A REVIEW OF FLUBENDAZOLE AND ITS POTENTIAL AS A MACROFILARIACIDE

A report submitted to Dr Gary Weil (PI DOLF) - a study supported by the BIll & Melinda Gates Foundation

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Goal: *This report covers data on flubendazole reviewed in preparation for preparing a full drug development proposal to the B&M Gates Foundation for the use of the drug for filariasis*

INDEX

1. Introduction
2. Basic data
3. Use in non-human species
4. Use in humans
5. Safety issues
6. Potential as a macrofilariacide
7. References
8. Appendices

1. INTRODUCTION

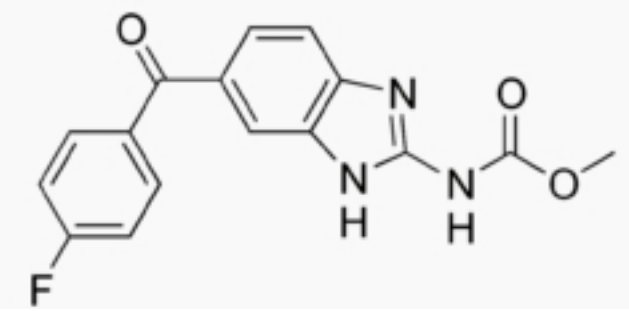
Flubendazole is a member of the benzimidazole class of heterocyclic aromatic organic compounds, a class that has been used extensively in a wide range of species. This class includes a range of active anthelminthic compounds that represent arguably the most important collection of anti-worm agents available today.

This report is the result of considering current literature, and of discussions with many experts in this field of work including those at pharmaceutical companies who are, or were, involved with the commercial distribution of this anthelmintic agent. The document does not attempt to review all the literature available but rather to present the main components that are relevant to the idea that this agent may have a major role as a macrofilaricide for improving the mass drug administration activities against river blindness (onchocerciasis) and lymphatic filariasis.

It should be noted that some information on this compound was not available due to unavoidable circumstances (e.g. data/information had been destroyed, data not released for consideration by scientists, etc.). However, it is believed that the information that was not available would not have affected the overall conclusions made in this present report and the consequent second B&MG grant submission.

2. BASIC DATA

Chemical Structure:



There are two major metabolites for flubendazole, namely the hydrolysed form (FLU-NH2) and the reduced form (FLU-OH).

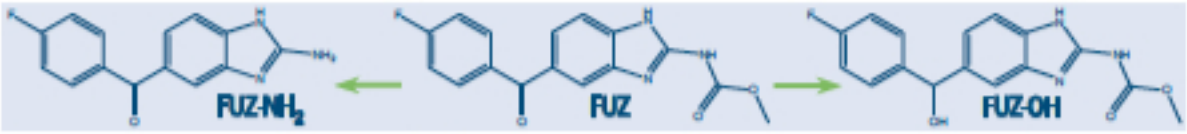


Figure 1. Structures of flubendazole (FUZ) and its metabolites, hydrolised flubendazole (FUZ-NH_2) and reduced flubendazole (FUZ-OH).

The three forms, parent and 2 metabolites are active in individuals that are treated with this drug and therefore all three compounds must be considered in the test procedures used to determine the safety of flubendazole if it to be used for filariasis.

Two polymorphs of flubendazole exist - flubendazole and flubendazole polymorph B (2011-03-22. CAS： 31430-15-6) with Form B being variably described as being active or inactive.

Flubendazole, as with the benzimidazole group, is a specific inhibitor of microtubule assembly, acting by binding to the heterodimeric subunit, the tubulin molecule. The preferential binding of the benzimidazoles for parasite tubulin is some 100-400 fold greater than that to host tubulin; this fact is an important key to their safe use anthelminthic agents.

Names used for Flubendazole

Flubendazole

Fluvermal

Tricyclo[5.2.1.0]decan-8-one

Tricyclo[5.2.1.0(2,6)] Decan-8-One

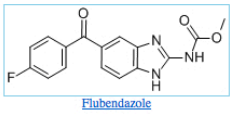
tricyclo(5.2.1.02,6)decane - 8 - one

Flubendazol

Tricyclo[5.2.1.02,6]decan-8-one

Flubenzimin

Flubendazole



Flubendazole

CAS No.	31430-15-6
Chemical Name:	**Flubendazole**
Synonyms:	R-17899;FLUMOXAL;FLUBENOL;FLUVERNAL;FLUMOXANE;fluvermal;FLUMOXANAL;FLUBENDAZOL;FLUBENDAZOLE;flubendazole standard
CBNumber:	CB2669630
Molecular Formula:	C16H12FN3O3
Formula Weight:	313.28
MOL File:	31430-15-6.mol

Flubendazole Property

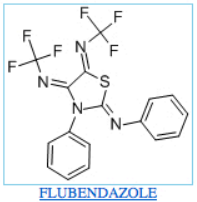
mp :	290°C
CAS DataBase Reference:	31430-15-6(CAS DataBase Reference)

Safety

RTECS :	DD6497500

Some minor differences exist in the commercial description of flubendazole.

FLUBENDAZOLE

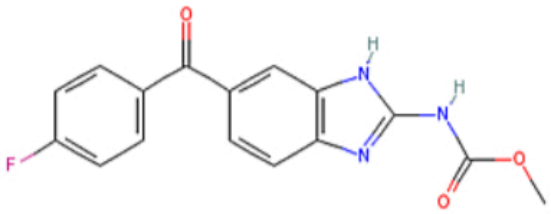


FLUBENDAZOLE

CAS No.	37893-02-0
Chemical Name:	**FLUBENDAZOLE**
Synonyms:	slj0312;cropotex;FLUMOXAL;FLUBENOL;FLUVERNAL;FLUMOXANE;FLUMOXANAL;bayslj0312;FLUBENDAZOL;FLUBENZIMIN
CBNumber:	CB5669631
Molecular Formula:	C17H10F6N4S
Formula Weight:	416.35
MOL File:	37893-02-0.mol

FLUBENDAZOLE Property

mp :	260°C
Fp :	>100 °C
storage temp. :	0-6°C

Substance Name	**Flubendazole**
Synonyms	* Flubendazolum [INN-Latin], * (5-(4-Fluorobenzoyl)-1H-benzimidazole-2-yl)carbamic acid methyl ester, * Methyl 5-(p-fluorobenzoyl)-2-benzimidazolecarbamate, * Methyl N-(5-(p-fluorobenzoyl)-2-benzimidazolyl)carbamate, * 2-Benzimidazolecarbamic acid, 5- (p-fluorobenzoyl)-, methyl ester, * AIDS-084892, * AIDS084892, * Carbamic acid, (5-(4-fluorobenzoyl)-1H-benzimidazol-2-yl)-, methyl ester, * Carbamic acid, [5- (4-fluorobenzoyl)-1H-benzimidazol-2-yl]-, methyl ester, * CCRIS 4480, * EINECS 250-624-4, * Flubendazol [INN-Spanish], * Flubendazole [USAN:BAN:INN], * Flubenol, * Flumoxal, * Flumoxane, * Fluvermal, * N-{5-[(4-Fluorophenyl)carbonyl]benzimidazol-2-yl}methyloxymethanamide, * NSC 313680, *NSC313680, * R 17899, * R 17,889,
Chemical Name	methyl N-[5-(4-fluorobenzoyl)-3H-benzoimidazol-2-yl]carbamate
Molecular Formula	$C_{16}H_{12}FN_3O_3$
Molecular Weight	313.283
CAS No.	31430-15-6
Chemical Structure	

Flubendazole is a synthetic anthelmintic belonging to the benzimidazole carbamates which acts by inhibiting the microtubular assembly in absorptive cells of nematodes. It acts by binding to tubulin, the dimeric subunit protein of the microtubules. It inhibits microtubular assembly in absorptive cells: i.e. of intestinal cells of nematodes. This is shown by disappearance of cytoplasmic microtubules,

Pharmacodynamic Properties	accumulation of secretory granules in the cytoplasm due to a block in their transport, leading to an impaired coating of the cellular membrane and a decreased digestion and absorption of nutrients. Irreversible lytic degeneration of the cell, due to the accumulation of secretory substances (hydrolytic and proteolytic enzymes), results in the death of the parasite. Flubendazole is a broad-spectrum anthelminthic agent effective against endoparasites such as gastro-intestinal ascarids, hookworms, whipworms found in dogs, and active a range of gastrointestinal parasites in pigs and poultry such as roundworms, and tapeworms, Ascaris suum (large roundworm), gapeworms, Hyostrongylus rubidus (red stomach worm), Oesophagostomum dentatum (nodular worm), Trichuris suis (whip worm), Strongyloides ransomi (adult), Metastrongylus apri (lungworm).Flubendazole is ovicidal.

