The European Agency for the Evaluation of Medicinal Products
Veterinary Medicines and Information Technology

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COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

CYFLUTHRIN

SUMMARY REPORT (2)

1. Cyfluthrin (CAS No 68359-37-5) is a synthetic type II pyrethroid insecticide and acaricide. It is authorised for use in veterinary medicines as a 1% pour-on solution in mineral oil for use in cattle of all ages for the control of flies and tabanids (dosage: 10 ml/animal, approximately 100 mg cyfluthrin; 0.2 to 0.5 mg/kg bw). Cyfluthrin is also used as a pesticide for the protection of plants and as protection agent in carpets. Cyfluthrin for veterinary medicinal and pesticide use consists of a mixture of 4 diasteriometric enantiomer pairs (8 enantiomers). The enantiomer pairs II and IV, also referred to as β-cyfluthrin, are regarded as the pharmacologically active components.

Enantiomer pair	I (*cis*)	II (*cis*)	III (*trans*)	IV (*trans*)
Specified content	23-27%	17-21 %	32-36%	21-25%

Currently cyfluthrin is included in Annex III of Council Regulation (EEC) No 2377/90 as follows:

Pharmacologically active substance(s)	Marker residue	Animal species	MRLs	Target tissue	Other provisions
Cyfluthrin	Cyfluthrin	Bovine	10 µg/kg 50 µg/kg 10 µg/kg 10 µg/kg	Muscle Fat Liver Kidney	Provisional MRLs expire on 01.01.2001
			20 µg/kg	Milk	Further provisions in Council Directive 94/29/EEC are to be observed Provisional MRLs expire on 01.01.2001

Further data were provided to support an entry of cyfluthrin in Annex I of Council Regulation (EEC) No 2377/90 for cattle.

2. The mode of action of cyfluthrin is due to changes in permeability of sodium channels of nerve membranes leading to prolonged depolarisation and hyperexcitability. Mammals efficiently reduce the effects of pyrethroids by rapid metabolism.

3. Most submitted studies were carried out using cyfluthrin with isomers ratios given above, i.e. *cis*:*trans* approximately 45:55. The *cis*:*trans* ratio of parent cyfluthrin residues in animal tissues appeared to be unchanged or only slightly changed. In rats, the acute oral toxicity of *cis*:*trans* 55:45 cyfluthrin in polyethylene glycol is approximately twice that of *cis*:*trans* 45:55 cyfluthrin in the same vehicle. The acute inhalation toxicity is also enhanced when the *cis*:*trans* ratio of cyfluthrin is changed to 55:45. No specific information on the toxicity of individual isomers was supplied.

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4. The pharmacodynamic effects of cyfluthrin (**2 % Cremophor EL/water)** include prolongation of the barbiturate sleeping time in mice (**0.1/0.3/1.0 mg/kg bw**; 10 animals/dose**)** at an oral dose of 1 mg/kg bw. At a dose of 0.3 mg/kg bw no statistically significant changes were observed (NOEL). By contrast**,** shortening of the barbiturate sleeping time was observed at relatively high doses of 30 mg/kg bw in polyethylene glycol, a dose which induced seizures and caused death in 60% of the mice when given in this vehicle.

   Oral cyfluthrin at doses of 10 and 30 mg/kg bw in polyethylene glycol led to elevated blood glucose levels, decreased urine volume and sodium excretion in rats, and had small effects on haemodynamic parameters (slight increase of heart rate, cardiac output, and contractility) in anaesthetized dogs. In vitro cyfluthrin had no antiallergic or pseudo-allergic effects on rat mast cells. Two metabolites inhibited Na^+, K^+ or Mg^{++}-dependent ATPase in brain tissue of rats and chickens more effectively than parent cyfluthrin.

5. The bioavailability and corresponding systemic effects of orally given cyfluthrin are highly dependent on the test formulation used. Direct comparison of pharmacokinetic parameters and also of biological effects is not possible if the information on the vehicle is not known or incomplete. Highest values for bioavailability were observed in cremophor emulsions. Cremophor is a complex mixture of polyoxylated castor oil derivatives with surface active properties. Increased bioavailability and toxicity of type II pyrethroids have also been described for other emulsions, e.g. 20% lecithin in water: For instance, bioavailability of cyfluthrin in rats (10 mg/kg bw, gavage) increased when given in 2 % cremophor as compared to polyethylene glycol reaching 5-fold peak plasma concentrations and attaining t_{max} significantly earlier.

