## 5.23 LUFENURON (286)

### TOXICOLOGY

Lufenuron is the ISO-approved common name for (*RS*)-1-[2,5-dichloro-4-(1,1,2,3,3,3-hexafluoropropoxy)phenyl]-3-(2,6-difluorobenzoyl)urea (IUPAC), for which the CAS number is 103055-07-8.Lufenuron is an insecticide initially registered for use on a wide range of crops for the control of larvae of many insect pests. Lufenuron inhibits chitin synthesis, probably through enzymatic interference, and prevents the larvae from moulting.

Lufenuron has not been evaluated previously by JMPR and was reviewed by the present Meeting at the request of CCPR.

All critical studies contained statements of compliance with GLP.

#### *Biochemical aspects*

Lufenuron is only partially absorbed following a single oral dose, with the extent of absorption being dose related; approximately 20% of a single 100 mg/kg bw dose appears to be absorbed, compared with about 70% of a single 0.1 or 0.5 mg/kg bw dose. A large proportion of the absorbed dose partitions into fat, with very much lower uptake by other tissues, including the brain. All tissue concentrations of radioactivity increased to a maximum 1 day after the last of 14 repeated low doses. The results suggest that most tissue concentrations would plateau within 2–3 weeks of similar repeated dosing. The fat depot is slowly released, with a terminal half-life of up to 5–13 days at 0.5 mg/kg bw and 10–37 days at 100 mg/kg bw, leading to an increase in concentrations of lufenuron in the brain over long periods (see below). Excretion of the absorbed dose is predominantly via faeces, with only about 1% of the dose being excreted in urine, independent of the dose. Metabolism of lufenuron is minimal, with only about 1% of an oral dose being metabolized by deacylation followed by cleavage of the ureido group. There is no marked sex difference in absorption, tissue distribution or excretion. The pattern of excretion and metabolism is not affected by repeated dosing.

#### *Toxicological data*

Lufenuron has low acute toxicity when administered orally or dermally ($LD_{50}$ > 2000 mg/kg bw) or via inhalation ($LC_{50}$ > 2.35 mg/L, maximal attainable concentration) to rats. Lufenuron produced very slight skin and eye irritation in rabbits and is considered to be a skin sensitizer in the guinea-pig.

The most significant toxicological end-point for lufenuron is convulsions, observed after prolonged treatment at high dose levels. Convulsions are observable in all species treated with lufenuron at daily doses of more than 20 mg/kg bw per day for extended periods (2–3 months in rodents, > 3 months in dogs). As lufenuron is a very lipophilic compound (log $K_{ow}$ = 5.12), it has the potential to accumulate in fatty tissues. It has been shown in toxicity studies with rats, mice and dogs that following prolonged exposure to high doses of 20 mg/kg bw per day or more, fat compartments may become saturated. If exposure is continued after saturation occurs, concentrations in the brain increase, leading to tonic-clonic convulsions.

In a dose range–finding study, lufenuron was fed to mice at a concentration of 0, 1000, 3000 or 9000 ppm (equal to 0, 151, 449 and 1470 mg/kg bw per day for males and 0, 189, 517 and 1440 mg/kg bw per day for females, respectively) for up to 65 days. As a result of mortality and neurotoxic effects of the test substance (tonic-clonic seizures) at all dose levels, it was concluded that the maximum tolerated dose was exceeded even at 1000 ppm (equal to 151 mg/kg bw per day).

In a second dose range–finding study, intended for test substance residue and blood level determination, lufenuron was fed to female mice at a concentration of 0, 4/8, 20, 100 or 1000 ppm (equal to 0, 0.47/1.1, 2.94, 14.5 and 143 mg/kg bw per day, respectively) for up to 91 days (only 71 days for the high dose). From day 57 onwards, the diet of the low-dose group inadvertently contained 8 ppm instead of 4 ppm. The NOAEL was 100 ppm (equal to 14.5 mg/kg bw per day), based on mortality and neurotoxicity (tonic-clonic seizures) at 1000 ppm (equal to 143 mg/kg bw per day).