3. USE IN NON-HUMAN SPECIES

Flubendazole is a very commonly used compound in the veterinary world and is freely available for aquatic, avian and mammalian species, There are very few validated descriptions of adverse reactions to its use and the few described are associated with very high doses or the use of pro-drugs (which have considerably different pharmacology to flubendazole itself or the two metabolites, reduced flubendazole and hydrolyzed flubendazole).

Use with Aquatic Species

In fish it is used for controlling a number of organisms, including hydra, intestinal parasites (Heximata, gill flukes and Camallanus) possible by adsorption through the fish's skin. Regularly used dose levels are 0.5 g of 10% flubendazole in 20 gallons (75 liters) of water. Overall it is reported to be safe at comparatively high levels in its use with fish and the like. No delayed expression of toxicity were observed for 21 d after a 96-h exposure to flubendazole was noted, probably reflecting to the relatively high elimination constants for the chemical.

Use in Birds

Flubendazole is commonly used in the management of avian species. For example commercially available flubendazole-based products are efficacious against three species of helminth parasites of chickens: Ascaridia galli, Heterakis gallinarum and Capillaria spp; flubendazole achieves an overall efficacy of 99.4% for the three parasite species without any adverse side effects.

Flubenvet (2.5%) as a poultry dewormer is used as a medicated feed supplement commonly used to deworm chickens, turkeys and geese. **Flubenvet** is active against mature and immature nematodes of the respiratory and gastrointestinal tract. There are 3 major worms that usually affect chickens - these are roundworms, gapeworms and tapeworms. Flubenvet contains the active ingredient Flubendazole which has no adverse effect on egg laying or hatching. It is the only licenced in feed wormer for chickens currently available in the UK. It is very effective and can prevent a large number of problems and long term damage to your birds. You do not need to withdraw eggs for consumption when it is given at the correct dose and it is simple to administer in food.

The PK/PD aspects of flubendazole have been well studied in birds with acceptable results such as the following example: After oral administration of the

veterinary medicine Flubenol 5% the concentrations of the flubendazole-derived residues were determined by a liquid chromatographic-mass spectrometric method. The highest residue concentrations were obtained for the reduced metabolite. With the therapeutic dose, the maximum mean residue concentrations obtained for this compound in thigh muscle, breast muscle and liver were 312, 288 and 1043 ug/kg, respectively. The values for flubendazole, the parent molecule, were 114, 108 and 108 ug/kg, respectively. The residues of the hydrolysed metabolite were negligible in the sampled muscle tissues. After 24 h of depletion, the sum of the residues of parent and metabolites in muscle tissue still exceeded 50 ug/kg. After 8 d of depletion, flubendazole-derived residues at low concentrations could still be measured in both muscle tissues and liver. Thus flubendazole in this species has a wide tissue distribution, and consequently can reach parasites in different tissues.

Use in Domestic Species

Flubendazole has been used extensively in poultry and swine but lesser so on ruminants. the pharmacology in the latter species has been carried out and the data available for studies that would need to be carried out with bovine onchocerciasis in teh development of the drug for use in filariasis. No major differences appear to be likely with ruminants compared to mono-gastric animals. Little is published concerning this drug's use in small domestic animals (e.g. dogs) but oral reports stated that it was safe and effective.

4. USE IN HUMANS

Flubendazole, as originally formulated, is used to treat intestinal nematodes in humans. Flubendazole is registered and sold in Europe (EMEA) as Fluvermal (Johnson and Johnson, Sante Bea). **Flubendazole** is reported as an ingredient of Fluvermal in the following countries:

- Algeria
- Benin

- Burkina Faso
- Cameroon
- Central African Republic
- Colombia
- Congo
- Cote D'ivoire
- Cyprus
- Ecuador
- Egypt
- France
- Gabon
- Guinea
- Jordan
- Lebanon
- Madagascar
- Mali
- Mauritania
- Niger
- Peru
- Portugal
- Saudi Arabia
- Senegal
- Sudan
- Togo
- United Arab Emirates
- Yemen

The excipients used in Fluvermal are Talc (E553b), Saccharose, Amidon de pomme de terre, Amidon, Sodium laurylsulfate (E487), Magnésium stéarate (E572), Cellulose microcristalline (E460).

A 100mg dose of Fluvermal is most commonly proscribed for treating pinwoms (Enterobius vermiculus)). This is followed by a second dose of 100mg 15-21 days later to ensure reinfection is avoided, as flubendazole does not kill pinworm eggs. 100mg taken 3 times a day for 3 days is effective against larger nematodes, but only marginally effective against tapeworms. Fluvermal is available over the counter for human use in Europe under this brand name, and in 100mg tablets or as a 20mg/ml oral solution.

FLUVERMAL INSERT DATA

The form of flubendazole available for human use

Flubendazole

FLUVERMAL, tablets, 100 mg
FLUVERMAL, oral suspension, 20 mg/ml
FLUVERMAL, tablets + oral suspension, 100 mg + 20 mg/ml

Contraindications
Fluvermal is contraindicated in persons with a known hypersensitivity to the drug or its components.

Special warnings and special precautions for use
Use in infants < 1 year: as well-documented experience in children below 1 year of age is scarce, Fluvermal should only be given to very young children if their worm infection interferes significantly with their nutritional status and physical development.
The tablets contain lactose. Patients with rare hereditary diseases of galactose intolerance, Lapp's lactose deficiency or malabsorption of glucose-galactose should not use this medicinal product.
The oral suspension contains parabenes that can cause allergic reaction (possibly delayed).

Interaction with other medicaments and other forms of interaction
None known.

Pregnancy and lactation
Fluvermal has shown embryotoxic and teratogenic activity in one study in rats. No such findings have been reported in teratology studies in the rabbit, mice or other studies in rats.
Experience in humans has not shown any increase in the risk of malformations. Nonetheless, it is better to avoid using the product in pregnant women or in those liable to become pregnant.
It is not known whether flubendazole is excreted in human milk. Therefore caution should be exercised when Fluvermal is administered to nursing women.

Effects on ability to drive and use machines
Fluvermal does not affect the mental alertness or driving ability.

Undesirable effects

Transient abdominal pain and diarrhoea have only rarely been reported, in cases of massive infestation and expulsion of worms.

Hypersensitivity reactions such as exanthema, rash, urticaria and angioedema have rarely been observed.

Overdose
Symptoms
In the event of accidental overdosage, abdominal cramps, nausea, vomiting and diarrhea may occur.
Although the maximum recommended treatment duration of Fluvermal is limited to three days there have been rare reports of liver function disturbances, hepatitis and blood dyscrasias described in patients who were treated for hydatid disease with massive doses for prolonged periods of time.
Treatment
There is no specific antidote. Within the first hour after ingestion, gastric lavage may be performed. Activated charcoal may be given if considered appropriate.

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As described below flubendazole was tested along with other benzimidazoles in humans for its effect on *Onchocerca volvulus* but as the preparation induced SAE's at the injections site it was not pursued further at that time (1981) - although it appeared to be very effective against this filarial pathogen.

5. SAFETY ISSUES

There are known issues with all this group of anthelminthics in terms of safety. The basic reason appears to be related to the effect of these agents in disrupting the tubulin of host cells and consequently the functions related to these structures. There are considerable differences in effects between species which may relate primarily to the pharmacodynamics in these species. However, it has been suggested that the vehicles that the primary compound is delivered in may also be important.

The use of this property of binding tubulin in maintaining the health of the host (patient) is considered a potential advantage when used at higher levels. Combined with other cancer inhibiting drugs it is being proposed as as a treatment for certain types of neoplasia. In a study with leukemia and myeloma it was found that flubendazole induced cell death in leukemia and myeloma cell lines and primary patient samples at nano-molar concentrations. Moreover, it delayed tumor growth in leukemia and myeloma xenografts without evidence of toxicity. Mechanistically, flubendazole inhibited tubulin polymerization by binding tubulin at a site distinct from vinblastine. In addition, cells resistant to vinblastine because of overexpression of P-glycoprotein remained fully sensitive to flubendazole, indicating that flubendazole can overcome some forms of vinblastine resistance. Thus it was suggested by these authors that flubendazole is a novel microtubule inhibitor that displays pre-clinical activity in leukemia and myeloma.