   Absorption of orally administered ^{14}C-labelled cyfluthrin (0.5 mg/kg bw; in cremophor) from the digestive tract was nearly complete in rats (80 to 100%). Single oral or intravenous doses (0.5 mg/kg bw) were excreted to 29% (males) and 35% (females) in faeces, and 70% (males) and 60% (females) in urine. Biliary metabolites accounted for about 50% of the faecal cyfluthrin equivalents. Like other pyrethroids, cyfluthrin is rapidly metabolised by ester cleavage and subsequent oxidation and/or hydroxylation steps and cyano group elimination. The resulting fluorophenoxybenzoic acid and cyclopropanecarboxylic acid derivatives were excreted mainly as glucuronide and sulphate conjugates in urine. Metabolism in rats, cow and chickens is largely comparable. Many of the metabolites prevail in one isomeric form. No information on pharmacokinetics of dermally applied cyfluthrin was available.

6. The acute oral toxicity of cyfluthrin is highly variable dependent on factors such as vehicle or sex. Clinical signs of acute oral toxicity were those of the CS-syndrome (choreo-athetosis, salivation, pawing, burrowing, tremor, tonic and clonic seizures). Oral LD_{50} values in male rats for cyfluthrin in polyethylene glycol, corn oil, or cremophor were 600, 250, or 15 to 20 mg/kg bw, respectively. In female rats the respective value was approximately 1200 for the vehicle polyethylene glycol. The oral LD_{50} of cyfluthrin in polyethylene glycol in mice was 291 mg/kg bw for males, 609 mg/kg bw for females, while 100 mg cyfluthrin/kg bw in cremophor killed more than 50% of female mice. The LD_{50} values greater than 100 mg/kg bw were reported in dogs in dogs. are questionable as oral doses greater than 20 mg cyfluthrin/kg bw in polyethylene glycol or cremophor caused vomiting. Oral LD_{50} for cyfluthrin in chicken is greater than or equal to 5000 mg/kg bw independent of the type of vehicle used.

   In rats using polyethylene glycol as vehicle, the acute oral toxicity of 7 cyfluthrin metabolites was lower than that of cyfluthrin.

   Polyethylene glycol or oily formulations of cyfluthrin were of low acute dermal toxicity in rats and hens with an LD_{50} greater than 5000 mg/kg bw. However, the LD_{50} of 1% cyfluthrin in dipropylene glycol monomethyl ether applied for 24 hours under an occlusion was as low as 59 mg cyfluthrin/kg bw in male rats. An LC_{50} of 400 mg/m^3 (240 min head/nose exposure, approximately 50 to 100 mg/kg bw) was seen in acute inhalation toxicity studies in rats.The intraperitoneal LD_{50} for cyfluthrin in polyethylene glycol in rats was 66 mg/kg bw for males and 104 mg/kg bw for females, the subcutaneous LD_{50} in mice was greater than 2500 mg/kg bw.

7. In two 3-month oral toxicity studies, the only treatment related effects rats (30 or 28 animals per sex and dose at 0, 30, 100 or 300 mg cyfluthrin/kg feed; approximately 0, 2, 7 or 23 in males and 0, 3, 9 or 28 mg/kg bw in females; or 0, 100, 300or 1000 mg cyfluthrin/kg feed corresponding to 0, 6, 21 or 65 mg/kg bw in both sexes) were small changes in haematological parameters at the mid and high dose, induction of liver enzymes after 1 week on treatment in all dose groups of the first study and decreased serum glucose levels at the mid and high dose in the second. At 1000 mg/kg feed clinical and histopathologically overt neurotoxic signs were observed. The second study, however, was available in summary form only so that a conclusive evaluation could not be made.

   In a 6-month dietary study (0, 65, 200 or 600 mg/kg feed corresponding to 0, 2, 7 or 20 mg/kg bw; 6 males and females/dose) dogs showed vomiting, diarrhoea, and neuromotor dysfunctions (unsteady gait, incoordinated hind leg movement) at 20 mg/kg bw and reduced mean bodyweight gain at 7 and 20 mg/kg bw. The low dose, 2 mg/kg bw, was established as NOEL.

