



COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

PIPERONYL BUTOXIDE

SUMMARY REPORT

1. Piperonyl butoxide is a benzodioxole compound used as a synergist to increase the effectiveness of pyrethroid insecticides and other compounds. In veterinary medicine it is used in a shampoo for horses (piperonyl butoxide 0.8 g/l in combination with pyrethrum extract 0.4 g/l) for killing and repelling flies and treatment of lice infestations. Normal treatment is at least 1 litre per animal, applied to the coat, left for at least 10 minutes, and then washed off. Alternatively, it is used as a lotion (piperonyl butoxide 5 g/l and pyrethrum extract 4 g/l) in the control of midge *Culicoides* infestation. Normal treatment is liberal application to the mane and tail with a brush, then once or twice daily with a smaller amount from spring to early autumn. For cattle, pigs, goats and sheep a solution containing 0.15 g/l pyrethrum extract and 0.25 g/l piperonyl butoxide is used, the recommended dosage is 1 l/animal for cattle, 0.5 l/animal for pigs, and 0.2 l/animal for sheep and goats. The treatment may be repeated once or twice weekly.

In human medicine piperonyl butoxide is used for the treatment of scabies, pediculosis and crab lice, and as an ingredient in insect, louse and mite repellents and in surface disinfectants used against house mites. Piperonyl butoxide is also used in combination with pyrethrins, pyrethroids, rotenone and carbamates in agricultural, garden and household insecticides.

2. Piperonyl butoxide itself has limited insecticidal activity. Its synergistic interaction with pyrethroids takes place at the microsomal level. The detailed mechanism has not been fully clarified. No data on pharmacodynamics in mammals were provided. Piperonyl butoxide causes biphasic effects on hepatic mixed-function oxidase activity. A short phase of inhibition is followed by a longer period of enzyme induction, in the rat the enzyme induction effect appears to be permanent following high repeated oral doses. The pharmacodynamic effects were investigated in mice following intraperitoneal administration. The ED₅₀ values for a maximal electroshock seizure study and a subcutaneous pentylenetetrazol test were 457 and 443 mg/kg bw, respectively. In a rotarod test peak impairment occurred between 7 to 8 hours after doses of 1500 to 1900 mg/kg bw, no effects on rotarod activity were observed at a dose of 1000 mg/kg bw.
3. Piperonyl butoxide is rapidly and almost completely absorbed following oral administration to laboratory rodent species. In mice and rats given oral doses of radiolabelled piperonyl butoxide, more than 70% of the dose was excreted within 48 hours in the urine or as expired CO₂. Male rats were given a single intravenous dose of radiolabelled piperonyl butoxide. Peak biliary levels occurred within 30 minutes and peak urinary levels about 25 hours later. After oral administration of 250 mg/kg bw to male rats, maximum plasma concentration was attained at 5 hours. Plasma, liver, kidney and brain levels were undetectable within 24 hours, but the compound was still present in fat up to 96 hours after dosing. Piperonyl butoxide was not detected in urine at 72 hours after dosing, but was present in faeces. In rats given a single oral dose of 500 mg/kg bw, around 0.18% was expired as CO₂ within 24 hours, plasma activity reached a peak 3 to 12 hours after dosing and dropped to 50% of peak levels within 24 hours. The majority of the radiolabel was recovered within 12 to 24 hours. In a human clinical trial, 4 volunteers were topically dosed with 100 µl of 4% piperonyl butoxide in water over an area equivalent to a dose of 160 µg/cm². After 8 hours the dose was washed off. Absorption of piperonyl butoxide in humans was 2.2% of the administered dose.

The metabolism of piperonyl butoxide is complex and not fully understood. There are species-, sex-, and dose-related differences in the metabolism of the compound. Four different pathways have been demonstrated, up to 14 metabolites have been characterised and about 10 more exist. Metabolism and residues studies in the goat and hen indicate that metabolism is incomplete, with parent compound comprising up to 100% of the residues in different tissues. However, no data were available for animals killed after more than 24 hours of dosing. In lactating goats, 0.44% of an oral dose was excreted in milk, 90% as parent compound. The metabolic pathway in ruminants and poultry appears to be markedly different to that in monogastric mammals.

Thirteen metabolites have the methylene group intact and 10 have between 2 and 4 of the side chain oxidation sites intact; these metabolites are likely to possess synergistic activity. No data on the potential of these metabolites to cause enzyme inhibition or induction or toxicity are available.