An EMEA report (EMEA/CVMP/33128/2006-FINAL July 2006) states that flubendazole has a low acute oral and subcutaneous toxicity. The acute oral LD50 values were greater than 5000 mg/kg bw in mice, rats and guinea pigs. Acute subcutaneous LD50 values were greater than 5000 mg/kg bw in the rat and the mouse and 4679 and 4834 mg/kg bw in male and female guinea pigs, respectively. Any toxicity occurring appears to depend on route and on formulation.

FOOD RESIDUES

Flubendazole is one of the safest of drugs used in food animals in terms of the food residues. Residues of veterinary medicinal products, as defined by the European Union, are "pharmacologically active substances (whether active principles, excipients or degradation products) and their metabolites which remain in foodstuffs obtained from animals to which the veterinary medicinal product in question has been administered". The MRL is the maximum concentration of residue following administration of a veterinary medicine which is legally permitted or acceptable in food under the laws of the EU.

This is particularly important in the poultry industry where benzimidazoles are veterinary drugs widely used for prevention and treatment of parasitic infections. Metabolites of benzimidazoles have been reported in several matrices including eggs. However, to date flubendazole is the only anthelminthic that has an established MRL of 400 µg kg-1 in egg. A value of 50 µg kg-1 was established for all other anthelmintics. Thus flubendazole appears to be in terms of residues safer than most other anthelminthic agents.

6. POTENTIAL OF FLUBENDAZOLE AS A MACROFILARICIDE

A safe, field-usable chemotherapeutic agent that will rapidly kill adult filarial worms is urgently needed in tropical medicine. Ivermectin, distributed as Mectizan® by Merck & Co.Inc. has had an enormous impact on two major human filarial infections of developing countries, onchocerciasis and lymphatic filariasis. However, this agent works primary against the microfilarial stage and lacks the ability to rapidly kill the adult parasites. Since the adult worms can survive for many years producing offspring, it has been necessary for control programs to continue drug distribution for more than a decade, i.e., until the adult worms eventually die; a labor-intensive and expensive proposition. Other agents used in filarial control programs, such as diethylcarbamazine and albendazole, may be more effective macrofilaricides than ivermectin, but for various reasons are not suitable, or are unable, to fill the role of a being rapidly-acting macrofilariacide. Thus, a drug, administered once, or at least in multiple doses over a very short period, that safely kills adult filarial worms would be a major contributor to the current efforts to rid the world of filarial infections and the diseases they cause. A field useful agent has typically been required to be administered in an oral dosage form, but a truly safe agent administered by another route, including parenteral approaches, could be acceptable and may even be advantageous.

Given the challenges of discovery and development of agents for human use, a drug as described above is arguably most likely, at least at present, to come from the benzimidazole group of anthelmintics. Although several benzimidazoles are currently employed in human chemotherapy, there are other potential candidate macrofilaricides in other drug classes. However, time is of the essence in finding a new drug for use in ongoing filarial control programs, the first priority is to consider the benzimidazoles as the most likely source of a macrofilaricide. This group has provided many important effective agents for both veterinary and human medicine over the past 50 years, beginning with thiabendazole and now most prominently including albendazole and mebendazole for human parasites and a whole range of agents in veterinary medicine. Benzimidazoles work by interfering with the equilibrium among tubulin subunits, tubulin and microtubules. Not surprisingly, benzimidazoles can affect host tubulin as well as that of the parasites, are typically positive in mammalian cell cytotoxicity assays and cause chromosomal non-disjunction during mitosis. However, the benzimidazole anthelmintics show a differential preference for binding to nematode tubulin compared to mammalian tubulin, an important factor for development of a drug against nematodes in mammals. Benzimidazoles are also anti-fungal agents as well as anthelmintics, a fact that may be important in filarial conditions such as elephantiasis that involve secondary infections often involving fungi; albendazole is one of the two drugs used in the global lymphatic filariasis elimination program.

The most appealing benzimidazole with regard to filarial parasites is flubendazole as it is highly active against filariae in a number of hosts. It has the typical

benzimidazole structure with an added fluorine as the major structural difference from other benzimidazoles. It is a very efficacious macrofilaricide in a variety of experimental animals, with perhaps its most dramatic and relevant action being its ability to completely eliminate adult *Dirofilaria immitis* from dogs after a single injection. Flubendazole is was developed by Janssen in the mid 1970's and is currently licensed in Europe for the use as an anthelmintic in humans for intestinal nematodes (at 5 mg /kg for 3 days). Flubendazole is a potent and efficacious anthelmintic for gastrointestinal nematode infections in swine, poultry and companion animals, as well as against lungworms in swine. It is usually given over 3 days at ~5 mg/kg, but is probably also efficacious even as a single dose at this same rate. In a number of experimental filarial rodent models, flubendazole was found to have essentially 100% efficacy as a macrofilaricide at reasonable doses and schedules. A trial in human onchocerciasis was also carried in Mexico in the early 1980's with promising results. However, wider testing in humans was restricted at that time by problems associated with the route of administration and the relatively unsophisticated carrier agent used at that time, some 39 years ago. In addition, the introduction of ivermectin at about this time lessened the urgency to replace diethylcarbamazine for onchocerciasis control with a new macrofilaricide.

As noted, flubendazole is highly efficacious in various experimental filariasis models, including the feline *Brugia pahangi* model, a host in which it occurs naturally. Efficacy varies with parasite species, location in the host, and host species (Table 1). It should be noted that flubendazole is highly efficacious and potent as a macrofilaricide in these models only when given parenterally (in keeping with its very low oral bioavailability in standard formulations). Given parenterally, flubendazole is arguably the best macrofilaricide tested in animal models. Importantly, no adverse reactions were reported in any of these animal studies. An important observation, relevant to current

problems faced by the global control and elimination programs for human lymphatic filariasis and onchocerciasis, is that in cats and jirds infected with *Brugia spp.*, flubendazole is active against adult worms but poorly active against the microfilarial stage. The significance of this observation lies in the fact that a major problem for filarial control programmes using ivermectin is that individuals co-infected with high levels of circulating *Loa loa* microfilariae may suffer severe adverse events. Over 124 people have died in the past ten years, usually with signs and symptoms of central nervous system pathology related to microfilarial death. An agent that will kill adult filariae but not microfilariae may be a breakthrough for this important practical problem, which currently limits ivermectin distribution programs in many Africa countries.

Table 1. Summary of lowest effective dose of flubendazole in filarial animal models.

Parasite	$LED_{90} \times 5$ (mg/kg)	$LED_{90} \times 1$ (mg/kg)	Ref.
Jird			
Brugia pahangi†	1.5	25	[7]
B. pahangi‡	1.56	ND	[19]
B. pahangi†	2.5	ND	[20]
B. pahangi‡	12.5	ND	[20]
B. pahangi†	20¶	ND	[21]
B. pahangi§	10¶	ND	[22]
Dipetalonema viteae	100¶	ND	[23]
Acanthocheilonema viteae	1.56	ND	[19]
Rat			
Brugia pahangi#	25	ND	[24]
B. malayi	12.5	50	[24]
A. viteae	3.1	1.6	[24]
Litomosoides carinii#	12.5	12.5	[24]
Mouse			
Onchocerca lienalis††	100	ND	[25]
Cat			
B. pahangi‡	ND	100	[7]

†Adult parasites in the peritoneal cavity.
‡Adult parasites in the lymphatics.
§L3 larvae.
¶Not titrated, only dose reported.
#Multimammate rat.
††Microfilariae transplanted into the skin.
Most of the efficacies reported at these doses in these studies were 100%. Efficacy determinations are dependent on the time of necropsy; efficacy is higher (i.e., number of worms observed) in jirds necropsied 8 weeks post-treatment compared with 6 weeks post-treatment. [McCall Pers. Comm.]
LED_{50}: Lowest dose that was at least 90% effective.