   The NOEL in 10 male and 10 female rats for repeated inhalation exposure to cyfluthrin (analytical concentrations of 0, 0.09, 0.71, 4.5 mg/m^3, 6 h/day for 63 days,) was 0.09 mg/m^3, (approximately 30 µg/kg bw/day). In other inhalation studies, concentrations greater than 0.5 mg/m^3 (extrapolated value) led to reduced respiration rates and changes in the acid/base status, and greater than or equal to 1.4 mg/m^3 caused behavioural effects, signs of acute toxicity.

8. Long term toxicity of cyfluthrin in the diet was studied in rats, dogs (24 and 12 months, respectively), and mice (23 months). In rats exposed for 24 months to 0, 50, 150 or 450 mg cyfluthrin/kg feed, corresponding to daily doses of approximately 0, 2, 6 or 19 mg/kg bw in males and 0, 2, 8 or 25 mg/kg bw in females, the 2 high dose levels resulted in dose-dependent weight gain retardation. All dose levels caused deviations of some haematological parameters from the control values, e.g. decreased glucose levels or increased Hb concentrations. In mice exposed for 23 months via powdered feed to 0, 50, 200 or 800 mg cyfluthrin/kg diet (0, 12, 46 or 195 mg/kg bw in males and 0, 15, 63 or 260 mg/kg bw in females), slight but significant deviations from haematological and clinical-chemical parameters of the controls were recorded in all dose groups. The high dose caused weight gain retardation.

   In dogs (6 per sex and dose) receiving 0, 40, 160 or 640 mg cyfluthrin/kg feed for 12 months (approximately 0, 1, 5 or 20 mg cyfluthrin/kg bw), treatment related effects were observed at the highest dose. They consisted of loose stools, vomiting, reduced mean bodyweight gain, and uncoordinated hind limb movements in 2 out of 12 dogs on 1 or more occasions. The dose of 5 mg/kg bw/day was the NOEL.

9. No teratogenic potential of cyfluthrin was recorded even at maternotoxic doses (rats: greater than 3 mg/kg bw in polyethylene glycol, rabbits greater than 30 mg/kg bw in 0.5% cremophor, and greater than 20 mg/kg bw in corn oil). An abortifacient effect of cyfluthrin in 0.5% cremophor in rabbits cannot be ruled out, since 2 does in the high dose group (45 mg/kg bw) aborted and another resorbed all foetuses. Another study in rats with orally administered cyfluthrin in 1% cremophor revealed no maternotoxic or teratogenic effects at doses up to 10 mg/kg bw. The results for maternotoxicity seem to be in conflict with other studies where cyfluthrin in 2% cremophor/kg bw had toxic effects in rats at lower doses.

   Impaired placental and foetal development in rats was caused by inhaled cyfluthrin concentrations greater than or equal to 1.1 mg/m^3 (approximately 0.4 mg/kg bw, 6 l/day for 10 days, analytical concentrations). Reflex bradypnoea due to sensory irritation, in turn inducing hypothermia and hypoxia may be the reason. The incidence of bone alterations, runts per litter and resorptions. was increased at 4.7 and 23.7 mg/m^3 but no clear teratogenic effects were identified. The NOEL was 0.59 mg/m^3 , approximately 0.2 mg/kg bw.

10. A multigeneration study (F0 to F3) with dietary cyfluthrin in rats (10 male, 20 females per group; 0, 50, 150 or 450 mg/kg feed, corresponding to 0, 5, 15or 50 mg/kg bw/day for female and 0, 4, 12 or 40 mg/kg bw/day in male parent animals) revealed no specific reproduction toxicity. Several nursing pups in the high dose group and 1 in the medium dose group had seizures. This may be attributable to a high susceptibility of pups to cyfluthrin and/or metabolites or to a high exposure to the substances via milk. The NOEL was 5 mg/kg bw/day.

In a recent inhalation study in rat pups (20 per dose and sex) exposed postnatally (for 7 days beginning with day 10 after birth) to doses of 0, 6, 15, 58 mg/m^3 for 6.3 hours daily and investigated for motor and locomotor effects as well as density and binding properties of muscarinic achetylcholine (mACh) receptors in the cortex at the age of 4 months, revealed increased motor and locomotor activity at this time point after exposure to 5 and 15 mg/m^3 which reached significance in females of the 15 mg/m^3 group. Pups exposed to 58 mg/m^3 were dead or died after the first exposure. No significant changes in mACh receptor properties were found at levels of 5 and 15 mg/m^3.