In a 28-day range-finding study, rats were administered lufenuron in the diet at a concentration of 0, 50, 400, 3000 or 20 000 ppm (equal to 0, 4.10, 30.8, 254 and 1692 mg/kg bw per day for males and 0, 4.07, 32.6, 254 and 1741 mg/kg bw per day for females, respectively). The NOAEL was 400 ppm (equal to 30.8 mg/kg bw per day), based on decreased thymus weight at 3000 ppm (equal to 254 mg/kg bw per day).

In a 90-day toxicity study, rats were fed diets containing 0, 25, 150, 1500 or 15 000 ppm lufenuron (equal to 0, 1.6, 9.68, 101 and 998 mg/kg bw per day for males and 0, 1.7, 10.2, 103 and 1050 mg/kg bw per day for females, respectively). The NOAEL was 150 ppm (equal to 9.68 mg/kg bw per day), based on clinical signs (tonic-clonic seizures), decreased body weight gain and feed consumption, slight changes in haematology and clinical chemistry parameters and increased adrenal weights at 1500 ppm (equal to 101 mg/kg bw per day).

In a 4-week range-finding study, dogs received lufenuron in their diet at a concentration of 2000 or 50 000 ppm (equal to 8.43 and 2200 mg/kg bw per day for males and 10.1 and 2648 mg/kg bw per day for females, respectively). The NOAEL was 50 000 ppm (equal to 2200 mg/kg bw per day), the highest dose tested.

In a 90-day toxicity study, dogs received lufenuron in their diet at a concentration of 0, 200, 3000 or 50 000 ppm (equal to 0, 7.8, 121.6 and 2023 mg/kg bw per day for males and 0, 7.9, 122.5 and 1933 mg/kg bw per day for females, respectively). The NOAEL was 200 ppm (equal to 7.8 mg/kg bw per day), based on increases in blood cholesterol levels and absolute and relative liver weights, reductions in blood potassium and phosphorus levels and an increase in serum alkaline phosphatase activity for some animals at 3000 ppm (equal to 121.6 mg/kg bw per day).

In a 1-year toxicity study, dogs received lufenuron in their diet at a concentration of 0, 100, 2000 or 50 000 ppm (equal to 0, 3.97, 65.4 and 1879 mg/kg bw per day for males and 0, 3.64, 78.3 and 1977 mg/kg bw per day for females, respectively). The main target organs were the brain, adrenals, liver, thyroid and lungs. The NOAEL was 100 ppm (equal to 3.64 mg/kg bw per day), based on mortality, neuromuscular signs, including convulsions, reduced body weight gains, changes in clinical pathology parameters and histopathological lesions in adrenals, liver, thyroid and lungs observed at 2000 ppm (equal to 65.4 mg/kg bw per day).

In another 1-year toxicity study, dogs received lufenuron in their diet at a concentration of 0, 10, 50, 250 or 1000 ppm (equal to 0, 0.31, 1.42, 7.02 and 29.8 mg/kg bw per day for males and 0, 0.33, 1.55, 7.72 and 31.8 mg/kg bw per day for females, respectively). The NOAEL was 250 ppm (equal to 7.02 mg/kg bw per day), based on treatment-related mortality and clinical findings, including convulsions, effects on body weight and effects on the liver and adrenals, with associated histopathology and/or clinical chemistry changes, at 1000 ppm (equal to 29.8 mg/kg bw per day).

An overall NOAEL of 250 ppm (equal to 7.02 mg/kg bw per day) can be identified on the basis of the two 1-year dog studies. The 90-day dog study should not be included in the overall NOAEL, as the observed effects (blood parameters and liver weights) are far less severe than the effects in the 1-year dog studies (e.g. mortality) at similar dose levels. This can be explained by the fat accumulation, which is not yet saturated in the 90-day study; this leads to higher concentrations of the parent compound in the brain in the longer-term studies.