5. Piperonyl butoxide is of low acute toxicity. LD₅₀ values from oral acute studies (generally using undiluted) compound ranged from 2650 to more than 10 600 mg/kg bw in most laboratory species. Clinical effects were non-specific (ano-genital and ocular staining, prostration and lethargy).

6. In short-term dietary studies in mice using doses of piperonyl butoxide of 1000 to 9000 mg/kg feed for up to 7 weeks, and rats using doses of 62.5 to 30 000 mg/kg feed for up to 13 weeks no NOELs were identified. The main findings were reductions in bodyweight and food consumption and effects on the liver of both species and the rat kidney. In rats adverse effects on bone marrow thymus and spleen were also reported at the highest doses.

Groups of beagle dogs were fed diets containing 500, 1000, 2000 or 3000 mg piperonyl butoxide (90.78% purity)/kg for 8 weeks. The main effects were reduced bodyweight gain and food consumption and effects on the liver. No NOEL was identified. For all 3 short-term studies doses were reported as dietary concentrations and insufficient data were available to convert these to mg/kg bw/day.

7. Groups of 4 male and 4 female beagle dogs were fed diets containing 0, 100, 600 or 2000 mg/kg feed piperonyl butoxide (90.78% purity) for 1 year (average consumption, males: 3, 16 and 53 mg/kg bw/day, respectively, females: 3, 16 and 71 mg/kg bw/day, respectively). No deaths occurred and there were no treatment-related clinical findings. Reduced bodyweight gain was reported in the high dose males and the high dose females showed a slight weight loss. Food consumption was significantly decreased in the 600 and 2000 mg/kg feed males. Small non-significant decreases in food consumption were seen in females. No treatment-related effects on haematology were reported. Alkaline phosphatase activities were increased by about 3 to 5 times in both sexes at 2000 mg/kg feed after 6 and 12 months and non-significant decreases in cholesterol levels were reported in females. Both sexes at this dose showed increased absolute and relative liver and gall bladder weights. Small increases in thyroid and parathyroid weights were seen in the females. There were also isolated significant effects on adrenal weights in females, and large non-significant effects on adrenal, gonad and kidney weights, some of which showed dose-related trends. Diffuse, mild hepatocyte hypertrophy was reported in males and females at 2000 mg/kg feed only. Mild testicular atrophy was reported in one male at a dose of 600 and one at a dose of 2000 mg/kg feed. No other treatment related effects were apparent. The effects at the low dose level were not of toxicological significance and the middle dose of 600 mg/kg feed (16 mg/kg bw/day) could be considered as the NOEL.

8. No data on target species tolerance was provided.

9. In a 2-generation study, CD-1 mice were fed diets containing 0, 1000, 2000, 4000 or 8000 mg piperonyl butoxide (purity unspecified)/kg feed, no NOEL was identified due to effects on pup weights in both generations. In a single-generation reproduction study, groups of CD-1 mice were fed diets containing 0, 1500, 3000 or 6000 mg piperonyl butoxide (purity unspecified)/kg feed. No NOEL was established with reductions in pup bodyweight at all doses and effects on survival and behavioural parameters at higher doses (compound intake in mg/kg bw in these studies could not be estimated due to lack of information).

In a 2-generation study groups of Sprague-Dawley rats received diets containing 0, 300, 1000 or 5000 mg/kg feed piperonyl butoxide from 7 weeks old, for 85 days before mating, through 2 matings, and until sacrifice 3 weeks after the second mating. Calculated mean compound intakes during the early part of the study were 0, 28, 68 and 350 mg/kg bw/day in males, respectively, and 0, 29, 94 and 480 mg/kg bw/day in females, respectively. No treatment related clinical or pathological effects were reported in the F₀ or F_{1b} adults. High dose adult bodyweights were reduced with occasional reductions in food consumption. Reproductive parameters and neonatal development was unaffected apart from a reduction in bodyweight in the high dose pups from day 4 of lactation. A NOEL for parental toxicity and pup development of 1000 mg/kg feed (68 mg/kg bw/day) was identified.

10. Groups of pregnant CD-1 mice were given a single oral dose of 0, 1065, 1385 or 1800 mg piperonyl butoxide (more than 95% purity)/kg bw, by gavage in olive oil on day 9 of gestation. No maternal toxicity was reported and maternal bodyweights in all groups were comparable. Reduced foetal bodyweights were observed in low dose females and reduced bodyweights, increased resorption rate and dose-related increases in forelimb oligodactyly at higher doses. The NOEL for foetotoxicity was less than 1065 mg/kg bw.