Following the encouraging findings in rodent models, a study was carried out in Mexico in the early 1980's in which several potential macrofilaricides, including flubendazole, were tested in humans infected with *Onchocerca volvulus*. This study was terminated early due to problems associated with reactions at the intra-muscular injection site where the flubendazole in its oil-based carrier was administered. Nevertheless, efficacy data on adult *O. volvulus* worms in surgically removed nodules from these patients suggested that flubendazole is a potent macrofilaricide. At 3 weeks after initiation of treatment (750 mg once per week for 5 weeks), significant degeneration of the adult worms was detected; at 5 weeks (Table 2), there was very effective destruction of the adult worms compared with the other anti-filarial agents.

Table 2. Effect of flubendazole and diethylcarbamazine on adult *Onchocerca volulus* isolated from human nodules.

Status of parasites	2 months post Rx		3 months post Rx	
	DEC†	FLUB†	DEC	FLUB
Degenerated adults	12	10	12	27
Intact adult worm	44	11	16	0
Females with empty uteri	6	1	5	0
Females with only oocytes	8	6	14	0
Reduction in dermal microfilariae‡	Yes	No	Yes	No

†DEC (100 mg) was administered twice daily for 14 days and 750 mg FLUB was injected intramuscularly once a week for five doses.
‡There was no significant ocular or skin pathology related to microfilarial death in those receiving FLUB. The only significant post-FLUB treatment reactions were associated with inflammation at the injection site. Dermal microfilarial loads stayed at pretreatment levels in the FLUB-treated individuals for approximately 6 months.
DEC: Diethylcarbamazine; FLUB: Flubendazole; post RX: After last treatment with flubendazole.
†Data taken from [6,10].

As mentioned above, flubendazole is currently registered for human use in Europe for treatment of gut-residing nematodes, an action that does not require efficient uptake into the host's circulation. A challenge for ensuring its suitability for filariasis will be to develop a new formulation that will produce blood and tissue levels sufficient to destroy tissue-resident parasites, such as the filariae. Efficacy against filariae was not observed following oral dosing of flubendazole in any the early animal studies, but it should be noted that none of these studies used any of the new formulation methods now common in the pharmaceutical industry. Encouraging results come from Lanusse's group, which showed that the tissue-residing stage of the cestode, *Ecchinococcus granulosis*, can be killed by an orally administered flubendazole formulated with the now commonly-used excipient hydroxypropyl-β-cyclodextrin. Newer formulations such as this could greatly enhance the likelihood of developing flubendazole as a suitable macrofilariacide for human filariasis for oral dosing. A hydroxypropyl-β-cyclodextrin formulation might indeed be suitable given the increased degree of bioavailability it provides; for example, it markedly enhances the bioavailability of albendazole, mebendazole and flubendazole. This material is approvable and is a gold-standard reagent for enhancing bioavailability of lipophilic drugs, and can be used in both liquid and solid dosage forms.

As the target infective adult filariae are complex and biochemically resourceful (many nematodes have the ability to switch biochemical pathways when stressed), it is likely that a relatively long duration of exposure to the drug will be needed. This may involve the need for dosing on multiple (e.g., 3-5) days to maintain lethal levels of the

agent for the needed period of time. For many nematodes, acute exposure to benzimidazoles has few noticeable effects, even at very high concentrations; this is true for flubendazole in various adult filariids. As the drug acts by disrupting the tubulin-microtubule equilibrium in cells, leading to cessation of nutrient transport and eventual cell death, these effects take time to become evident. *In vitro* experiments have shown that flubendazole concentrations as low as 100 ng/ml (incubated for 32 hours) disrupt tissue structure in parasitic nematodes in the same clade as filariae.

In addition to pharmacodynamic challenges, there are other hurdles to developing a safe and effective formulation of a drug for the treatment of complicated infections such as lymphatic filariasis and onchocerciasis. A primary concern with the benzimidazoles is safety. As these drugs interfere with microtubules, they have the potential of interfering with host cells, especially during cell division. Thus, the use of drugs such as albendazole is generally contra-indicated for pregnant women; this is likely to apply with a new flubendazole formulation that provides for systemic exposure. However, it should be noted that albendazole has been used very successfully in mass drug programs across the world since 1999, and that inadvertent treatment studies in pregnant women have not detected adverse effects on the unborn. Nevertheless, a major hurdle for a formulation that produces enhanced bioavailable flubendazole will need to be carefully evaluated for embryotoxicity. It may turn out that flubendazole is only useful for filarial infections in males and females outside childbearing ages. However, such a product still would be a most useful advance for control programs.

What will it take to determine if flubendazole is an important answer to the needs of filarial control and elimination programs? Scientifically, it will initially require the determination of the blood and tissue levels needed for macrofilaricidal efficacy; closely related is the need to determine the levels that induce toxicity. Both issues are central to moving forward with development of flubendazole. Based on recent experimental data from animal models, it is highly likely that current modern formulation techniques, including micronization, hydroxypropyl-β-cyclodextrin complexing or another new approach, will be able to provide the blood levels needed to kill adult worms. The testing of newly developed formulations for efficacy against filariae itself poses some challenge. Filarial infections are generally host specific and thus each filariae-host model is to some degree unique in form and properties. Flubendazole in a new formulation should be evaluated in a range of filarial models to encompass all the variations and characteristics of these infections, and to make predictions about the pharmacokinetic parameters likely to be required for efficacy in human infections; this would allow formulations to be evaluated on the basis of pharmacokinetic data rather than efficacy per se, which requires extended periods of time post-treatment. A combination of many disciplines and institutions will be needed, including, as with the pioneering onchocerciasis-ivermectin control program, “public-private partnerships” between the pharmaceutical industry, non-governmental organizations and academic scientists. Drug companies have the expertise needed to develop new formulations and are central to the final production phase needed; field-based expertise (Ministries of Health, NGDO’s, academics) are essential for developing a practical field-based mass drug administration intervention and will be important partners in any successful effort.

The benefit of developing a safe and practical agent that needs distribution only once, or perhaps twice, is substantial when compared to what is currently in place, i.e., annual distribution for 8-12 years in filarial control and elimination programs; a highly

effective macrofilaricide would still be important even if a 3-5 daily course of treatment is needed. Financial savings as well as significant savings in terms of health personnel time commitment would be realized.

Flubendazole has great potential as a macrofilaricide. Its reformulation using modern pharmaceutical platforms should be expedited to enable efficacy testing as soon as possible. Although flubendazole faces, as does any new anthelmintic, important challenges with regard to safety and formulation, the potential benefits that could result relatively quickly from a safe, usable formulation of flubendazole make this a top priority for the filarial world today.

7.

FLUBENDAZOLE REFERENCE LIST

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8. APPENDICES

8.1

FLUVERMAL INSERT

Flubendazole

FLUVERMAL, tablets, 100 mg
FLUVERMAL, oral suspension, 20 mg/ml
FLUVERMAL, tablets + oral suspension, 100 mg + 20 mg/ml

Contraindications
Fluvermal is contraindicated in persons with a known hypersensitivity to the drug or its components.

Special warnings and special precautions for use
Use in infants < 1 year: as well-documented experience in children below 1 year of age is scarce, Fluvermal should only be given to very young children if their worm infection interferes significantly with their nutritional status and physical development.
The tablets contain lactose. Patients with rare hereditary diseases of galactose intolerance, Lapp's lactose deficiency or malabsorption of glucose-galactose should not use this medicinal product.
The oral suspension contains parabenes that can cause allergic reaction (possibly delayed).

Interaction with other medicaments and other forms of interaction
None known.

Pregnancy and lactation
Fluvermal has shown embryotoxic and teratogenic activity in one study in rats. No such findings have been reported in teratology studies in the rabbit, mice or other studies in rats.
Experience in humans has not shown any increase in the risk of malformations. Nonetheless, it is better to avoid using the product in pregnant women or in those liable to become pregnant.
It is not known whether flubendazole is excreted in human milk. Therefore caution should be exercised when Fluvermal is administered to nursing women.

Effects on ability to drive and use machines
Fluvermal does not affect the mental alertness or driving ability.

Undesirable effects
Transient abdominal pain and diarrhoea have only rarely been reported, in cases of massive infestation and expulsion of worms.

update_21092009

Hypersensitivity reactions such as exanthema, rash, urticaria and angioedema have rarely been observed.