In an 18-month dietary toxicity and carcinogenicity study, mice received lufenuron at a concentration of 0, 2, 20, 200 or 400 ppm (equal to 0, 0.222, 2.25, 22.6 and 62.9 mg/kg bw per day for males and 0, 0.217, 2.12, 22.0 and 61.2 mg/kg bw per day for females, respectively). As a result of high mortality in the high-dose group, surviving animals in this dose group were terminated in weeks 9 and 10. The NOAEL was 20 ppm (equal to 2.12 mg/kg bw per day), based on increased mortality, clinical signs (tonic-clonic convulsive episodes), increased incidences of fatty liver (in females accompanied by necrotic changes) and a higher incidence of inflammatory changes in the prostate at 200 ppm (equal to 22.0 mg/kg bw per day). No treatment-related tumours were observed.

In a 2-year dietary toxicity and carcinogenicity study, rats received lufenuron at a concentration of 0, 5, 50, 500 or 1500 ppm (equal to 0, 0.19, 1.93, 20.4 and 108 mg/kg bw per day for males and 0, 0.23, 2.34, 24.8 and 114 mg/kg bw per day for females, respectively). As a result of

overt toxicity at 1500 ppm, all animals in this group were terminated in week 14. The NOAEL was 50 ppm (equal to 1.93 mg/kg bw per day), based on clinical signs (tonic-clonic convulsions), decreased body weight and (histo)pathological effects on lungs, liver, non-glandular stomach, intestines and urinary tract at 500 ppm (equal to 20.4 mg/kg bw per day). No treatment-related tumours were observed.

The Meeting concluded that lufenuron is not carcinogenic in mice or rats.

Lufenuron was tested for genotoxicity in an adequate range of assays, both in vitro and in vivo. No evidence of genotoxicity was found.

The Meeting concluded that lufenuron is unlikely to be genotoxic.

In view of the lack of genotoxicity and the absence of carcinogenicity in mice and rats, the Meeting concluded that lufenuron is unlikely to pose a carcinogenic risk to humans.

In a two-generation study on reproductive toxicity, rats received lufenuron in their diet at a concentration of 0, 5, 25, 100 or 250 ppm (equal to 0, 0.41, 2.1, 8.3 and 20.9 mg/kg bw per day for males and 0, 0.44, 2.2, 8.9 and 22.2 mg/kg bw per day for females, respectively, based on mean intakes for combined P and F1 generations during the premating period). The NOAEL for parental and reproductive effects was 250 ppm (equal to 20.9 mg/kg bw per day), the highest dose tested. The NOAEL for offspring toxicity was 100 ppm (equal to 8.3 mg/kg bw per day), based on the slight delay in righting reflex in pups at 250 ppm (equal to 20.9 mg/kg bw per day).

In a study of developmental toxicity, rats were administered lufenuron via gavage at a dose of 0, 100, 500 or 1000 mg/kg bw per day. The NOAEL for maternal toxicity was 500 mg/kg bw per day, based on a transient reduction in body weight gain at GDs 7–9 and feed consumption on GDs 6–9 at 1000 mg/kg bw per day. The NOAEL for embryo/fetal toxicity was 1000 mg/kg bw per day, the highest dose tested.

In a study of developmental toxicity, rabbits were dosed at 0, 100, 500 or 1000 mg/kg bw per day with lufenuron via gavage. The NOAEL for maternal toxicity and embryo/fetal toxicity was 1000 mg/kg bw per day, the highest dose tested.

The Meeting concluded that lufenuron is not teratogenic.

In a repeated-dose neurotoxicity study, male rats received lufenuron in their diet at 0, 5, 25, 100 or 500 ppm (equal to 0, 0.26, 1.22, 5.43 and 27.0 mg/kg bw per day, respectively) for 4 months. No systemic toxicity was observed. The NOAEL for neurotoxicity was 100 ppm (equal to 5.43 mg/kg bw per day), based on spontaneous tonic-clonic convulsions or fasciculations and facilitated pentylenetetrazol-induced generalized convulsions at 500 ppm (equal to 27.0 mg/kg bw per day), observed in weeks 13–18.

