold dose (Herd *et al.*, 1996). In goats, subcutaneous ivermectin at 200 µg/kg lead to an AUC 4.5-fold that after topical administration at 500 µg/kg (Scott *et al.*, 1990; Alvinerie *et al.*, 1993).

Endectocide resistance

Parasite resistance refers to the recommended dose of drug now removing 95% or less of the resident parasite population (Hennessy, 1997). Resistance is now considered a major threat to parasite control world-wide (Waller, 1994, 1997). The first reports on ML endectocide resistance in nematodes emerged within 5 years after the introduction of ivermectin in 1981. Resistance has been observed mostly in *Ostertagia* and *Haemonchus* nematodes of small ruminants (Gill & Lacey, 1998). Endectocide resistance has been observed also in *Cooperia* species in a herd of cattle where oral ivermectin had been the only anthelmintic used in the strategic control programme over the previous two years (Vermunt *et al.*, 1995). Generally, factors contributing to anthelmintic resistance include frequent treatment and under-dosing, while alternating between different anthelmintic groups will slow down the establishment of resistance (Waller, 1990). So far, there are no reports on endectocide resistance in reindeer parasites; the low efficacy of ivermectin against the brainworm *E. rangiferi* is not a sign of resistance as ivermectin has never been regarded as effective against this parasite. After treatment of an animal with endectocides, declining drug levels over time will allow establishment of resistant infective larvae, while still eliminating susceptible larvae. To elucidate the population-level importance of these resistant larvae, computer simulations have been performed. The results from such simulations indicate that adult survivors of treatment have much greater importance than selection of infective larvae by decaying drug concentrations (Dobson *et al.*, 1996). The persistent efficacy of endectocides is favourable in preventing resistance, because more persistent drugs will remove resistant adult parasites more effectively. As anthelmintic resistance does not disappear spontaneously, it is important to try to prevent its initial establishment (Waller, 1990).

Also insects may become resistant to endectocides. In a trial with house flies resistance against abamectin developed rapidly and to a very high level (60 000-fold) (Scott *et al.*, 1991). So far there are obviously no reports on endectocide resistance in oestrid parasites, but there is no reason to believe that development of resistance would not be fully possible.

Gains of endectocidic treatment in domestic ruminants

Because of the high antiparasitic efficacy of the ML endectocides, it is not surprising that different

treatment programs have been observed to increase meat production (e.g. Suarez *et al.*, 1991; Baggott *et al.*, 1994; Williams *et al.*, 1995) or milk production (Ploeger *et al.*, 1989; Walsh *et al.*, 1995). In all of these five papers, pharmaceutical industry is represented, either as authors or acknowledged, which does not reduce the value of the individual papers, but indicates that animal health companies have interest in this kind of research. Therefore, publication bias appears possible, perhaps some studies with undesired results of treatment have remained unpublished.

Environmental aspects

The possible adverse effects ML endectocides might have to dung degradation fauna have raised much concern. After the first study (Wall & Strong, 1987), discussion has been lively. A number of studies have been performed on the degradation of cattle dung from ivermectin treated animals. Most scientists have found that degradation is retarded and insect fauna disturbed in dung following ivermectin treatment (e.g. Strong, 1993; Holter *et al.*, 1994). Researchers affiliated to Merial (former MSD) have stressed the importance of methodology when planning such studies (e.g. Barth, 1993). They showed that in addition to diptera and beetle larvae, treatment reduced the numbers of dung specific nematodes. However, they did not see retardation in dung degradation (Barth *et al.*, 1994). In a comparison of sustained release bolus, pour-on and subcutaneous injection ivermectin treatments, it was found that maximum concentration (2 days post treatment) in the faeces of pour-on treated animals was 12-fold higher than of the sc injected animals, but after one week the concentrations declined at a similar rate. The animals treated with a sustained release bolus, by contrast, produced faeces with a high ivermectin concentration till the end of the trial, 7 weeks post treatment. Both the sustained release bolus and pour-on treatments were considered more ecotoxic than the sc injection as judged by their higher faecal ivermectin concentrations (Herd *et al.*, 1996). This is not surprising, because the total treatment doses are higher. Oral ivermectin formulations were regarded as least ecotoxic due to the rapid excretion (Herd, 1995).

Apparently, no life cycle assessment (LCA) (e.g. Consoli *et al.*, 1993) of these compounds/drugs have been published, but obviously, the less the use, the less the production, and the less the environmental concern due to the manufacturing, and the less the risks of environmental damage due for example to accidental leaks during production or delivery.

Ivermectin in reindeer

Because antiparasitic treatment of reindeer was a subject of common interest (Nieminen *et al.*, 1980; Rehbinder *et al.*, 1981; Persen *et al.*, 1982) at the time of the introduction of ivermectin, it was natural that ivermectin given as a sc injection at the dose 200 µg/kg was immediately to be evaluated as an endectocidic antiparasitic to reindeer. In Sweden, a trial was done with 37 reindeer calves to compare the efficacy of four antiparasitics (ivermectin, fenthion, fenbendazole and mebendazole) against warbles, throat bots, brainworms, lungworms and abomasal and intestinal nematodes (Nordkvist *et al.*, 1983). Ivermectin was 100% efficient against warbles, throat bots, lungworms and abomasal and intestinal nematodes (*Nematodirus* species). The efficacy against brainworm larvae was lower. This is concomitant with results from white-tailed deer (Kocan, 1985). Fenthion had 100% efficacy against throat bots and 86% against warbles, but no efficacy against nematodes, while the benzimidazoles fenbendazole and mebendazole were 100% efficient against brainworm larvae and moderately-highly efficient against other nematodes. The benzimidazoles had no efficacy against warbles or throat bots. The high antiparasitic efficacy of ivermectin was confirmed in the next trial, performed in 1982-83 (Nordkvist *et al.*, 1984), which also showed a smaller weight loss during winter in ivermectin treated reindeer calves than in non-treated ones. To gain approval by the United States Food and Drug Administration (FDA) for ivermectin to be used in reindeer, a series of trials was performed in Alaska in 1982-83 (Dieterich & Craigmill, 1990). Ivermectin was considered safe to reindeer and efficient against warbles, and the tissue residues decreased rapidly, approaching zero by day 24. Based on these data, the FDA established a 56 day withholding period (double that of cattle). The next reported trial was initiated in 1984 in Norway. The live weight of reindeer calves about six months of age, treated with ivermectin during the autumn increased during the subsequent year on average 3 kg more than that of similar untreated animals (Heggstad *et al.*, 1986). In December, 1990, eighty reindeer calves were ivermectin treated in Kautokeino, Norway. In February, 14 of these treated and 19 control calves were slaughtered. The efficacy against throat bots was 100% and against the sinus worm, *Linguatula arctica*, 98% (Haugerud *et al.*, 1993).