Groups of pregnant COBS rats were given daily oral doses of 0, 300 or 1000 mg piperonyl butoxide (purity unspecified)/kg bw/day, by gavage in olive oil on days 6 to 15 of gestation. Reductions in maternal bodyweight gain were seen in both dose groups, mainly between days 15 to 20 of gestation. No significant effects on reproductive parameters were reported. No effects on foetal development were reported. The NOEL for maternal toxicity was less than 300 mg/kg bw/day, and the NOEL for foetotoxicity was more than 1000 mg/kg bw/day. Groups of pregnant Wistar rats were given daily oral doses of 62.5 to 500 mg piperonyl butoxide (80% purity)/kg bw/day, by gavage in olive oil on days 6 to 15 of gestation. No effects on maternal, litter or foetal parameters were reported. The NOEL for maternal and foetal effects was more than 500 mg/kg bw/day.

Groups of pregnant Sprague-Dawley rats were given daily oral doses of 0, 200, 500 or 1000 mg piperonyl butoxide (90.78% purity)/kg bw/day, by gavage (undiluted) on days 6 to 15 of gestation. No effects on gestational or foetal parameters were observed. The NOEL for maternal toxicity (reduced bodyweight and food consumption, and increased liver weight) was 200 mg/kg bw/day and the NOEL for foetotoxicity was 1000 mg/kg bw/day.

In a range-finding study, pregnant New Zealand White rabbits received oral doses 50 to 400 mg piperonyl butoxide (purity unspecified)/kg bw/day by gavage in corn oil daily from days 7 to 19 of gestation. Maternal toxicity occurred at doses of more than 200 mg/kg bw/day. No treatment-related effects on uterine parameters were reported. Groups of pregnant New Zealand White rabbits received oral doses of 0, 50, 100 or 200 mg piperonyl butoxide (100% purity)/kg bw/day by gavage in corn oil daily from days 7 to 19 of gestation. Slight bodyweight losses occurred at the mid and high doses, but these were recovered during the post-dosing period; overall there was no effect on bodyweight gain. Increased incidences of some skeletal anomalies were reported. A NOEL for maternal toxicity of 50 mg/kg bw/day and 200 mg/kg bw/day for foetotoxicity were identified.

11. Three *in vitro* bacterial gene mutation studies using *Salmonella typhimurium*, with and without metabolic activation and *Escherichia coli*, at concentrations of piperonyl butoxide up to 5000 µg/plate gave negative results. A positive result was reported in an L5178Y mouse lymphoma cell assay at concentrations of 30 to 75 µg/ml; the assay was not carried out with metabolic activation. In point mutation assay (HPRT locus) in Chinese hamster ovary cells, no evidence of mutagenic effects were found in the presence of metabolic activation at doses of 25 to 500 µg/ml. Without metabolic activation, an equivocal result was obtained. An *in vivo* dominant lethal mutation assay using male ICR/Ha Swiss mice given single intraperitoneal doses of 200 or 1000 mg/kg bw, or 5 daily oral doses of 1000 mg/kg bw in tricapylin vehicle was conducted. Foetal deaths were significantly increased in the first mating period at 200 mg/kg bw, but not at 1000 mg/kg bw intraperitoneally. In the orally dosed animals the incidence of foetal deaths/pregnancy was significantly increased only in the second mating period at the 5% level. This was interpreted as a negative result.

An *in vitro* unscheduled DNA synthesis (UDS) assay was conducted in rat primary liver cell cultures. No effect on nuclear grain counts was reported at doses from 1 to 74.9 µg/ml. *In vitro* UDS was also investigated in human liver slices. No significant increases in net grain counts compared to control (dimethyl sulfoxide) values were observed in the piperonyl butoxide-treated slices (0 to 2.5 mM). Piperonyl butoxide was reported to have no significant effect on replicative DNA synthesis. Negative results were obtained in an *in vitro* chromosomal assay using Chinese hamster ovary cells in which replicate cultures were incubated in concentrations of piperonyl butoxide of 9.99 to 49.9 µg/ml for 10 hours and 49.99 to 99.9 µg/ml for 20 hours without metabolic activation, and at concentrations of 25.1 to 251 µg/ml in 10 and 20 hours assays with metabolic activation.