Convulsions are observed in all species after prolonged treatment with lufenuron, due to saturation of the accumulation in fatty tissues, with subsequent increased lufenuron levels in the brain. The neurotoxic effects are not expected to occur after a single dose. The Meeting concluded that lufenuron is not acutely neurotoxic, but is neurotoxic after prolonged treatment.

A study was performed to determine the effects of treatment of lufenuron for 3 weeks on the estrous cycle in female rats and various plasma hormone levels (estradiol, progesterone, corticosterone, aldosterone, prolactin, luteinizing hormone, follicle stimulating hormone, adrenocorticotrophic hormone and testosterone) in male and female rats administered a dietary concentration of 0, 500 or 1500 ppm (equal to 0, 30.5 and 92.5 mg/kg bw per day for males and 0, 39.4 and 120.1 mg/kg bw per day for females, respectively). The results of this investigation, focused on the pituitary, adrenal and genital organs, suggest that there is no effect of lufenuron on the endocrine system in rats of either sex. This conclusion is supported by the reproductive toxicity studies in rats, which showed no effect of lufenuron on any reproductive end-point.

No specific studies on immunotoxicity were submitted. The available repeated-dose studies do not indicate an immunotoxic potential for lufenuron following exposure by the oral route.

### *Toxicological data on metabolites and/or degradates*

No metabolites of concern were identified.

### *Human data*

In reports on manufacturing plant personnel, no adverse health effects were noted. Several incident reports indicate no significant toxicity in humans.

The Meeting concluded that the existing database on lufenuron was adequate to characterize the potential hazards to the general population, including fetuses, infants and children.

## Toxicological evaluation

An ADI of 0–0.02 mg/kg bw was established on the basis of the NOAEL of 1.93 mg/kg bw per day for tonic-clonic seizures and findings in lungs, gastrointestinal tract, liver and urinary tract in the 2-year dietary study in rats, using a safety factor of 100.

The Meeting concluded that it was not necessary to establish an ARfD for lufenuron in view of its low acute oral toxicity and the absence of developmental toxicity and any other toxicological effects that would be likely to be elicited by a single dose.

A toxicological monograph was prepared.

### *Levels relevant to risk assessment of lufenuron*

| Species | Study | Effect | NOAEL | LOAEL |
|---|---|---|---|---|
| Mouse | Eighteen-month study of toxicity and carcinogenicity[a] | Toxicity | 20 ppm, equal to 2.12 mg/kg bw per day | 200 ppm, equal to 22.0 mg/kg bw per day |
| | | Carcinogenicity | 400 ppm, equal to 61.2 mg/kg bw per day[b] | – |
| Rat | Two-year study of toxicity and carcinogenicity[a] | Toxicity | 50 ppm, equal to 1.93 mg/kg bw per day | 500 ppm, equal to 20.4 mg/kg bw per day |
| | | Carcinogenicity | 1 500 ppm, equal to 108 mg/kg bw per day[b] | – |
| | Two-generation study of reproductive toxicity[a] | Reproductive toxicity | 250 ppm, equal to 20.9 mg/kg bw per day[b] | – |
| | | Parental toxicity | 250 ppm, equal to 20.9 mg/kg bw per day[b] | – |
| | | Offspring toxicity | 100 ppm, equal to 8.3 mg/kg bw per day | 250 ppm, equal to 20.9 mg/kg bw per day |
| | Developmental toxicity study[c] | Maternal toxicity | 500 mg/kg bw per day | 1 000 mg/kg bw per day |
| | | Embryo and fetal toxicity | 1 000 mg/kg bw per day[b] | – |
| | Four-month neurotoxicity study[a] | Neurotoxicity | 100 ppm, equal to 5.43 mg/kg bw per day | 500 ppm, equal to 27.0 mg/kg bw per day |

| Species | Study | Effect | NOAEL | LOAEL |
|---|---|---|---|---|
| Rabbit | Developmental toxicity study[c] | Maternal toxicity | 1 000 mg/kg bw per day[b] | – |
| | | Embryo and fetal toxicity | 1 000 mg/kg bw per day[b] | – |
| Dog | One-year studies of toxicity[a,d] | Toxicity | 250 ppm, equal to 7.02 mg/kg bw per day | 1 000 ppm, equal to 29.8 mg/kg bw per day |