Overdose
Symptoms
In the event of accidental overdosage, abdominal cramps, nausea, vomiting and diarrhea may occur.
Although the maximum recommended treatment duration of Fluvermal is limited to three days there have been rare reports of liver function disturbances, hepatitis and blood dyscrasias described in patients who were treated for hydatid disease with massive doses for prolonged periods of time.
Treatment
There is no specific antidote. Within the first hour after ingestion, gastric lavage may be performed. Activated charcoal may be given if considered appropriate.

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8.2

The European Agency for the Evaluation of Medicinal Products
Veterinary Medicines Evaluation Unit

COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

FLUBENDAZOLE

SUMMARY REPORT (1)

1. Flubendazole is a benzimidazole anthelmintic which is administered for therapeutic applications in pigs, chickens, turkeys and game birds. The preparations available include tablets, pastes, pellets and premixes. In some countries it is also available as an antheimintic for human use.

2. Flubendazole was shown to be poorly absorbed from the gastro-intestinal tract with most of the administered drug excreted unchanged in the faeces. It was of low acute toxicity.

   Daily oral doses of up to 40 mg/kg bw per day of flubendazole were given to dogs for 3 months. Some slight histological changes, which were difficult to interpret, were seen in both the male and female genital tracts. The changes in females were considered to be within age-range normal limits and not related to treatment. It was also considered that the changes in males (prostatic fibrosis) were probably not treatment-related. However, as a precautionary measure, and due to the absence of conclusive evidence regarding the aetiology of the findings, it was agreed that the dose level of 2.5 mg/kg bw per day should be regarded as a NOEL for the study. No adverse effects were observed in a 3-month feeding study in which rats were given up to 1600 mg/kg flubendazole in the diet, equivalent to 117-147 mg/kg bw per day.

   Flubendazole was tested for mutagenicity in a wide range of *in vitro* and *in vivo* assays, all of which gave negative results. In carcinogenicity studies, rats and mice were fed dietary concentrations of flubendazole intended to provide up to 40 mg/kg bw flubendazole per day; no increase in tumour incidence was observed and there were no other treatment-related effects.

   The reproductive toxicity of flubendazole was investigated in a range of species. No effects on fertility were observed in rats or dogs. In some studies in rats and rabbits, evidence of foetotoxicity (increased incidences of abortions and resorptions and reduced foetal weights) was observed at very high dose levels. There was also evidence of teratogenicity in the rat. The results of a published study, in rats, in which the apparent NOEL for teratogenicity, was 10 mg/kg bw per day were discounted because the flubendazole used had been extracted from a commercial formulation and was of doubtful purity. Instead, it was concluded that a more reliable NOEL for teratogenicity of 40 mg/kg bw per day had been established in a better-documented unpublished study, in rats.

3. Flubendazole had no significant antimicrobial activity.

4. It was noted that the JECFA had estimated an ADI of 0-12 µg/kg bw per day by applying a safety factor of 200 to the NOEL of 2.5 mg/kg bw per day in the 3-month dog study.

   The safety factor of 200 was used to take into account the fact that the doses were administered 6 days per week only.

   It was agreed that the JECFA evaluation was not significantly different from the CVMP Working Group on Safety of Residues interpretation of the data and it was therefore agreed that the JECFA ADI should be adopted.

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5. Carbamate hydrolysis and ketone reduction were the main biotransformation pathways in pigs and the (2-amino-1H-benzimidazol-5-yl)-4-fluorophenyl-methanone metabolite was the major drug-related component in pig kidney. However, there was no validated analytical method for the routine determination of this metabolite in tissues and it was therefore agreed that the flubendazole parent compound should be considered the marker residue.

   The following provisional MLRs were elaborated :

   Chicken: liver 0.5 mg/kg; muscle 0.2 mg/kg; eggs 0.4 mg/kg;

   Porcine: edible tissues (muscle, liver, kidney, fat) 0.01 mg/kg.

   It was calculated that the intake of total extractable flubendazole-derived residues, arising from consumption of animal products containing residues which did not exceed these MRLs, would not exceed the ADI proposed above.

6. An analytical method was available for the determination of the parent flubendazole using HPLC with UV detection at 312 nm. The limit of detection of the method was 0.01 mg/kg for all tissues. Validation data for this analytical method was provided only for pheasant tissues.

7. The following data are required before 31 December 1994:

   7.1 Further information on the relationship between extractable flubendazole-related residues and total (extractable & bound) residues in swine tissues;

   7.2 Information on whether M7 is the appropriate marker residue in pigs and other species; if it is, a satisfactory analytical method for determination of this metabolite should be developed and fully validated;

   7.3 Further information on the relative distributions of parent flubendazole and its metabolites in edible tissues in the chicken after treatment with 60 ppm flubendazole in the feed (the higher recommended dose);

   7.4 Data for residues in individual animals and for analytical method validation for all pharmacokinetic, metabolism, depletion and distribution studies presented for swine and poultry;

   7.5 Data on quantitative similarities between pharmacokinetic, metabolism, depletion and distribution of flubendazole in chicken and turkey (to allow MRLs to be set for turkey);

   7.6 The sensitivity of the analytical methods for the determination of residues should be improved and the methods should be validated for food-producing species (other than pheasants).

8.3

flubendazole

> Indications
> Dosage
> Contraindications
> Special Precautions
> Adverse Drug Reactions
> Drug Interactions
> Mechanism of Action
> MIMS Class
> ATC Classification

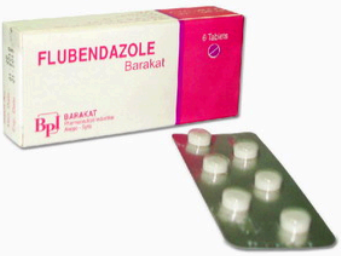
Related Information flubendazole Concise Info

See related flubendazole information

Abbreviation Index

Indications	Listed in Dosage.
Dosage	*PO* **Enterobiasis** 100 mg as a single dose. Repeat 2-3 wk later if needed. **Ascariasis; Hookworm infections; Trichuriasis** 100 mg twice daily for 3 days. Click to view flubendazole Dosage by Indications
Contraindications	Pregnancy.
Special Precautions	Lactation. Monitor blood counts and liver function tests regularly during treatment.
Adverse Drug Reactions	GI disturbances; headache, dizziness; allergic reactions; raised liver enzyme values; alopoecia; bone marrow suppression.
Drug Interactions	Enzyme inducers eg phenytoin or carbamazepine; and inhibitors eg cimetidine.
Mechanism of Action	For details of the mechanism of action, pharmacology and pharmacokinetics and toxicology ... click to view flubendazole
MIMS Class	Anthelmintics
ATC Classification	P02CA05 - Flubendazole ; Belongs to the class of benzimidazole derivative agents. Used as antinematodal.

8.4



Brand name:	FLUBENDAZOLE Barakat
Formula:	Tablets
Categories:	Gastrointestinal System Drugs
Code:	7-20
Composition:	Flubendazole 100mg

Detailed Information:

Composition:
Each tablet contains: flubendazole lOOmg

Properties:
Flubendazol, a benzimidazole carbamate anthelmintic, is an analogue of mebendazole it is active against most nematodes and other worms, Flubendazol acts by inhibition or destruction of cytoplasmic microtubules in the worm' s intestinal or absorptive cells leading to death of the worm within several days.