It was concluded that piperonyl butoxide was not genotoxic.

12. Groups of B6C3F1 mice received diets containing 5000 or 10 000 mg piperonyl butoxide (88.4% purity)/kg feed for 30 weeks and diets containing 500 or 2000 mg/kg feed for another 82 weeks. Survival was unaffected by treatment. There was a dose-related reduction in bodyweight. No treatment-related increase in tumour incidence or non-neoplastic lesions was reported. Male CD-1 mice were fed diets containing 0, 6000 or 12 000 mg piperonyl butoxide (94.3% purity)/kg feed for 12 months. Mortality was increased in the high dose and final bodyweights were reduced in both doses. Incidence of hepatocellular adenomas, carcinomas, and haemangio-endothelial sarcomas were increased in a dose-related fashion. Hepatocellular hyperplasia was increased in both doses, the incidence was greater in the low dose, but the true incidence in the high dose may have been obscured by neoplastic lesions in the high dose. Hepatocellular necrosis was also reported in the high dose. No NOEL was identified.

Groups of CD-1 mice received piperonyl butoxide in the diet corresponding to doses of 0, 30, 100 or 300 mg piperonyl butoxide (90.78% purity)/kg bw/day for 78 weeks. No effects on clinical signs or survival were reported. Decreased bodyweight gain was reported for the high dose. Dose-related increases liver weights were seen in both sexes at the middle and high doses and in the low dose males. Increased incidences of a number of neoplastic and non-neoplastic hepatic lesions were observed in the middle and high doses. Hepatocellular hypertrophy and adenomas were significantly increased in the groups receiving 100 and 300 mg/kg bw/day (males) and 300 mg/kg bw/day (females). Hepatocellular hyperplasia was slightly increased at 300 mg/kg bw/day. Hepatocellular carcinomas were slightly increased in the 300 mg/kg bw/day (males), and incidence of combined adenomas and carcinomas were significantly increased in the 100 mg/kg bw/day males and both sexes at 300 mg/kg bw/day. No NOEL could be identified.

Groups of Sprague-Dawley rats were fed diets corresponding to doses of 0, 30, 100 or 500 mg piperonyl butoxide (89% purity)/kg bw/day for 104 to 105 weeks. Bodyweights were reduced at 500 mg/kg bw. High dose females showed increased cholesterol levels through the study and raised blood urea nitrogen at 98 days. Increased liver weights were seen at more than 100 mg/kg bw/day, accompanied by centrilobular hepatocyte hyperplasia and hypertrophy, with enlarged eosinophilic cells with occasional brown pigment. Increased kidney weights were seen in females at more than 100 mg/kg bw/day, with a higher incidence of chronic interstitial glomerulonephritis. Other histological effects were confined to the endocrine system, predominantly at the high dose and appeared to be secondary to the enzyme-inducing effects of the compound. The NOEL for hepatic effects was 30 mg/kg bw/day.

Two 2-year studies were conducted in F344 rats fed diets containing 0, 5000 or 10 000 mg/kg feed piperonyl butoxide (about 89% purity) for 104 weeks. In the first study, there was a dose-related increase in mortality with many animals showing signs of anaemia and blood in faeces before death. A dose-related decrease in bodyweight without decreased food intake was reported. No increases in tumour incidence were observed and the only treatment-related lesions were reported in the gastrointestinal tract. No NOEL was identified. In the second study survival in males was unaffected, all control females and about 80% of treated females survived. There was a dose-related reduction in bodyweight. A statistically significant increase in lymphoreticular malignant lymphoma was reported in females and a non-significant decrease in males. No NOEL was reported.

In a 104-week study, groups of F344 rats were fed diets containing 0, 6000, 12 000 or 24 000 mg piperonyl butoxide (94.3 to 94.5% purity)/kg feed. These dose levels were equivalent 547, 1 052 and 1 877 mg/kg bw in males and 537, 1 061, 2 002 mg/kg bw in females. The study was terminated early (males week 95, females week 96) due to high mortality of the middle dose males. Most deaths were associated with caecal haemorrhage. A dose-related reduction in bodyweight was reported. All organ weights except liver were reduced at the high dose, absolute liver weights were increased in both sexes at the middle dose and in low dose females. A dose-related increase in hypochromic microcytic anaemia was reported. Plasma cholinesterase activity and triglyceride were decreased at all dose levels, blood urea nitrogen was raised in high dose male and all female groups. Nodular hepatic lesions and tumours were seen from week 74 and only occurred in treated animals and incidence, multiplicity and size were dose-related. Increased incidence of thrombocythaemia was reported in male animals only. Increased incidences of non-neoplastic, non-hepatic lesions were also noted in the gut, kidney and lungs. No overall NOEL was identified from this study, the NOEL for carcinogenic effects was 547 mg/kg bw/day in males and 537 mg/kg bw/day in females.