The arctic and subarctic dung degradation fauna can be expected to be less tolerable than that of more temperate regions. The concern on the possible negative effects of ivermectin treatment has been discussed in Norwegian newspapers (e.g. Berg 1991). Recently, a method was developed to analyse ivermectin residues in reindeer faeces (Åsbakk *et al.*, 1999), and one trial was done to investigate the degradation fauna of reindeer faeces after sc ivermectin injection (Nilssen *et al.*, submitted). Although measurable concentrations could be shown in faeces produced for 30 days post treatment, the impact on dung insect fauna was negligible, because the winter faeces from lichen-fed animals did not attract insects during the next summer regardless of ivermectin treatment, obviously due to its nutrient-poor and dry structure.

The difference in antiparasitic activity of the various endectocides and their various formulations in domestic ruminants makes it necessary to compare the activity in reindeer, where high efficacy against insect parasites is required. Because of the inhibited development of hypobiotic nematode parasite larvae during the time of treatment (Nordkvist *et al.*, 1984), there are also special nematocidal efficacy requirements.

Aims of the research

The aims of the present study were:

1. To find ways to optimise the current endectocidic antiparasitic treatment methods of reindeer, taking into account the efficacy of the treatment and economical as well as ecological considerations. The goal was thus to look for the best drug and the best way of administration as well as the ideal timing.

2. To develop research methods needed to fulfil the aim #1.

3. To investigate, whether summer treatment against subclinical infections of calves to be slaughtered in the autumn might be economically feasible.

Materials and methods

Study design

Most of the trials described in these publications were designed for aim #1 (Table 2). Trial I compared the antiparasitic efficacy of oral (as the equine paste formula) and subcutaneous administration of ivermectin against nematodes and warbles. Work III added pour-on ivermectin, and efficacy was also measured against throat bots, according to the method described in paper II (aim #2). Paper IV used chemical analyses to explain the differences in antiparasitic efficacy discovered in trials I and III. Trial V was designed to evaluate a new drug, moxidectin, as a reindeer endectocide. Publication VI described the insecticidic efficacy (against warbles and throat bots) of doramectin in reindeer. Paper VII compared the antiparasitic efficacy of oral ivermectin given at different times

Table 2. Experimental animals and their endectocide treatments.

Paper	Untreated group	IVM inj. 200 µg/kg	IVM oral 200 µg/kg	IVM topical 500 µg/kg	Other treatment	Year
I	A[a] 31 (28)[b]	A 31	A 30 (29)			1989-90
II	C 8					1991
III	A 13	A 13 (12)	A 13	A 13	A 13 (10)[d]	1990-91
IV		C 5	C 5	C 4, A 6, C 5		1991, 1993
V	A 14 (13)	A 14			A 14 (13)[e]	1991-92
VI	A 20 (19)				A 20[f]	1994-95
VII	A 18 (16)		A 54 (51)[g]			1995-96
VIII	C 177 (75) (8)[c]	C 177 (59) (9)		C 175 (62) (9)		1995

[a] A=adults, C=calves

[b] the number in parenthesis is the final sample size after exclusion of missing animals.

[c] counted alive (breeding replacements).

[d] IVM injection 20 µg/kg, [e] MXD injection 200 µg/kg, [f] DRM injection 200 µg/kg, [g] oral IVM 200 µg/kg, either in September, December, or February.

IVM ivermectin, DRM doramectin, MXD moxidectin.

during the autumn or winter.

Papers I, III, V, VI and VII include development of methodology to evaluate efficacy against hypobiotic nematode parasites (aim #2).

One trial (VIII) was performed exclusively for aim #3.

Animals and experimental design

Most of the experiments (I to VII) were done in the Kaamanen Experimental Reindeer Herd of the Finnish Association of Reindeer Herding Co-operatives in Kaamanen, Inari (69°09'N, 27°00'E) during the winters 1989-1990 to 1995-1996. Most trials used naturally infected adult hinds (females) (I, III, V, VI, VII), but in two trials, also males were included (I, VI). If animals were to be slaughtered, yearlings were used (II). If frequent blood sampling was required (III), reindeer calves about 8 months old were used, in addition to Norwegian adult reindeer and Swedish yearlings (see below). All experimental animals were individually marked, either with numbered collars or ear tags, or both. It is a routine in Kaamanen to gather the herd monthly for weighing and occasional blood sampling. There are slightly over 100 hinds in the herd, the number of calves varies a lot between years. The area for the herd is about 43 km^2 of pine and birch forests and fells (Nieminen, 1998).

The hinds were allocated to the groups using stratified randomisation according to age (I, III, V, VII), or just randomically by lot (VI). The calves were allocated according to sex and weight (IV). The group size varied between 10 (III) and 31 (I). Paper (IV) described three trials; A, five yearlings from Könkämö, Sweden; B, six adult reindeer from Dielddasuolo (Tjeldøy), Norway; and C, three groups of five calves each in Kaamanen.

Endectocide treatment

The endectocidic treatments were performed in December (I, III, V, VI), in November, January or May (IV), in September, December or February (VII), or in July (VIII). The drugs used were ivermectin, Ivomec® 10 mg/ml vet inj., MSD (Merial) (I, III, IV, V, VIII), Ivomec® vet 18.7 mg/g pasta (=Eqvalan® paste), MSD (I, III), Ivomec® vet mixt. 0.8 mg/ml, MSD (VII), Ivomec® pour-on for cattle, MSD (III, IV, VIII), moxidectin, Cydectin® 1% vet inj., American Cyanamid (Fort Dodge) (V), or doramectin, Dectomax® 1% vet inj., Pfizer (VI). Subcutaneous injections were given in front of the left shoulder (lateral midline of the neck) at a dose of 200 µg/kg (I, III, IV, V, VI, VIII) or similarly at a dose of 20 µg/kg (III). Oral administration was given over the base of tongue at a dose of 200 µg/kg (I, III, IV, VII). Topical pour-on treatment was given under the hair coating over the back between the shoulder blades ("spot-on") at a dose of 500 µg/kg (III, IV), or as a narrow strip along the back from withers to the base of tail at the same dose rate (IV, VIII). The untreated controls were given no placebo (I, III, V, VII, VIII) or were given physiological saline at 1 ml/50 kg sc (VI).