Indication:
Flubendazol is used in the treatment of single or mixed infections caused by: Enterobiasis, ascariasis, hookworm, and trichuriasis

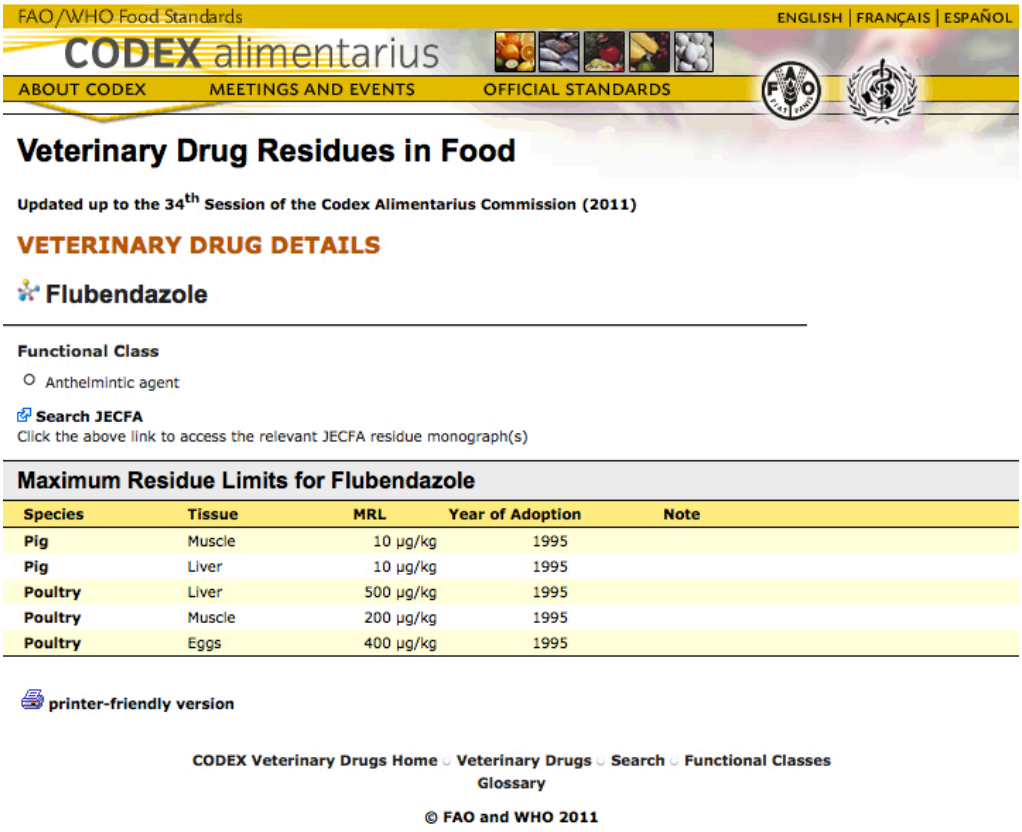
Contraindications:
Hypersensitivity to the drug Pregnancy and Lactation

Side effects:
Flubendazol is well tolerated but may cause: transient abdominal pain, diarrhea, headache, allergic reactions and raised liver enzyme values with the high doses.

Precautions:
Patients receiving high doses, should be supervised closely with blood counts and liver function being monitored. No special diet or laxatives

Dosage and administration:
For the treatment of enterobiasis:
Adults and children: l00mgas a single dose repeated if necessary after 2-3 weeks.
For ascariasis, hook worm, and Trichuriasis: l00mg twice daily for 3 days

8.5



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CODEX alimentarius

ABOUT CODEX MEETINGS AND EVENTS OFFICIAL STANDARDS

Veterinary Drug Residues in Food

Updated up to the 34th Session of the Codex Alimentarius Commission (2011)

VETERINARY DRUG DETAILS

Flubendazole

Functional Class

○ Anthelmintic agent

Search JECFA
Click the above link to access the relevant JECFA residue monograph(s)

Maximum Residue Limits for Flubendazole

Species	Tissue	MRL	Year of Adoption	Note
Pig	Muscle	10 µg/kg	1995	
Pig	Liver	10 µg/kg	1995	
Poultry	Liver	500 µg/kg	1995	
Poultry	Muscle	200 µg/kg	1995	
Poultry	Eggs	400 µg/kg	1995	

printer-friendly version

CODEX Veterinary Drugs Home ○ Veterinary Drugs ○ Search ○ Functional Classes
Glossary

8.6

European Medicines Agency
Veterinary Medicines and Inspections

EMEA/CVMP/33128/2006-FINAL
July 2006

COMMITTEE FOR MEDICINAL PRODUCTS FOR VETERINARY USE

FLUBENDAZOLE (extrapolation to poultry)

SUMMARY REPORT (4)

1. Flubendazole is a benzimidazole anthelmintic. It is the fluoro- analogue of mebendazole and has many similar properties. Is administered orally to pigs, chickens and game birds.

   Flubendazole is currently entered into Annex I of Council Regulation (EEC) No. 2377/90 for turkey, chicken, game birds and porcine species as follows:

Pharmacologically active substance(s)	Marker residue	Animal species	MRLs	Target tissues	Other provisions
Flubendazole	Sum of flubendazole and (2-amino-1*H*-benzimidazole-5-yl) (4-fluorophenyl)-methanone	Chicken, turkey, game birds and porcine	50 µg/kg 50 µg/kg 400 µg/kg 300 µg/kg	Muscle Skin + fat Liver Kidney	
	Flubendazole	Chicken	400 µg/kg	Eggs	

2. A request was submitted to the EMEA for the extrapolation of the existing entry in Annex I of Council Regulation (EEC) No. 2377/90 for turkey, chicken and game birds. The scientific justification for this extension was assessed taking into account the Note for Guidance on Risk Analysis Approach for Residues of Veterinary Medicinal Products in Food of Animal Origin (EMEA/CVMP/187/00-FINAL). Based on the approach explained in this guideline the CVMP considered whether the extrapolation to poultry would be possible.

3. In setting the ADI in the original assessment of flubendazole, the data summarised in the paragraphs below were considered:

4. Flubendazole had low oral bioavailability in the rat, dog and the target species. In rats, the half-life for plasma elimination was around 6 hours. In all species, more than 50% of the administered dose was excreted in the faeces as unchanged flubendazole. The absorbed portion of the drug was rapidly metabolised so that concentrations of the parent drug in the blood and urine were very low. The urine contained a mixture of metabolites. The main metabolic pathways were the same in all the species studied and involved reduction of the ketone functional group and hydrolysis of the carbamate moiety.

5. Flubendazole was of low acute oral and subcutaneous toxicity. The acute oral LD50 values were greater than 5000 mg/kg bw in mice, rats and guinea pigs. Acute subcutaneous LD50 values were greater than 5000 mg/kg bw in the rat and the mouse and 4679 and 4834 mg/kg bw in male and female guinea pigs, respectively. The substance was more toxic when administered intraperitoneally with an acute intraperitoneal LD50 of 528 and 434 mg/kg bw in male and female rats, respectively.

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8.7

8.8 WHO REPORT 832 VETERINARY DRUG RESIDUES

WHO Technical Report Series

832

EVALUATION OF CERTAIN VETERINARY DRUG RESIDUES IN FOOD

Fortieth report of the
Joint FAO/WHO Expert Committee on
Food Additives

World Health Organization

Geneva 1993

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Contents

1. Introduction 1

2. General considerations 2
2.1 Principles governing the safety evaluation of residues of veterinary drugs in food 2
2.2 Modification of the agenda 2
2.3 Evaluation of veterinary drugs with a long history of use 2
2.3.1 General principles 3
2.3.2 Toxicological data 3
2.3.3 Residue data 4
2.4 General safety concerns and pharmacological effects 4
2.5 ADI and MRL "not specified" 5
2.6 Food consumption surveys 6
2.7 Target tissues and marker residues 6
2.8 Identity and quality of veterinary products 7

3. Comments on residues of specific veterinary drugs 7
3.1 Anthelminthic agents 7
3.1.1 Closantel 7
3.1.2 Flubendazole 10
3.1.3 Ivermectin 17
3.1.4 Tiabendazole (thiabendazole) 21
3.1.5 Triclabendazole 25
3.2 Antimicrobial agents 32
3.2.1 Furazolidone 32
3.2.2 Nitrofural (nitrofurazone) 37
3.3 Production aids 40
3.3.1 Bovine somatotropins 40
3.3.2 Ractopamine 42
3.4 Trypanocide 49
3.4.1 Isometamidium 49

4. Recommendations 54

Acknowledgements 54

References 54

Annex 1
Reports and other documents resulting from previous meetings of the Joint FAO/WHO Expert Committee on Food Additives 55

Annex 2
Recommendations on compounds on the agenda 61

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closantel, with the remaining residue consisting of 3- and 5-monoiodoclosantel. No evidence for the existence of other metabolic pathways was reported. In cattle liver, approximately 10% of the radioactivity was unchanged closantel, and 40–77% was accounted for by 3-monoiodoclosantel. In faeces, 6% of the radioactivity was identified as a sulfate conjugate of a closantel derivative.

Residue depletion of closantel from plasma parallels that from the edible tissues. Within a given species, there is a reasonably constant tissue : plasma ratio which is independent of time. The tissue : plasma ratios in liver and in fat are, respectively, approximately four times and 12 times as large in cattle as in sheep. The tissue : plasma ratios for muscle and kidney in sheep and cattle are comparable.