In conclusion, behavioural effects were discernible after high inhaled concentrations, but no final statement on long lasting changes in mACh receptor properties in rat brain can be drawn. Test conditions and analytical methods for the evaluation of such changes are not validated so far. No specific investigations on pre- and perinatal influence of oral cyfluthrin are available.

11. Most of the mutagenicity studies on cyfluthrin were pre-GLP. With this reservation no mutagenic effect was observed in the *Salmonella*/microsome assay (Ames test) and other bacterial test systems with and without metabolic activation (S9 mix). Overall negative results were obtained in several mutation reduction assays with *Saccharomyces cerevisiae*. An *in vitro* cytogenetic study with human lymphocytes, a sister chromatid exchange (SCE) assay with Chinese hamster ovary (CHO) cells and an unscheduled DNA synthesis test on rat hepatocytes revealed negative results. The results of 2 *in vivo* tests (micronucleus test and dominant lethal test in mice) did not provide any indication for genotoxic or mutagenic effects of cyfluthrin. Seven possible cyfluthrin metabolites gave negative results in the *Salmonella*/microsome assay (with and without metabolic activation). Based on these results cyfluthrin can be considered non mutagenic.

12. No tumorigenic effects of cyfluthrin were seen in lifetime carcinogenicity studies in rats and mice.

13. In a previous study, single oral doses greater than or equal to 0.03 mg cyfluthrin/kg bw in 2% cremophor were found to change neuromotor function in rats in the inclined plane test. The dose without effect in this test system appeared to be 0.01 mg/kg bw. This no effect dose had been taken as the basis for the preliminary ADI. In a recent repetition of this study under comparable conditions in female rats, the previous results could not be reproduced. The repeated test showed a dose as high as 3 mg/kg bw as the no effect dose for changes in the inclined plane test even in the presence of clinical signs in some of the animals. As there was no consistancy between the results of the 2 inclined plane tests, no reliable conclusion could be drawn regarding the NOEL.

    In a recent acute oral neurotoxicity screening study, β-cyfluthrin dissolved in 1% cremophor EL was administered via gavage to rats (12 per sex and dose) at single doses of 0, 0.5, 2 or 10 mg/kg bw. Animals were sacrificed 15 days after exposure. Animals were subjected to a functional observational battery and motor and locomotor activity were studied at days 0 (approximately 2 hours post dose), 7 and 14. Compound related clinical signs were observed in males and females that received a dose of 2 and 10 mg/kg bw. At the lowest dose of 0.5 mg/kg bw no clinical signs were apparent with the exception of chewing movements, which are ascribed to a local effect of the test substance on the oral mucosa. No compound-related gross or microscopic lesions were evident in the high dosed animals as compared to controls. Statistically significant compound related behavioral and motor or locomotor effects were evident only in the first hours after exposure (approximately 2 hours post dose) in males and females receiving 2 and 10 mg/kg bw. Effects resolved before the second testing (7 days p.a.). Except for chewing movements following administration which were ascribed to a local effects of the test substance on the oral mucosa, likely due to paresthesias, the dose of 0.5 mg/kg bw showed no statistically significant changes and may be considered as a LOEL.

In a recent subchronic dietary neurotoxicity screening study, β-cyfluthrin was administered via diet for 13 weeks to rats (12 per sex and dose) at concentrations of 0, 30, 125 or 400 mg/kg feed (corresponding to average intake of 0, 2, 8 or 27 and 0, 2, 9 or 31 mg/kg bw/day for males and females, respectively). Animals were subjected to a functional observational battery and motor and locomotor activity testing before exposure and during week 4, 8, and 13. Body weight and food consumption were reduced in males at 400 mg/kg feed and females at 125 and 400 mg/kg feed. The NOEL for both parameters was determined as 125 mg/kg feed (approximately 8 mg/kg bw) in males and as 30 mg/kg feed (approximately 2 mg/kg bw) in females.