To investigate the possibilities of endectocides used as «growth promoters» in reindeer calves, 529 calves from two herding co-operatives (Palojärvi and Kemin-Sompio) in Finnish Lapland were allocated systematically to three groups during ear-marking in July, 1995. One group was left untreated, the other was injected subcutaneously with ivermectin at 200 µg/kg and the third received pour-on ivermectin topically at 500 µg/kg. Carcass weights of animals slaughtered during the autumn or winter were then compared between treatment groups (VIII).

Examination for adverse reactions

Because both the standard injection and oral applications of ivermectin had been used in reindeer husbandry and also experimented with in the Kaamanen herd (Soveri *et al.*, 1990), no specific follow-up for adverse reactions was undertaken in the first trial (I), but the animals were observed in connection with other animal management tasks. In trial (III) with the new topical ivermectin treatment, the animals were released after treatment into an outdoor enclosure where they were observed at times for 24 hours. A similar follow-up for adverse reactions, but of different durations, was undertaken following moxidectin and doramectin treatments (V, VI). Were animals found dead due to unknown cause during the experiments, they were autopsied, if possible.

Faecal examination for nematode eggs or larvae

To facilitate the evaluation of nematocidal efficacy, faecal egg counts (FEC) were done. The nematode eggs were identified to the genus *Capillaria* if they were rough-shelled, about 50 µm in length, dark-stained, of barrel shape and with slightly protruding polar plugs, to the genus *Skrjabinema* if they were typical to the genus: about 50 to 70 µm long, thin-shelled and markedly asymmetrical (rather like an orange section), or as trichostrongylids if they were indistinguishable from those of the family Trichostrongylidae: oval or ellipsoid, not markedly asymmetrical, thin-shelled and length 60 to 100 µm. As the trichostrongylid egg counts were expected frequently to be negative due to hypobiosis at the time of treatment in midwinter,

faecal examination was performed several times during winter and spring. The FECs were done with modified McMaster technique using saturated NaCl solution with sucrose (Christensson *et al.*, 1991), each egg observed representing 40 epg (I, III) or 20 epg (V, VII). The individual monthly trichostrongylid FECs were used to calculate Faecal Egg Count Mean (FECM) (V, VII). Microphotographs of parasite egg specimens are presented in Appendix 2.

Brainworm and lungworm larvae were examined according to a Baermann technique (Holmström *et al.*, 1989) (I, III). Larvae were identified as those of the brainworm, *Elaphostrongylus rangiferi*, if they were of the proper size (0.3 to 0.4 mm) and had one cuticle and the characteristic dorsal spine over the tail. Similar sized larvae with one cuticle, but without the dorsal spine over the tail were classified as those of the lungworm, *Dictyocaulus* sp. (*Dictyocaulus eckerti*).

Warble and throat bot examination

Warbles were counted as described earlier (Nordkvist, 1967; Dieterich & Craigmill, 1990). In late March - early May, when the larvae had reached the 3rd instar stage, but before a considerable amount of them had left the host (Nilssen & Haugerud, 1994), the backs of the experimental reindeer were examined visually and by digital palpation (I, III, V, VI, VII). If the number of warbles exceeded 30, the count was done in tens as adjacent warbles might blend together and prevent exact enumeration.

Warbles from the calves slaughtered in January were counted by visual examination of the inside of the skin (VIII).

The endoscopy method for counting throat bots (II) was used in late April or early May (III, V, VI, VII).

Animal weighing

The Kaamanen reindeer were weighed using an ovine balance modified to enable the weighing of reindeer (Poldenvale lambway, Precision Weighers, Reading, England, 1 kg reading intervals) (I, III, IV, V, VI, VII). The new-born calves were weighed within 24 hrs of birth (spring balance, 100 g intervals) (III, V, VII). Other than Kaamanen animals were weighed using available apparatus. The calves in paper VIII were in the trial start weighed on a standard bathroom balance (1 kg reading intervals), and their carcass weights were taken from the slaughter records.

Chemical analysis

To help explain the difference in antiparasitic efficacy, plasma concentrations were measured from reindeer calves treated with ivermectin administered in different ways (IV). The analyses were performed by Merck Research Laboratories, Lauterbach, Germany, using a HPLC (high pressure liquid chromatographic) method with fluorescence detection (Downing, 1989).

Statistical analysis

Faecal egg counts (FECMs) and animal weights were compared by one-way analysis of variance. If the group effects were statistically significant ($P< 0.05$), Tukey test was used for pairwise comparison of the group means. In paper VIII, Student's t test, χ^2 test, Mann-Whitney test, and one-way analysis of covariance were performed. The number of warbles and throat bots differed so much between treatment groups (treatment efficacy often 100%) that it was usually not tested at all. However, in one trial (VI) the proportion of animals infested with warbles and throat bots was compared by χ^2 test. In paper VIII, Mann-Whitney test was used to compare the number of warbles. To compare the weights of calves born to hinds treated with untreated controls during the different years, Kruskal-Wallis one way analysis of variance was used. The statistical analyses were carried out using the Statgraphics® 2.6 program package or the Statistix® software package, either version 3.5, 4.0, or 4.1. One-way analysis of covariance was done with BMDP software.

Results

Adverse reactions

No adverse reactions were noticed following any of the ML endectocidic treatments administered in any of the various ways of application. The single autopsied animal showed no signs of tissue irritation at injection sites. The death was not associated with endectocide treatment.

Efficacy against nematodes

No effect of ivermectin or moxidectin treatment could be seen against the sporadic *Skrjabinema* egg production (V). The eggs were found only in April and May, 4 to 5 months post treatment. The question remains if the treatment however had had efficacy, and the egg production was caused by reinfection. In study I, both oral and injected ivermectin reduced the *Capillaria* egg production. In trial III, this post-treatment reduction could be

seen in all the groups, including the untreated control group. In trial V, both moxidectin and ivermectin appeared to reduce the *Capillaria* egg production, but the difference in the egg counts was not significant. In trial VII, *Capillaria* eggs were detected so infrequently, and in so small numbers, that they were totally omitted from the paper.