[a] Dietary administration.
[b] Highest dose tested.
[c] Gavage administration.
[d] Two or more studies combined.

*Estimate of acceptable daily intake (ADI)*

0–0.02 mg/kg bw

*Estimate of acute reference dose (ARfD)*

Unnecessary

*Information that would be useful for the continued evaluation of the compound*

Results from epidemiological, occupational health and other such observational studies of human exposure

***Critical end-points for setting guidance values for exposure to lufenuron***

| | |
|---|---|
| *Absorption, distribution, excretion and metabolism in mammals* | |
| Rate and extent of oral absorption | ~70% within 24 h at 0.1 or 0.5 mg/kg bw; ~20% within 24 h at 100 mg/kg bw |
| Dermal absorption | No data |
| Distribution | Widely distributed; highest concentrations in fat; a plateau within 2–3 weeks of dosing is suggested for all tissues. Brain levels are initially low, but rise after prolonged exposure due to saturation of fat storage. |
| Potential for accumulation | High fat accumulation, with slow release (terminal half-life 5–13 days at 0.5 mg/kg bw and 10–37 days at 100 mg/kg bw) |
| Rate and extent of excretion | Predominantly in faeces, with < 1% in urine, independent of dose |
| Metabolism in animals | Minimal |
| Toxicologically significant compounds in animals and plants | Parent compound |
| *Acute toxicity* | |
| Rat, $LD_{50}$, oral | > 2 000 mg/kg bw |
| Rat, $LD_{50}$, dermal | > 2 000 mg/kg bw |
| Rat, $LC_{50}$, inhalation | > 2.35 mg/L, maximal attainable concentration |
| Rabbit, dermal irritation | Mildly irritating |
| Rabbit, ocular irritation | Mildly irritating |

| | |
|---|---|
| Guinea-pig, dermal sensitization | Sensitizing (Magnusson and Kligman maximization test) |
| *Short-term studies of toxicity* | |
| Target/critical effect | Mortality and neurotoxicity (tonic-clonic convulsions) |
| Lowest relevant oral NOAEL | 7.02 mg/kg bw per day (1 year; dog) |
| Lowest relevant dermal NOAEL | 1 000 mg/kg bw per day (28 days; rat) |
| Lowest relevant inhalation NOAEC | No data |
| *Long-term studies of toxicity and carcinogenicity* | |
| Target/critical effect | Neurotoxicity (tonic-clonic convulsions), (histo)pathological findings in lungs, liver, non-glandular stomach, intestines and urinary tract |
| Lowest relevant NOAEL | 1.93 mg/kg bw per day (2 years; rat) |
| Carcinogenicity | Not carcinogenic in mice or rats[a] |
| *Genotoxicity* | |
| | No evidence of genotoxicity[a] |
| *Reproductive toxicity* | |
| Target/critical effect | Slight delay in righting reflex in pups |
| Lowest relevant parental NOAEL | 20.9 mg/kg bw per day (highest dose tested; rat) |
| Lowest relevant offspring NOAEL | 8.3 mg/kg bw per day (rat) |
| Lowest relevant reproductive NOAEL | 20.9 mg/kg bw per day (highest dose tested; rat) |
| *Developmental toxicity* | |
| Target/critical effect | Transient reduction in maternal body weight gain and feed consumption (rat) |
| Lowest relevant maternal NOAEL | 500 mg/kg bw per day (rat) |
| Lowest relevant embryo/fetal NOAEL | 1 000 mg/kg bw per day (rat, rabbit; highest dose tested) |
| *Neurotoxicity* | |
| Acute neurotoxicity NOAEL | No evidence of acute neurotoxicity |
| Subchronic neurotoxicity NOAEL | 5.43 mg/kg bw per day (4 months; rat) |
| Developmental neurotoxicity NOAEL | No data |
| *Other toxicological studies* | |
| Immunotoxicity | No data |
| Studies on toxicologically relevant metabolites | No metabolites of concern were identified |
| *Medical data* | |
| | No evidence of adverse effects in personnel exposed to lufenuron; several incident reports indicate no significant toxicity in humans |