Maximum Residue Limits

Taking into account this information and the specific residue data discussed on pages 8–10, the Committee recommended amended MRLs for closantel in sheep (Table 2) and new MRLs for cattle (Table 3). The recommendations for cattle are based on the studies in which an oral dose of closantel of 10 mg per kg of body weight and an intramuscular dose of 2.5 mg per kg of body weight were given; from these the Committee calculated that the theoretical maximum daily intake of closantel residues at 42 days withdrawal time would be below the ADI of 1.8 mg for a 60-kg person. It should be noted that the manufacturer recommends an oral dose of 5 mg per kg of body weight for cattle. Residues from such an oral dose will be lower than those given in Table 3.

3.1.2 *Flubendazole*

Flubendazole had not been previously reviewed by the Committee. The compound is used as an anthelminthic in pigs and poultry. It belongs to the group of benzimidazole carbamates.

Toxicological data

A substantial database was available for assessment, including data on kinetics and metabolism, acute toxicity, short-term and long-term toxicity, reproductive and developmental toxicity, and genotoxicity.

The absorption, metabolism, and excretion of flubendazole have been studied using radiolabelled drug. Flubendazole is poorly absorbed and is metabolized in a qualitatively similar way in all species studied. More than 50% of the ingested drug is eliminated unchanged in the faeces. The absorbed drug is rapidly metabolized, so that levels of parent drug in the blood and urine are extremely low. The main site of metabolism is the liver, and major metabolic pathways are carbamate hydrolysis and ketone reduction. It seems probable that flubendazole undergoes enterohepatic circulation.

Single oral doses of flubendazole were slightly toxic to experimental animals, the median lethal dose (LD_{50}) being greater than 5000 mg per kg of body weight in mice, rats, and guinea-pigs.

Table 2
Recommended MRLs for closantel in sheep[a]

Tissue	Observed residue (mg/kg parent drug)		Estimated daily intake[b, c] (mg closantel equivalents)		Recommended MRL (µg/kg parent drug)	Theoretical maximum daily intake[c] (mg closantel equivalents)
	Oral dose[d]	Intramuscular dose[e]	Oral dose[d]	Intramuscular dose[e]		
Muscle	< 0.4	1.1	0.12	0.33	1500	0.45
Liver	0.8 (1.14)[f]	0.7 (1.17)[g]	0.11	0.12	1500 (2500)[g]	0.25
Kidney	0.7	1.2	0.04	0.06	5000	0.25
Fat	0.7	0.4	0.04	0.02	2000	0.10
Total			0.31	0.53		1.05

[a] Based on concentrations at 28 days withdrawal time. For the original discussion of residue data for sheep, see Annex 1, reference *91*.
[b] Calculated from the observed residue levels.
[c] Based on a daily intake of 0.5 kg of meat made up of 0.3 kg of muscle, 0.1 kg of liver, 0.05 kg of kidney, and 0.05 kg of fat.
[d] 10 mg/kg of body weight.
[e] 5 mg/kg of body weight.
[f] Estimate of total residues; after oral administration, closantel accounted for 70% of the total residues in liver.
[g] Estimate of total residues; after intramuscular administration, closantel accounted for 60% of the total residues in liver.

Table 3
Recommended MRLs for closantel in cattle

Tissue	Observed residue (mg/kg parent drug)		Estimated daily intake[a, b] (mg closantel equivalents)		Recommended MRL (µg/kg parent drug)	Theoretical maximum daily intake[b] (mg closantel equivalents)
	Oral dose[c]	Intramuscular dose[d]	Oral dose[c]	Intramuscular dose[d]		
Muscle	0.19	0.29	0.06	0.09	1 000	0.30
Liver	0.16 (1.6)[e]	0.56 (5.6)[e]	0.16	0.56	1 000 (10 000)[e]	1.00
Kidney	0.83 (1.0)[f]	1.39 (1.7)[f]	0.05	0.09	3 000 (3 750)[f]	0.19
Fat	0.7 (1.0)[g]	2.36 (3.4)[g]	0.05	0.17	3 000 (4 290)[g]	0.21
Total			0.32	0.91		1.70

[a] Calculated from the observed residue levels.
[b] Based on a daily intake of 0.5 kg of meat made up of 0.3 kg of muscle, 0.1 kg of liver, 0.05 kg of kidney, and 0.05 kg of fat.
[c] 10 mg/kg of body weight, 28 days withdrawal time.
[d] 2.5 mg/kg of body weight, 42 days withdrawal time.
[e] Estimate of total residues; closantel accounted for 10% of the total residues in liver.
[f] Estimate of total residues; closantel accounted for 80% of the total residues in kidney.
[g] Estimate of total residues; closantel accounted for 70% of the total residues in fat.

Flubendazole was given orally in gelatin capsules to dogs at doses of 2.5, 10, or 40 mg per kg of body weight per day, 6 days a week for 3 months. Some atrophic changes and congestion of the epididymis were observed in the male genital tract at doses of 10 and 40 mg per kg of body weight per day, and atrophic changes occurred in the female genital tract at all doses. The changes in the female genital tract were considered to be within normal limits for dogs of the age of those used in the study. On histological examination of male sex organs, changes in the testes could not be clearly associated with flubendazole treatment. The findings in male dogs may not be compound-related, but because of the lack of conclusive evidence as to the cause of these changes, the Committee concluded that the no-observed-effect level (NOEL) was 2.5 mg per kg of body weight per day.

Carcinogenicity studies were performed in mice and rats at doses up to 30 and 20 mg per kg of body weight per day, respectively; no treatment-related effects were observed. There was no treatment-related increase in any type of neoplasm. The Committee was of the opinion that flubendazole had no carcinogenic potential at the highest doses administered in these studies.

The results from a range of *in vitro* and *in vivo* genotoxicity tests were all negative.

The Committee considered data from reproduction, embryotoxicity, and teratogenicity studies. Studies in mice, rabbits, and pigs were negative. Flubendazole was extensively studied in segmented reproduction studies in rats performed as required for human drug regulation purposes and accepted by the Committee in lieu of a multigeneration reproduction study. In several rat developmental studies, doses of up to 40 and 160 mg per kg of body weight per day, given on gestation days 6-15, did not produce any embryotoxic or teratogenic effects. In a rat teratogenicity study published in 1987, using material extracted from a commercial preparation, gross skeletal and internal fetal malformations were recorded at doses of 40 and 160 mg per kg of body weight per day. The NOEL in this study was 10 mg per kg of body weight per day.

An ADI of 0-12 µg per kg of body weight was established for flubendazole, based on the NOEL of 2.5 mg per kg of body weight per day in the 3-month study in dogs and a safety factor of 200. This safety factor was used by the Committee to take account of the fact that the doses were administered only 6 days per week in this study, the precise consequences of which could not be assessed.

The Committee noted that the ADI also provided a safety margin corresponding to a factor of about 1000 with respect to the NOEL of 10 mg per kg of body weight per day derived from the rat teratogenicity study. Furthermore, the Committee considered that further carcinogenicity studies would not be required, since the highest dose used in the negative studies that it had evaluated exceeded the ADI by a factor of approximately 2000.

Residue data

The Committee considered data on the metabolism of flubendazole and the depletion of flubendazole residues from the edible tissues of pigs, and on the depletion of flubendazole residues from the edible tissues and eggs of laying hens.

When pigs or poultry are treated with flubendazole, the tissue with the highest residue concentration and slowest depletion rate is the liver. The major metabolite in pig liver is (2-amino-1*H*-benzimidazol-5-yl)-4-fluorophenylmethanone, which is found at a much higher concentration than parent flubendazole. Residue concentrations are higher and more persistent in egg yolk than in egg white.

Pigs. A residue-depletion study was conducted using 18 feeder pigs given a dose of 1.5 mg per kg of body weight of [^{14}C]flubendazole daily for 5 days (Table 4). Total residue concentrations were highest in liver throughout the 30-day withdrawal period.

Three male pigs received flubendazole at 30 mg per kg of body weight in the feed for 5 consecutive days. Flubendazole levels measured by high-performance liquid chromatography (HPLC) were less than 0.01mg/kg (the sensitivity limit of the method) in plasma, liver, kidney, muscle, and fat at withdrawal times of 16, 30, and 54 hours.