In chronic dietary studies, piperonyl butoxide is hepatotoxic and hepatocarcinogenic. In the mouse slight increases in incidence of both parameters were noted at the lowest dose tested (30 mg/kg bw/day), although this dose may be regarded as a LOEL. In rats, NOELs for hepatocarcinogenicity and hepatotoxicity were identified as 537 and 30 mg/kg bw/day, respectively. It can be concluded that the neoplastic effects are due to a non-genotoxic mechanism related to the effects of the compound on hepatic enzymes and the neoplastic effects occurred only at or above doses causing toxicity.

13. A sensitisation study was conducted in guinea pigs using a modified Buehler method. No erythematous or oedematous reactions were reported in animals treated with 0.4 ml piperonyl butoxide applied to the skin for 6 hours, 3 times weekly for 3 weeks during the induction or challenge phases or in the naive controls. Groups of male F344 rats were fed a diet containing 25 000 mg piperonyl butoxide/kg feed or subjected to a 64% restriction of food intake for 2 weeks. It was concluded overall that the toxicological profile observed in both treatment groups was essentially similar and the high dose effects of piperonyl butoxide of the lymphohaemopoietic system were probably due to reduced food intake and not a direct immunotoxic effect. Reduced platelet count and occasional elevations in reticulocyte counts were reported in splenectomised dogs exposed to piperonyl butoxide fogs for four 5-minute exposures on four days.
14. Co-administration of piperonyl butoxide and pyrethrins can potentiate the acute toxicity of both. The interactions of pyrethrins on the acute and subacute mammalian toxicity of piperonyl butoxide and other xenobiotics have been investigated. In acute oral studies in rats, co-administration of pyrethrins and piperonyl butoxide reduced LD₅₀ values to 50% and 40%, respectively. Conversely, in 90-day sub-acute studies in which animals received doses equivalent to 25% of the oral LD₅₀ values, alone or in combination, toxicity was reduced in the combination group. These data may indicate that enzyme induction may reduce toxicity in combination. Piperonyl butoxide is prepared from dihydrosafrole, a known co-carcinogen and piperonyl butoxide has been shown to have a co-carcinogenic action with 3,4-benzpyrene in rats. Additive and synergistic activity has been demonstrated with pyrethrum and DDT in rats and freon in mice.
15. No microbiological data are required for the assessment of this compound.
16. No adverse effects in humans have been reported following topical use of ectoparasiticide or insect repellent formulations containing piperonyl butoxide. No clinical effects were reported oral in or dermal pharmacokinetic studies in human volunteers.
17. Piperonyl butoxide was evaluated in 1996 by the Joint FAO/WHO Meeting on Pesticide Residues (JMPR) and an ADI of 0-0.2 mg/kg bw was established.

18. No oral pharmacological ADI was identified, but parenteral studies indicated systemic pharmacodynamic effects only at doses considerably higher than those causing hepatotoxic effects. Toxicological NOELs can be identified for both hepatotoxic and hepatocarcinogenic effects in rats and mice, neoplastic changes only occurred at, or above, doses causing toxicity. The lowest NOEL for hepatotoxicity was identified as 16 mg/kg bw/day from a 12-month dietary study in the beagle dog which applying a safety factor of 100 results in an ADI of 0.2 mg/kg bw (rounded to one decimal place) i.e. 12 mg/person.

19. No pharmacokinetic or residues depletion studies were provided for horses, pigs, poultry and sheep.

In a study in humans the dermal absorption of piperonyl butoxide was found to be 2.2%. Taking into account that humans typically have a much higher absorption of hydrophobic molecules than the horse it was estimated that the total absorbed residues from a dermal therapeutic dose of piperonyl butoxide would amount to less than 2% of the ADI.