[a] Unlikely to pose a carcinogenic risk to humans from the diet.

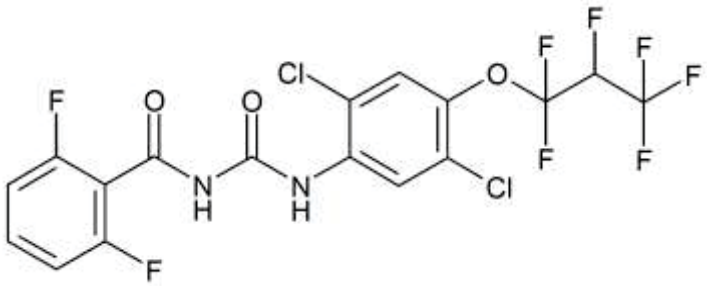
### *Summary*

| | Value | Study | Safety factor |
|---|---|---|---|
| ADI | 0–0.02 mg/kg bw | Two-year toxicity and carcinogenicity study (rat) | 100 |

| | Value | Study | Safety factor |
|---|---|---|---|
| ARfD | Unnecessary | – | – |

## RESIDUE AND ANALYTICAL ASPECTS

Lufenuron (ISO common name) is an insect growth inhibitor that is active against larvae of Lepidoptera and Coleoptera. When ingested, lufenuron interferes with chitin synthesis, and prevents larvae from moulting. It was considered for the first time by the 2015 JMPR for toxicology and residues.



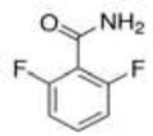
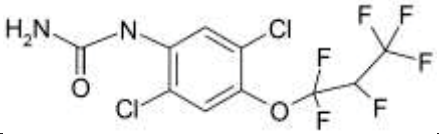
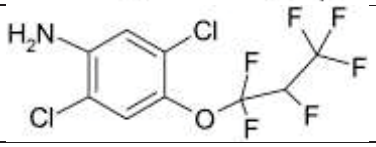
The IUPAC name of lufenuron is (RS)-1-[2,5-dichloro-4-(1,1,2,3,3,3-hexafluoropropoxy)phenyl]-3-(2,6-difluorobenzoyl)urea and the CA name is N-[[[2,5-dichloro-4-(1,1,2,3,3,3-hexafluoropropoxy)phenyl]amino]carbonyl]-2,6-difluorobenzamide.

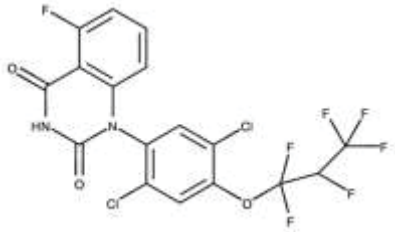
Lufenuron consists of a pair of enantiomers. A chiral centre exists at the 2-position of the hexafluoropropoxy side-chain. Lufenuron technical active ingredient is manufactured under non-stereospecific conditions giving a racemate (R:S 50:50).

The physical-chemical properties of lufenuron indicate low volatility and no accelerated photochemical degradation in water. The octanol-water partition coefficient, log $P_{ow,}$ is 5.12.

Lufenuron radio-labelled either in the dichlorophenyl- or difluorophenyl-moiety was used in the metabolism and environmental fate studies.