There was a statistically non-significant reduction of lungworm larva production in animals treated with ivermectin. The reduction was more pronounced following injection than oral administration (I). In study III, the lungworm larva output followed the same pattern as in trial I: the larvae were absent from the samples of February, and the mean value remained low (it only equalled or exceeded 1 lpg in the orally treated and control groups in May). The difference between the treatment groups was not statistically significant, but the average larva production was lowest in the standard (200 µg/kg) injection group. The number of brainworm larvae in faeces (I, III) was so low and their excretion so sporadic that no calculations on treatment efficacy were justified, but efficacy was definitively not very high.

Trichostrongylid FEC was reduced by both the sc and oral treatments in trial I. Egg output was first observed in the untreated control group, and followed in successive intervals by the orally treated group and the injection group. The FEC was significantly lower in the injection group than in the untreated group in March and June, and in the injection group than in the oral group in April. No Faecal Egg Count Means (FECM) for individual animals were calculated in this trial.

Similar reduction in trichostrongylid egg output was seen in the next study (III). Egg production of the standard injection group was first observed in April, a month later than in the other groups. The FECMs of the standard injection group were significantly lower than those of the other groups. The standard sc injection reduced the FECM by 80%, both oral treatment and 20 µg/kg injection by 39%, and the topical pour-on application by 35%.

Injectable moxidectin and ivermectin reduced the trichostrongylid FECM by 92% and 95%, respectively (V).

In trial VII, oral ivermectin (Ivomec® vet mixt. 0.8 mg/ml, MSD) reduced the trichostrongylid FECM by 62 to 74%.

Efficacy against warbles and throat bots

All ivermectin treatments in autumn/winter at 200 or 500 µg/kg were 100% effective against warbles and throat bots (I, III, V, VII). Injectable ivermectin at 20 µg/kg had also 100% efficacy against warbles, the efficacy against throat bots was 92% (III, data not fully shown). Injectable doramectin at 200 µg/kg had 100% efficacy against both warbles and throat bots (VI). Moxidectin at 200 µg/kg had 93% efficacy against warbles and 71% against throat bots (V).

The persistent (prophylactic) efficacy of injected (200 µg/kg) or pour-on (500 µg/kg) ivermectin reduced the number of warbles in hides of reindeer calves treated in midsummer by about 60%.

Pharmacokinetics

Plasma concentrations were constantly higher in reindeer calves given ivermectin as sc injection than in those that received it either orally or as pour-on (IV). The mean maximum concentration following standard sc treatment was about 5-fold that of the orally treated animals. The concentration also decreased more slowly following sc treatment; after 7 days the difference in concentrations was 14-fold between the injection and oral groups. The mean maximum concentration after topical treatment varied much between the three trials, the highest one was in the animals treated in May (about one third of that of the standard sc treatment in January). The lowest mean maximum concentration was in the animals treated in January (about one twenty-fifth of that of the standard sc treatment). No AUC was calculated due to the small number of sampling times, but it was clearly much larger following sc injection than other treatments, despite the higher dose given topically.

Weight development

In the first trial (I), the (mostly pen-fed) animals gained weight during the winter, the untreated group 4.8 (s.e.m. 1.1) kg, compared with 5.5 (1.3) and 8.8 (1.5) kg, respectively, for the orally and injection treated hinds. The difference was not significant in ordinary one-way analysis of variance, but using the treatment as a continuous variable (0, untreated control; 1, oral treatment; 2, sc injection) the effect of treatment became significant. In the next study (III), weight loss was observed in all the groups between the time of treatment and early April, with no significant differences between the groups. In the trial with moxidectin and ivermectin injection (V), the mean weight gain between December and April was highest in the untreated group, 1.8 (1.5) kg compared to 1.0 (0.8) and 0.8 (1.3) for moxidectin and ivermectin treated animals, respectively. The difference between the groups was not significant.

Table 3. Mean birth weights (s.e.m.) of reindeer calves born to differently treated Kaamanen hinds.

Study nr.	Birth year	Untreated control	IVM inj. 200 pg/kg December	Other treatment
III	1991	5.14 (0.32)	5.51 (0.23)	5.53 (0.17) [a]
				5.45 (0.30) [b]
				5.55 (0.25) [c]
V	1992	5.24 (0.21)	5.63 (0.29)	5.55 (0.25) [d]
VI	1995	5.79 (0.25)		5.47 (0.28) [e]
VII	1996	5.69 (0.26)		6.22 (0.26) [f]
				6.65 (0.22) [b]
				6.42 (0.29) [g]

[a] IVM injection 20 µg/kg December, [b] IVM oral 200 µg/kg December.
[c] IVM topical 500 µg/kg December, [d] MXD injection 200 µg/kg December.
[e] DRM injection 200 µg/kg December, [f] IVM oral 200 µg/kg September.
[g] IVM oral 200 µg/kg February.

If two extreme weight gain/loss values were omitted as outliers, the weight gain of the control group was 0.5 (0.9) kg, compared to 1.0 (0.8) and 1.7 (1.0) kg for moxidectin and ivermectin treated animals. In hinds treated orally (Ivomec® vet mixt. 0.8 mg/ml, MSD) at different times (VII), the mean weight gain/loss of the groups of hinds varied between a loss of 2.6 kg and a gain of 1.6 kg, the untreated controls lost 0.1 kg.

No difference was seen in slaughter weights between reindeer calves treated with ivermectin during the summer and those untreated (VIII).

Birth weights

The mean weight of calves born to treated animals was often higher than that of untreated controls (Table 3). However, the differences between treatment groups were not statistically significant.

Discussion

The necessity to study endectocides in reindeer

The differences reported in endectocide efficacy, and especially pharmacokinetics (Table 1), between various animal species makes it impossible to reliably extrapolate efficacy and pharmacokinetics expectations from other ruminants. The closest relative to reindeer to which pharmacokinetics data was available is the red deer. In this species, the C_{max} was low, about 15 ng/ml, as compared with about 44 ng/ml in reindeer (trial IV). In red deer the C_{max} was reached about 1 day after subcutaneous injection at 200 µg/kg, but in reindeer about 3 days after similar treatment. The low plasma concentrations in red deer were also associated with insufficient antiparasitic efficacy (Andrews *et al.*, 1993).