20. Two lactating goats were given daily oral doses of around 50 mg ¹⁴C-piperonyl butoxide/kg w/day of for 5 consecutive days. Milk samples were collected daily. Twenty-three hours after the last dose the goats were killed. Total residues in milk and tissues were determined by liquid scintillation counting and residues of piperonyl butoxide and its metabolites were determined using HPLC and Mass Spectrometry. The mean total residues in fat, muscle, liver and kidney were 56 283, 1 821, 21 808 and 31 392 µg equivalents/kg, respectively. Piperonyl butoxide comprised 90% of the residues in fat, 100% in muscle, 26% in liver and 13% in kidney. Residues of 3 unidentified metabolites and 3 identified metabolites were also present in tissues. An unidentified metabolite accounted for 38% of the residues in kidney and 11% of the residues in liver and a second unidentified metabolite 16% of the residues in kidney and 22% of the residues in liver. Over the duration of this study, around 71% of the dose was excreted in urine, 18% in faeces and approximately 5% in milk. Piperonyl butoxide represented 35% of the residues in milk. Two identified metabolites accounted for 26% and 22% of the residues in milk and an unidentified metabolite accounted for a further 16%.

21. A lactating goat was dosed topically with 0.23 mg piperonyl butoxide/kg bw/day for 5 days. Two further goats were dosed orally, one with 0.34 mg/kg bw/day for 5 days, the other with 3.4 mg/kg bw/day for 5 days. The goats were killed 22 hours after the last dose. Total residues in liver were 149, 363 and 2007 µg equivalents/kg for the goats treated topically, with the two low oral doses and the one high oral dose, respectively. The corresponding residues in kidney were 113, 71 and 398 µg equivalents/kg, and in fat they were 196, 9 and 234 µg equivalents/kg, respectively. The pattern of distribution of the metabolites in both milk and tissues was similar for the 3 goats. Four metabolites were identified; all 4 involved modification of the side chain and one also involved reduction of the dioxole moiety. On the basis of these data a total maximum daily intake of 0.037 mg equivalent to 0.3% of the ADI was estimated with a withdrawal period of less than 24 hours.

22. Three lactating cows were dosed topically with 3.78 mg/kg bw/day piperonyl butoxide for 28 days. Milk samples were collected twice daily and composite milk samples were prepared from each cow. The cows were killed 16 to 24 hours after the last dose. The piperonyl butoxide content of milk and tissue samples were determined by a combination of GC/MS and GC/MS/MS with an limit of quantification or 50 µg/kg for tissues and 10 µg/kg for milk. The mean piperonyl butoxide content of the tissues were 80, 200, 180 and 2530 µg/kg for liver, kidney, muscle and fat, respectively. On the basis of these data a total maximum daily intake of 0.199 mg equivalent to 1.66% of the ADI was estimated, with a withdrawal period of less than 24 hours.

23. Data from pesticidal use on food crops and use as a domestic pesticide suggest that maximum consumer intakes from these sources 3.2 to 3.6 mg/day represents approximately 27 to 30% of the ADI.

24. An analytical method was provided for the determination of residues of piperonyl butoxide in goat tissues, based on HPLC. The method was not validated in accordance with Volume VI of the Rules Governing Medicinal Products in The European Community and was not described in the ISO 78/2 format.

Conclusions and recommendation

Having considered that:

- a toxicological ADI of 0.2 mg/kg bw/day was established, based on the NOEL for hepatotoxicity in the dog and a safety factor of 100,
- data from pesticidal use on food crops and use as a domestic pesticide suggest that maximum consumer intakes from these sources represents approximately 27 to 30% of the ADI,
- in horses, to which the highest dermal dose is indicated, it was estimated that total absorption accounted less than 2% of the ADI,
- in cattle and goats, total maximum daily intake of residues was estimated as 1.66% and 0.3% of the ADI, respectively, within 24 hours after multiple applications in excess of the recommended posology,
- although no residues data were provided for sheep, it was considered that the total daily maximum intake was unlikely to exceed that for goats in light of the identical posology for these species,
- no data were provided on absorption and tissue distribution of residues for chickens and pigs, no data were provided for residues in skin in any of the species studied and skin forms part of the edible tissues of poultry and pigs;

the Committee for Veterinary Medicinal Products concludes that there is no need to establish an MRL for piperonyl butoxide and recommends its inclusion in Annex II of Council Regulation (EEC) No 2377/90 in accordance with the following table:

Pharmacologically active substance(s)	Animal species	Other provisions
Piperonyl butoxide	Bovine, ovine, caprine, equidae	For topical use only