Behavioural effects were most evident during week 4 of exposure, whereafter there was indication of developing tolerance. Changes in motor/locomotor activity in males reached statistical significance at the 2 higher doses only. No significant changes were observed in the females. The dose of 2 mg/kg bw may be regarded as NOEL. No microscopic lesions in neural tissues or skeletal muscle were disclosed.

Neurotoxicity of cyfluthrin in respect to possible delayed effects was also studied in rats and chickens at sub-lethal doses. Repeated oral administration of sub-lethal doses to rats for several days to weeks caused motor function disturbances with slight histopathological correlates in nerve tissue, which were largely reversed during a 1 to 3 month recovery period. Near lethal single or repeated oral doses of cyfluthrin (1500 to 5000 mg/kg bw) in hens resulted in motor function losses, severely impaired health state and, frequently, death 3 to 6 weeks following treatment. Possible explanations were an unknown type of delayed neurotoxicity or late effects of general toxicity. Five repeated dermal applications of 5000 mg cyfluthrin/kg bw caused death in 2 of 10 treated chickens, and slight brain and sciatic nerve fibre degeneration in 2 others. The latter symptoms were also observed in hens used as controls in other studies.

14. Cyfluthrin was mildly irritating to rabbits' eyes but not to their skin. No sensitising potential was observed. The potency of cyfluthrin to induce sensory stimulation of the skin was not investigated.

15. Human occupational exposure (dermal contact) resulted in itching and burning sensations of exposed areas of the body, which lasted for several hours. Several studies demonstrating interindividual sensitivity differences in respect to dermal, oral, or inhaled cyfluthrin have recently been published. Remarkable quantitative differences in pyrethroid detoxifying esterases in humans have been made partly responsible for these results.

16. Cyfluthrin had been reviewed by the Joint FAO/WHO Meeting on Pesticide Residues (JMPR) in 1987. An ADI for cyfluthrin of 1.2 mg/person was established, based on a NOEL of 2 mg/kg bw/day derived from a 2 year oral toxicity study in rats using a safety factor of 100. This ADI was adopted by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) in the latest evaluation in 1997.

17. The CVMP did not adopt the JMPR NOEL and ADI as there is evidence from pharmacological data and recent acute neurotoxicity investigations that specific effects of cyfluthrin or β-cyfluthrin may occur at lower doses, especially when vehicles mimicking fat/water emulsions are used. These observations include e.g. extension of barbiturate sleeping time (NOEL of 0.3 mg/kg bw) and neurotoxic effects on motor and locomotor activity at single doses via gavage in chremophor (LOEL of 0.5 mg/kg bw). On the basis of the lowest NOEL of 0.3 mg/kg bw observed (barbiturate sleeping time in the mouse) and a safety factor of 100 an ADI of 3 µg/kg bw (i.e. 180 µg/person) may be estimated. This ADI also provides a sufficient margin of safety to the LOEL of 0.5 mg/kg bw observed in the acute neurotoxicity study, especially if one considers that this study used β-cyfluthrin, which consists of the 2 pharmacologically most active enatiomeric pairs of cyfluthrin and cremophor as a vehicle largely enhancing bioavailability.

18. Disposition of radiolabelled cyfluthrin was investigated in a lactating cow following 5 oral doses of ^{14}C-cyfluthrin in gelatine capsules at a dose level of 0.5 mg/kg bw. Highest total residues were found in liver, fat and kidney. Concentrations in other tissues were considerably lower. Tissues had total radioactive residues of 622 µg equivalents/kg in liver, 120 µg equivalents/kg in subcutaneous fat to 230 µg equivalents/kg in renal and omental fat, 188 µg equivalents/kg in kidney, 40 µg equivalents/kg in heart and 21 µg equivalents/kg in shoulder and 28 µg equivalents/kg in loin muscle. The major residue component was parent cyfluthrin (liver: 86%, muscle: 98 to 100%, fat: 93 to 100%, heart: 71%, kidney: 56%). Highest concentrations in milk were seen 24 hours after the 3rd application, 98% of it parent cyfluthrin. From the results of this study it can be deduced that parent cyfluthrin is the marker residue.