Study methods

In the current studies, the treatment efficacy determination against warbles and throat bots was based on direct parasite counts, which is the most reliable basis of efficacy calculation, and thus the method to be recommended (Wood *et al.*, 1995). These experiments (III, V, VI, VII) have apparently been the first utilisation of the endoscopic method for detecting throat bots in live reindeer (II). The inspection requires special equipment (human fibreoptic bronchoscope), but, apart from that, is quick, simple and relatively easy to perform. The examination takes generally less than one minute per animal, and most often the animals do not react to the insertion of the bronchoscope.

Because of limited funding, animals could not be slaughtered, so it was essential to be able to use FEC as an indirect measure of nematode parasite burden. As the treatments were performed during winter when nematodes are hypobiotic and start to produce eggs only months later, the common practice of performing FEC reduction test 1-3 weeks post treatment (e.g. Coles *et al.*, 1992) could not be applied. The spring FECM used in the

current trials has the drawback that reinfection cannot be excluded as a source of parasite burden in any individual animal, or even a group of animals. However, if the comparison of FECMs can show difference between treatment groups, given that the groups are otherwise similar, this difference has to be caused by differences in treatment efficacy. Reinfection can only diminish the differences, and the reductions in FECM may be smaller than the actual antiparasitic efficacy. Therefore the differences observed tend to be conservative estimates.

The McMaster technique (Christensson *et al.*, 1991) as it was used in the first trials (I, III) had a sensitivity (40 epg) that was later considered suboptimal because of the rather low FECs common in reindeer during the winter and spring. Therefore the technique was modified so that each egg observed represented 20 epg. The change increased the laboratory work needed, but it increased even more the value of the examination. Together with the calculation of FECM based on several samples, probably a fair measure of the gastro-intestinal nematode burden was achieved.

Endectocide treatment of reindeer is different from domesticated ruminants

The treatment of reindeer with ML endectocides is different from their most common use in domestic ruminants as the treatment is directed against both insect and nematode parasites. In domestic ruminants endectocides are mostly used against nematode parasites, in fact they are often referred to as «anthelmintics» in this context. The other use of endectocides is as an insecticide in herd level or larger control programs, e.g. against lice or bovine warbles. Seldom can the broad spectrum of the compounds be utilised as thoroughly as in the yearly strategic antiparasitic treatment of reindeer.

Endectocidic efficacy of different ways of application

Antiparasitic treatment of reindeer with ML endectocides is a sequel to the organophosphate treatment against warbles and throat bots started in Finland in the 1970's. Killing warbles and throat bots with the current ML endectocides is easy; from the treatment protocols tried, only moxidectin at 200 µg/kg did not kill all warbles. The low dose of ivermectin at 20 µg/kg killed all warbles, but did not have complete efficacy against throat bots.

The endectocide doses used in the current trials are those used in other ruminant species, too. The sc ivermectin injection at 200 µg/kg is also officially registered for use in reindeer in Finland. The sc injection at 20 µg/kg in trial III was chosen to be a dose clearly smaller than the registered one.

The broad spectrum of ML endectocides gives reindeer owners, and especially reindeer veterinarians, a new responsibility when compared to insecticide treatments. As the endectocides have high efficacy against various nematode parasites, the treatment creates a selection pressure on the nematode fauna. Some of the reindeer nematodes, like those from other cervids, may also be shared with domestic ruminants (Nilsson, 1971; Borgsteede, 1982; Bye & Halvorsen, 1983). Frequent use of the drugs increases the risk of the rise of resistant nematode strains. Even though reindeer treatment cannot currently be considered frequent, it is important to minimise also other factors that might favour endectocide resistance. One of the best-known of them is underdosage (Waller, 1990), i.e. treatment that does have lower killing efficacy than expected. Obviously, the higher the efficacy, the better.

In reindeer, probably only intestinal nematodes, such as *Nematodirus*, *Nematodirella*, *Capillaria*, and *Skrjabinema*. may be significantly affected by the unabsorbed fraction of orally administered ML endectocide. The importance of these parasites to reindeer health is unknown. Abomasal nematodes living in close connection to abomasal mucosa probably are very little influenced by the drug concentration in the bypassing digesta. To ensure maximal efficacy of ivermectin treatment against warbles, throat bots, sinus worms, lungworms, abomasal nematodes, brainworms and other nematodes, such as *Setaria, Onchocerca* and *Lappnema*, the drug should be given so that maximal AUC is achieved, as standard sc injection.

It is known that ivermectin treatment decreases the fertility of surviving (resistant) nematode females (McKellar *et al.*, 1988b; Le Jambre *et al.*, 1995). Because no animals were killed following treatment in the current studies, actual worm counts could not be performed. It is therefore not known whether the trichostrongylid gastrointestinal nematodes were killed after ivermectin (or moxidectin) injection or not. However, the time lag between the treatment and the first recording of egg production was so long ($\geq$ 3 months) that a reversible reduction in fecundity would perhaps already have receded. The prepatent period, time from infection to the start of egg production, of various *Ostertagia* spp. is about three weeks (Soulsby, 1982), so, reinfection might well explain the trichostrongylid egg production in April-May. In any case, the efficacy of sc ivermectin injection has been unmistakably superior to that of the other

administration methods. The difference in FECs clearly indicates that oral and topical ivermectin did not have desired nematocidal efficacy. Orally applicated ivermectin is mostly adsorbed to ingesta, and goes therefore into dung. Topically applicated ivermectin is very uncertainly absorbed, which may be associated with the thick haircoat and hollow hairs (Timisjärvi *et al.*, 1984).

Unfortunately, market economics strongly affect the pricing of different ivermectin preparations. For example in Norway, where both injection, oral paste, oral mixture and pour-on preparations are available, a treatment dose (200 pg/kg as injection or given orally and 500 µg/kg as pour-on) to a 50 kg reindeer calf will cost NOK 8.11 (≈EUR 0.94) as sc injection, NOK 12.10 as equine paste, NOK 8.59 as pour-on, and only NOK 3.72 as oral mixture (Galligani *et al.*, 1996). The latter price is obviously so much lower to enable it to compete with benzimidazoles as an ovine anthelmintic. The active ingredient is cheapest as pour-on, to compensate for the higher dosage; pour-on at 200 pg/kg would cost NOK 3.44 for the same 50 kg animal.