A similar residue study was conducted using single oral doses of 5 mg per kg of body weight in three groups of five male pigs. Tissues and plasma were analysed using a radioimmunoassay with quantification limits of 1 µg/kg in plasma and 5 µg/kg in tissues. Animals were slaughtered in groups of five at 24, 72, and 168 hours after dosing. At 24 hours withdrawal time, the tissues contained 7–12 µg/kg of parent flubendazole. All residues were below the detection limit at 72 hours.

In another study, seven sows were treated with 30 mg per kg of body weight flubendazole in the diet for 10 consecutive days. The sows were

Table 4
Total residues (µg of flubendazole equivalents per kg) in tissues of pigs given [^{14}C]flubendazole in the diet at 1.5 mg per kg of body weight for 5 days[a]

Withdrawal time	Muscle	Liver	Kidney	Fat
6 hours	262	3865	2678	212
5 days	35.5	1863	435	50.1
10 days	10.5	529	78.2	16.3
16 days	8.66	433	76.6	15.6
23 days	8.67	194	49.9	13.5
30 days	2.51	106	22.5	3.38

[a] For each withdrawal time, values are means for three pigs.

Table 5
Total residues (flubendazole equivalents) in tissues and plasma of laying hens given [^{14}C]flubendazole in the diet at 30 mg per kg of body weight for 6 days[a]

Withdrawal time (days)	Plasma (mg/l)	Muscle (mg/kg)	Liver (mg/kg)	Kidney (mg/kg)	Fat (mg/kg)
1	0.007	≤ 0.01	0.210	0.080	≤ 0.01
2	0.005	≤ 0.01	0.146	0.054	≤ 0.01
4	0.002	≤ 0.01	0.069	0.010	≤ 0.01
7	0.001	≤ 0.01	0.073	≤ 0.01	≤ 0.01
11	≤ 0.001	≤ 0.01	0.030	≤ 0.01	≤ 0.01
14	≤ 0.001	≤ 0.01	0.016	≤ 0.01	≤ 0.01

[a] For liver and kidney at 1 day withdrawal time, values are means for three animals; all other values are means for four animals.

slaughtered 7 days after the last treatment with flubendazole. Mean levels of flubendazole measured by HPLC were 59, 67, 13, and 33 µg/kg for liver, kidney, muscle, and fat, respectively.

Poultry. A total of 28 laying hens received [^{14}C]flubendazole at a dose equivalent to 30 mg per kg of body weight in food for 6 consecutive days. At all withdrawal times tested from 1 to 14 days after treatment, the concentration of radioactive equivalents of flubendazole in blood and plasma was less than 0.01 µg/ml, which suggests that absorption was poor. After total radioactivity levels reached a steady state in 5–6 days, eggs contained an average of 0.12 mg of flubendazole equivalents per kg. Radioactivity in the yolks (0.34 mg/kg) was much higher than in the egg white (0.02 mg/kg). The highest observed levels of radioactivity in individual tissues, calculated in terms of flubendazole equivalents, were 0.21 mg/kg in liver and 0.08 mg/kg in kidney 24 hours after the last dose. Table 5 shows residues in plasma and tissue for various withdrawal times.

When chickens were treated with flubendazole at 60 mg per kg of body weight for 7 days, residues were detectable in egg yolk for 11 days after treatment ended. Residue levels were higher in yolk than in white. Eggs and tissues were analysed by an HPLC method sensitive to 0.01 mg/kg. Of the tissues, liver had the greatest amount of residue at zero withdrawal time, although flubendazole could not be detected in any tissue by 6 and 7 days withdrawal time. The residue data are summarized in Table 6.

Methods of analysis for residues in tissues

For the studies described on pages 14–15, plasma and tissue levels of flubendazole in pigs were measured by radioimmunoassay or by an HPLC method with ultraviolet detection at 313 or 254 nm, which is sensitive to 0.01 or 0.02 mg/kg, respectively. Another HPLC method has been developed for flubendazole, with ultraviolet detection at 254 nm, that gives excellent separation between flubendazole and the major metabolite

Table 6
Unchanged flubendazole (mg/kg) in eggs and tissues of chickens given flubendazole in the diet at 60 mg per kg of body weight for 7 days

Withdrawal time (days)	Egg yolk	Egg white	Muscle	Kidney	Liver
0	0.592	0.036	0.079	0.173	0.198
4	NM	NM	0.071	0.236	0.200
6	NM	NM	≤ 0.01	≤ 0.01	≤ 0.01
7	0.318	≤ 0.01	≤ 0.01	≤ 0.01	≤ 0.01
11	0.019	≤ 0.01	NM	NM	NM
28	NM	NM	≤ 0.01	≤ 0.01	≤ 0.01

NM: not measured.

resulting from carbamate hydrolysis. However, the method described applies to the analysis of pure substances and does not include extraction procedures for tissues.

An HPLC method that has detection limits of 20–50 µg/kg has been developed for simultaneously determining eight benzimidazoles in tissue. This method might be suitable for measuring flubendazole and the major metabolite found in pig tissue, (2-amino-1*H*-benzimidazol-5-yl)-4-fluorophenylmethanone. Typical recoveries from spiked samples (0.1 mg/kg) were above 70% for flubendazole in liver, kidney, and muscle.

Maximum Residue Limits

In reaching its decision on MRLs, the Committee took into account the following points:

- An ADI of 0–12 µg per kg of body weight was established. This would result in a maximum ADI of 720 µg for a 60-kg person.
- The marker residue is the parent drug for all tissues and for eggs.
- The total daily intake of flubendazole-related residues in food would be about 620 µg (see Table 7), if assumed to be accounted for by pig tissue and eggs at zero withdrawal time, and calculated on the basis of the data presented in Table 4 and the study in chickens treated with a dose of 30 mg per kg of body weight.

Eggs. The daily intake of flubendazole-related residues will probably remain below the ADI even when flubendazole is given at 60 mg per kg of body weight, although this dose produces a much higher concentration of residues in eggs. The argument that increased doses of flubendazole will not increase residue levels because of the drug's low systemic availability appears not to be valid for eggs: the levels of parent flubendazole in egg yolk found in the study with 60 mg per kg of body weight are double the residue levels of all flubendazole-related residues found in the study with 30 mg per kg of body weight.

An MRL for whole egg of 400 µg/kg of parent flubendazole is recommended.

Table 7
Estimated total daily intake of flubendazole-related residues in food

Tissue	Observed residue (mg/kg parent drug equivalents)	Estimated daily intake[a] (µg parent drug equivalents)
Pig tissue		
Muscle	0.262[b]	79
Liver	3.865[b]	386
Kidney	2.678[b]	134
Fat	0.212[b]	11
Eggs	0.12 [c]	12
Total		622

[a] Calculated from the observed residue levels. Based on a daily intake of 0.5 kg of meat (made up of 0.3 kg of muscle, 0.1 kg of liver, 0.05 kg of kidney, and 0.05 kg of fat) and 0.1 kg of eggs.
[b] Based on concentrations at 6 hours withdrawal time in a study in which pigs received an oral dose of [^{14}C]flubendazole at 1.5 mg per kg of body weight daily for 5 days.
[c] Average concentration detected in eggs on day 6 of a study in which laying hens received [^{14}C]flubendazole in the diet at 30 mg per kg of body weight for 7 days.

Poultry. As no withdrawal period is required for poultry, parent flubendazole is an adequate marker residue. MRLs of 500 and 200 µg/kg are recommended for parent flubendazole in poultry liver and muscle, respectively.

Pigs. Although edible tissues from pigs require no withdrawal period from a human food safety perspective, a withdrawal period based on good practice in the use of veterinary drugs has been applied.

Parent flubendazole is the only analyte available as the marker residue for pig liver. Methods are available for determining flubendazole, and the residue data indicate that misuse can be detected by monitoring for parent flubendazole in pig tissue.

An MRL of 10 µg/kg is recommended for the parent compound in pig liver and muscle.

3.1.3 *Ivermectin*

Ivermectin (a mixture of $\geq$ 80% 22,23-dihydroavermectin B_{1a} (H_2B_{1a}) and $\leq$ 20% 22,23-dihydroavermectin B_{1b} (H_2B_{1b})) had previously been evaluated at the thirty-sixth meeting of the Committee (Annex 1, reference *91*), when an ADI of 0–0.2 µg per kg of body weight was established, based on a NOEL of 0.1 mg per kg of body weight per day for maternal toxicity in the CF_1 mouse and a safety factor of 500.

Toxicological data

The Committee reappraised the developmental toxicity of ivermectin and