19. Various non-radiolabelled residue depletion studies using dermal administration in cattle showed that fat was the tissue with highest concentrations of cyfluthrin being approximately 10 to 20 fold higher than in any other edible tissues. Three days after 1, 2 or 3 applications at a dose of 0.44 mg/kg bw, maximum cyfluthrin concentrations were 40 µg/kg, 100 µg/kg and 150 µg/kg, respectively. A concentration up to 240 µg/kg was found 1 days after 5 doses of 0.9 mg/kg bw/day, which were administered within 26 days. However, with respect to the time course of residue formation and depletion, highest residue levels in fat were measured 4 to 14 days after treatment (broad maximum followed by slow depletion). After 1 treatment, the maximum residue concentrations at different dose levels were in the range of 40 to 10 µg/kg at day 14 post dose.

    In muscle and kidney, cyfluthrin concentrations up to 20 µg/kg were detected after a total of 5 administrations within 26 days. In liver, however, no residue above the limit of detection of 2 µg/kg was found, even after 5 treatments.

20. In milk, highest residue concentrations up to 26 µg/kg were found 2 to 4 days after a single treatment at a dose of 0.63 mg/kg bw. At a dose of 0.2 mg/kg bw, no residues above 5 µg/kg could be detected in any of the milk samples until day 21 after a single treatment. After 3 treatments at 24-hour intervals at a dose of 0.9 mg/kg bw, the highest cyfluthrin concentration found was 54 µg/kg. In several other studies, residues in milk were below the limit of detection of the analytical method (10 µg/kg) at 9 to 96 hours after administration of the therapeutic dose.

21. Using established EU MRLs for cyfluthrin on food items of plant origin according to Directive 94/30/EC (June 1994), the European diet (JMPR, 1993) and the Guidelines for Predicting Dietary Intake of Pesticide Residues (WHO 1989), a Theoretical Maximum Daily Intake (TMDI) of 48 µg cyfluthrin from plant protection usage was calculated (meat and milk MRLs according to Council Directive 94/29/EC of June 1994 were not considered in this calculation) .

22. An analytical method for the determination of parent cyfluthrin based GC/MS was provided in an ISO 78/2 format. The four diastereomers of cyfluthrin could be determined separately under these conditions. The method description was supported by data on validation. The limits of quantitation for the sum of the 4 cyfluthrin diastereomers were 10 µg/kg for liver, kidney and muscle, 25 µg/kg for fat, and 10 µg/kg for milk.

23. In the latest evaluation in 1997, JECFA proposed MRLs for cyfluthrin of 200 µg/kg for fat, 20 µg/kg for muscle, liver and kidney (cattle) and 40 µg/kg for milk (cattle). These MRL values differ from the ones previously established in the EU for the pesticide use of cyfluthrin.

Conclusions and recommendation

Having considered that :

- an ADI has been set at 0.003 mg/kg bw (i.e. 0.18 mg/person),
- the marker residue is the sum of the 4 cyfluthrin diastereomers,
- the recommended MRLs of 50 µg/kg for bovine fat and 10 µg/kg for muscle, kidney and liver and of 20 µg/kg for cow's milk are compatible with those already set by Council Directive 94/29/EC of 1994 for cattle fat and meat (with fat content 10% or less) and milk,
- the recommended MRLs approximately reflect tissue distribution of cyfluthrin with fat being the major target tissue,
- a validated physico-chemical analytical method is available,
- the fact that MRLs for muscle, liver and kidney equal the limit of quantification of the analytical method is acceptable, because in practice only fat is the edible tissue most suitable for residue surveillance of this lipophilic compound,

the Committee recommends the inclusion of cyfluthrin into Annex I of Council Regulation (EEC) No 2377/90 in accordance with the following table:

Pharmacologically active substance(s)	Marker residue	Animal species	MRLs	Target tissues	Other provisions
Cyfluthrin	Cyfluthrin (sum of isomers)	Bovine	10 µg/kg 50 µg/kg 10 µg/kg 10 µg/kg	Muscle Fat Liver Kidney	
			20 µg/kg	Milk	Further provisions in Directive 94/29/EEC are to be observed

Taking into account the recommended MRLs, a daily intake of 37 µg parent cyfluthrin may be calculated. The MRLs established for cyfluthrin residues in food of plant origin resulted in an additional daily intake (Theoretical Maximum Daily Intake, TMDI) of 48 µg/person. Combined consumer intake from the veterinary and pesticide uses would result in a dietary intake of 85 µg which is well below the ADI of 180 µg/person.