Parasite adaptation to the Arctic

Although trichostrongylid eggs cannot be positively identified to species or even genus, in reindeer faeces they are mostly *Ostertagia gruehneri* (Bye, 1987; Fruetel & Lankester, 1989). The reindeer trichostrongylids appear to be well-adapted to the arctic climate by hypobiosis; the development is sustained so that egg production is ceased in mid-winter, which obviously saves both the parasites and the host. The parasite does not waste energy in reproduction when the eggs would be deposited on snow, where their chances of development might be small. The host, in turn, would be unnecessarily stressed by parasite activity in midwinter when food is scarce. It appears that the reindeer *Capillaria* parasites do not follow the same pattern, but produce eggs in mid-winter. Later, however, the egg production might decrease, while that of trichostrongylids increases. The *Capillaria* pattern is not as clear as that of trichostrongylids, and the factors behind are unknown.

Eradication?

In many countries, eradication programs have been established against cattle warbles (*H. bovis* and *H. lineatum*) These programs are based on the common conclusion that warbles harm the cattle industry enough to justify the costs of the campaigns (e.g. Tarry *et al.*, 1992). It is common to both reindeer warbles and throat bots that the total overwintering population is in the reindeer host. If it was possible to once treat all reindeer, total eradication of these parasites would be just a matter of antiparasitic efficacy of the treatment, which is very high for subcutaneously administered ivermectin. However, all the reindeer are virtually impossible to find during any winter. Moreover, the wild reindeer populations could still serve as a reservoir. Even though the reindeer husbandry locally could agree that getting rid of these nuisances would be a common benefit, such agreement would probably not be accepted in all the reindeer herding areas. The adult flies when attacking reindeer are said to help to collect the animals in flocks (e.g. Nilssen & Haugerud, 1994), which is needed for the ear-marking in the summer. Some reindeer herders refuse to believe that the flies would be totally unnecessary and only harmful for reindeer. People who have lived long with the animals may understand that the evolution of the symbiosis between the reindeer and its parasites to the current stage has taken a long time; the parasites are part of the natural biodiversity and should therefore not be eradicated.

Economic feasibility

Only one of these studies (VIII) was designed to measure economic benefit of endectocidic treatment to reindeer, and that trial investigated summer treatment of calves, which is not currently practised in reindeer husbandry. In that trial, no increase in slaughter weights could be demonstrated. Because of the rather big sample size, it appears very unlikely that the result would have been caused by error alone. All the winter treatment trials were done in the Kaamanen herd, which might differ from commercial co-operative herds in terms of nutrition and parasitism. However, it is interesting to note that significant differences in weight development between treatment groups were only seen in one trial (I), and even then not in ordinary analysis of variance. The differences in calf birth weights between groups in trials III, V, VI and VII were not significant, either. This does not prove wrong the view expressed by many reindeer owners that ivermectin treatment enhances the condition of reindeer and helps the animals to survive over winter and produce healthy offspring. However, the lack of significant weight gain effects of endectocide treatment indicates that such effects might be dependent on other factors, such as crowding and nutrition. Such management differences may at least partly be the cause of the difference in results in weight gain studies of reindeer calves following summer antiparasitic

treatment. Unlike in trial VIII, in the two trials reported from Kaamanen, summer antiparasitic treatment increased the weight gain. Both of those trials were done with a relatively small amount of animals, so the results may be erroneous. However, it appears logical to think that year- and husbandry-related differences in parasite burden may have been the major source of difference in results. This should get practising veterinarians cautious in advocating treatment. Both the existing scientific results and the costs of treatment should be considered. Perhaps in some cases a good alternative to treatment would be not to treat. After all, reindeer meat is, and is expected to be, a natural product, and chemical antiparasitics do not fit well into this image. Ivermectin residues were found in the liver of one reindeer of 35 randomically selected for control by the Finnish National Veterinary and Food Research Institute in 1997 (Aalto *et al.*, 1998).

Timing

It seems that the current «treat them when you catch them» timing of the endectocide treatment is fully adequate. Parasites can be effectively treated anytime during the winter although nematodes are hypobiotic and oestrid fly larvae develop slowly. Similar antiparasitic efficacy and small and non-significant differences in weight gain/loss and in birth weights between groups treated either in September, December, or February (trial VII) indicate that the timing of endectocide treatment of reindeer is not critical.

Future research

Future research challenges are many. The low insecticidic efficacy of moxidectin in reindeer requires an explanation. Was it caused purely by the lower intrinsic efficacy of moxidectin against insects, or did the drug perhaps not reach the parasites? To clarify this, pharmacokinetics of moxidectin in reindeer should be studied. Those studies might also help to understand other differences, perhaps still unnoticed. For example it is not known how the nutritional status of animals, reindeer or other, affects the pharmacokinetics and antiparasitic efficacy of ML endectocides.

Pharmacokinetics of ivermectin in reindeer also need to be worked on further. The results from trial VII might indicate that the active ingredient of the oral ivermectin mixture could be better bioavailable than that of the equine ivermectin paste. That possible difference might be caused by the mixture bypassing the rumen, as it has been shown that the biovailability of abomasally applicated ivermectin is far higher than that of ruminally applicated. If such bypass exists, it should obviously be utilised thoroughly when ivermectin is administered orally to ruminants, as is now common in sheep industry.

To assess the relative economic importance of various reindeer parasite groups, narrow-spectrum antiparasitics should also be experimented with. Benzimidazole compounds do not have insecticidic efficacy, so they could be used as anthelmintics, while some insecticides, such as fenthion do not have anthelmintic efficacy.

If the nematocidal efficacy of doramectin eventually proves to be equal to that of ivermectin, doramectin is a good alternative in reindeer endectocidic treatment. Based on the knowledge from other animal species, this would not seem unlikely. However, it would be wrong to assume efficacy based on other animal species, so the nematocidal efficacy has to be tested.

Some of the currently commercially available ML endectocides have not been tested in reindeer at all. Abamectin is obviously a better nematocide than insecticide, which might be a benefit in reindeer treatment. The interest in under-dosage would be reduced, if its consequences were seen as warbled animals. However, for abamectin to be useful its insecticidid efficacy should be higher than that of moxidectin. If eprinomectin (as pour-on) is absorbed through the reindeer skin as it is designed to do through the bovine skin, it might be a good endectocide to reindeer. The general concern of wasting the active ingredient applies also to reindeer, but not necessarily more than to cattle. Perhaps eprinomectin also will be marketed as an injection sometimes, and possibly there will be other ML endectocides marketed in the future, too. All of them will apparently have similar mode of action, and therefore also cross-resistance will exist if it first has been established. To minimise the risk of endectocide resistance alternative antiparasitic methods should be investigated.

Conclusions

Subcutaneous administration

To direct the endectocide against important parasites, maximal bioavailability of the drug is needed. Having the standard sc injection as reference treatment, oral dosing (at least as the equine paste) of ivermectin can only be regarded as underdosing. To get comparable endectocidic efficacy, the oral dose should probably be at least 3- or 4-fold, which would not be ecologically nor economically feasible. Therefore, oral administration of ivermectin (perhaps all ML endectocides) to reindeer is principally to be condemned.

The results from these experiments, together with those from many trials in domestic ruminants, raise concern regarding the oral application of ML endectocides to ruminants, a common practice in sheep husbandry. Is this treatment really directed against relevant parasites? The most important ovine parasites are obviously nematodes of the abomasum, and it is in this group that endectocide resistance has been observed. Perhaps the treatments should be directed more specifically against these parasites. Then, the use of oral administration should be reconsidered in earnest.

Possible economic benefits of treatment still poorly known

The results from the summer ivermectin treatment of reindeer calves show that it is erroneous to expect gains based on trials with domestic animals. The economic feasibility of antiparasitic treatment of reindeer is poorly documented and not well-known. These experiments did not clarify the matter.

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Appendixes

Appendix 1. Names of some important nematode and arthropod reindeer parasites in some languages.

Latin	English	Norwegian	Swedish	Finnish	Saami
Ostertagia gruehneri	medium stomach worm	løpe-rundmark	löpmagsmask	juoksutus-mahamato	civzzamähtu
Dictyocaulus eckerti[a]	lungworm	lungemark	lungmask	keuhkomato	geahpesmähtu
Elaphostrongylus rangiferi	brainworm	hjernemark	hjärnmask	aivomato	liw'zamáhtu
Hypoderma tarandi[b]	warble, grub fly	hudbrems	hudbroms, renstyng	kurmu, kurmupaarma	gurbmä-loddi, lávzá
Cephenemyia trompe[c]	throat bot, nasal bot	svelgbrems, nesebrems	svalgkorm, nässvalgstyng	saulakka, saulalintu,	njunne-loddi, sávla
Solenopotes tarandi	sucking louse	blodlus	blodlus	täi	varradihkki
Damalinia tarandi	biting louse	pelslus	pälslus	väive	náhkedihkki
Linguatula arctica[d]	sinus worm	bihulemark, neseflyndre	näshälemask	kielimato	njunnemáhtu, njunneguovdni

(Bergman, 1916; Nordkvist, 1966; Skjenneberg & Slagsvold, 1968; Nilssen & Anderson, 1986; Folstad, 1986; Hemmingsen, 1986; Haugerud & Nilssen, 1986; Paliskuntain yhdistys, 1992; J. Kitti, pers., comm. 1998, English names from the text).

[a] Formerly regarded as *D. viviparus*, the bovine lungworm.

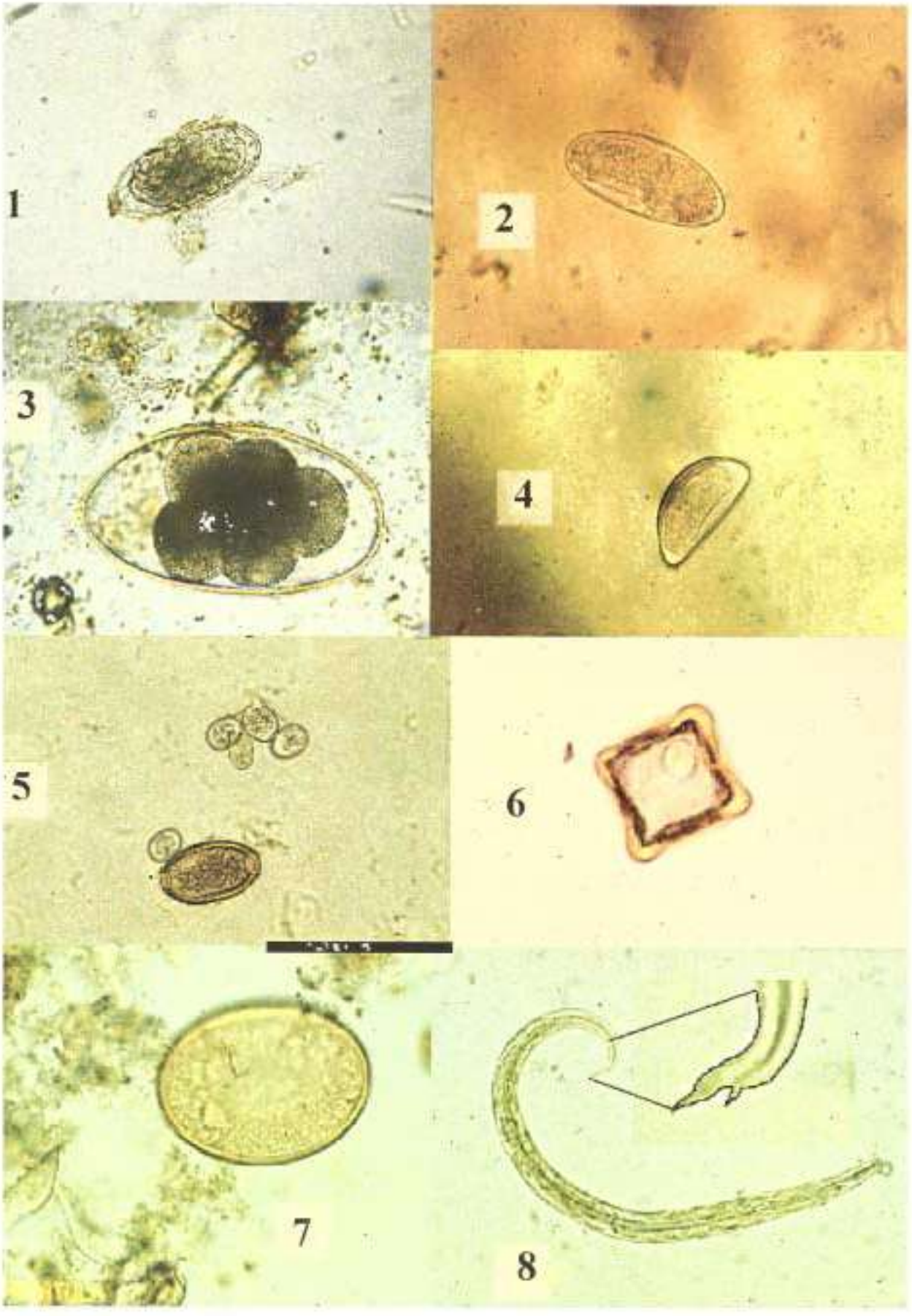
[b] Formerly called *Oedemagena tarandi*.

[c] Often used the erroneous form *Cephenomyia trompe*.

[d] Often in older literature erroneously called *L. serrata*, the canine sinus worm.

Appendix 2. Photomicrographs of parasite eggs and larvae in reindeer faeces and photographs of other reindeer parasites (diagnostic aids).

1-2. Gastro-intestinal trichostrongylid.
3. *Nematodirus* sp. Seen almost exclusively in reindeer calf faeces.
4. *Skrjabinema* sp.
5. *Capillaria* sp., together with *Eimeria* sp. coccidia oocysts.
6. *Moniezia* sp. (Cestode). Seen almost exclusively in reindeer calf faeces.
7. *Linguatula arctica* (Pentastomid).
8. *Elaphostrongylus rangiferi* l_1, dorsal spine not easily visible in print, therefore enlargened. Scale bar 100 µm for Figures 1-8.
9. Fibrous tissue caused by *Lappnema auris* in the auriculum of reindeer («wart-ear» or «hot ear»).
10. Histological section of fibrous tissue caused by *Lappnema auris*. Numerous parasites in capillaries (arrows). H-E staining.
11. Warbled reindeer hind in early May. The barren female has lost its antlers.
12. Warbled reindeer hide slaughtered in May. Inside view.
13. Cross-section of the skin of a reindeer calf, died in March, partly due to heavy warble infection.
14. Massive throat bot infection (101 bots) in a reindeer calf killed in May.
15. Throat bots seen in reindeer by fibreoptic pharyngoscopy.
16. *Linguatula arctica* from a reindeer calf slaughtered in May. Scale bar 8.5 cm.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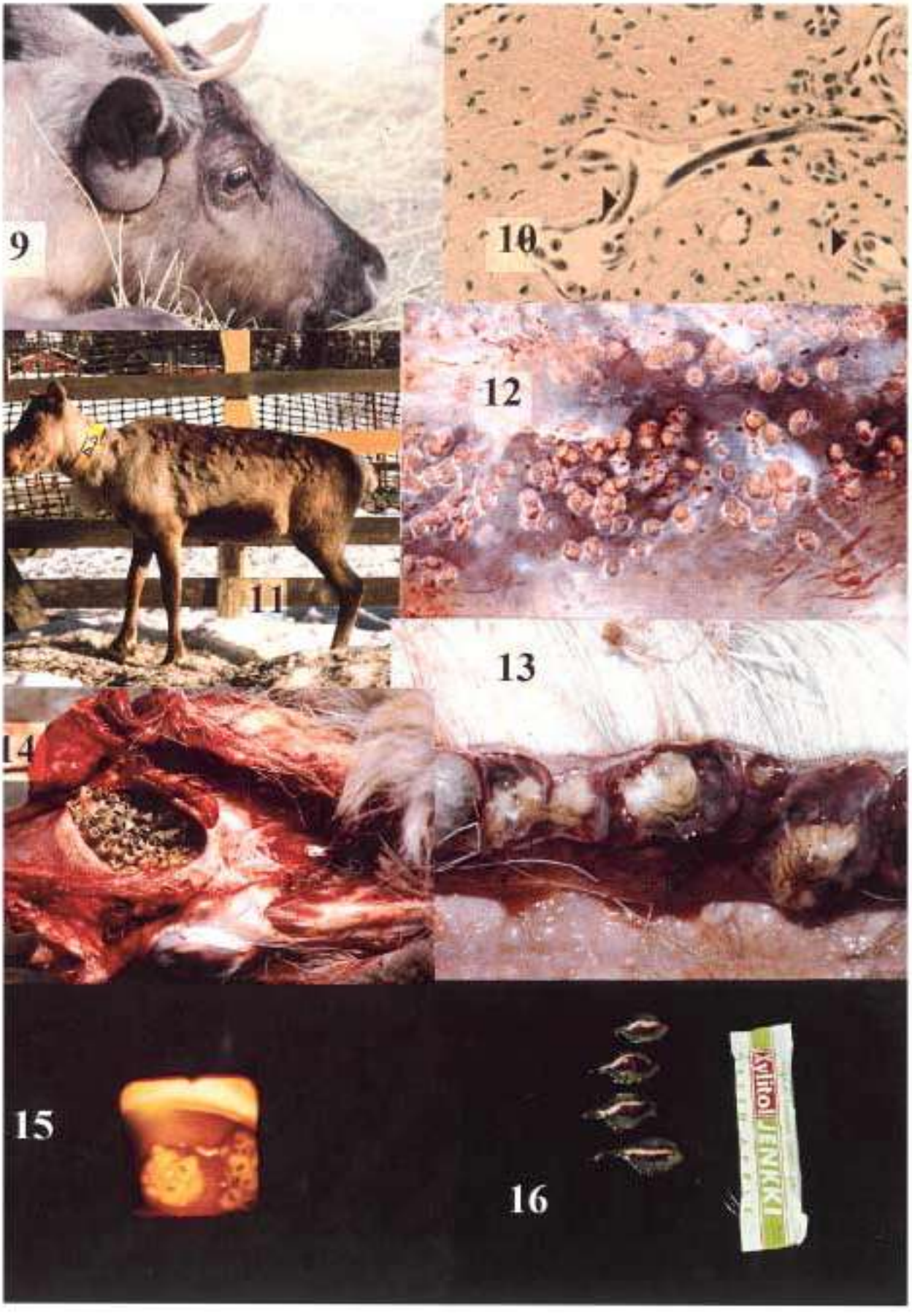
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Xylitol
JENKKI