The following abbreviations are used for the metabolites discussed below:

| | | |
|---|---|---|
| CGA149776 | 2,6-Difluoro-benzoic acid |  |
| CGA149772 | 2,6-Difluoro-benzamide |  |
| CGA238277 | 2,5-Dichloro-4-(1,1,2,3,3,3-hexafluoropropoxy)-phenyl-urea |  |
| CGA224443 | N-[2,5-dichloro-4-(1,1,2,3,3,3-hexafluoropropoxy)-benzenamine |  |

| | | |
|---|---|---|
| CGA301018 | no chemical name submitted |  |

***Environmental fate in soil***

The Meeting received information for lufenuron on soil photolysis, aqueous hydrolysis, aerobic soil metabolism and soil degradation.

Soil photolysis using [dichlorophenyl-$^{14}$C]-lufenuron and [difluorophenyl-$^{14}$C]-lufenuron revealed no significant degradation (84–99% parent remaining after 17 days of continuous irradiation).

Hydrolysis in aqueous solutions representative of environmental conditions (25 °C) showed virtually no degradation at pH 5, 7 and 9 within 5 days. Under more extreme conditions the parent substance was stable at pH 1 and 70°C, representing more than 90% of the radioactivity. At pH 9 an accelerated degradation was observed at 50 °C and 70 °C with 0–53% of the parent remaining after 1–5 days. Depending on the label the cleavage products CGA224443 and CGA238277 and its counterparts CGA149776 and 2,6-difluorobenzamide (CGA149772) were observed. In addition both labelled compounds produced CGA301018 by loss of fluoride and ring closure.

In the aerobic soil metabolism studies lufenuron was degraded with half-lives of 9–24 days in microbial active soil and 17–83 days in sterilised soil. Cleavage of the parent molecule was the primary degradation step, leaving CGA238277 and CGA224443 for [dichlorophenyl-$^{14}$C]-lufenuron. For [difluorophenyl-$^{14}$C]-lufenuron no metabolites were identified. Unextracted residues in soil at the end of the studies were between 25–79% of the AR. Mineralisation ranged up to 59% AR.

2,6-difluorobenzamide (CGA149772), which is a common soil metabolite to other active substances, e.g., diflubenzuron, was investigated separately for its behaviour in soil. Within 120 days it was completely degraded, leaving CGA149776 as its main degradate within the first two weeks. Afterward the radioactivity was further degraded and remained unextracted (up to 41% AR) or was mineralized (up to 65% AR).

The soil degradation of lufenuron and its metabolites CGA238227 and CGA224443 was also investigated on three different soils under laboratory conditions. Following 1$^{st}$-order kinetic, $DT_{50}$ and $DT_{90}$ values of 13.7 d and 81.1d for lufenuron, 12.8 d and 42.5 d for CGA238277 and of 35.8 d and 119 d for CGA224443 were calculated, respectively.

In summary the Meeting concluded that lufenuron is moderately quickly degraded in soil under laboratory conditions, presumably by microbial activity. To assess the degradation behaviour under field conditions, field dissipation studies would be required. The residue is stable against photolysis and hydrolysis under environmental conditions, however at high temperature and basic conditions cleavage of the parent molecule was observed.

***Plant metabolism***

The Meeting received plant metabolism studies for lufenuron following foliar application of either [dichlorophenyl-$^{14}$C]-lufenuron or [difluorophenyl-$^{14}$C]-lufenuron in cabbage, tomato and cotton.

For cabbage the metabolism of lufenuron was investigated with [dichlorophenyl-$^{14}$C]-lufenuron only. Greenhouse plants received three spray applications equivalent to 0.02 kg ai/ha each in two week intervals. Samples were taken one hour after the first and last application, and at crop maturity, 28 days after the last application.

In mature cabbage heads TRR levels were 0.195 mg eq/kg (up to 1.8 mg eq/kg in withered leaves). 97.5% of the TRR (0.19 mg eq/kg) was recovered as unchanged lufenuron. In the head cabbage as well as in withered leaves, CGA238277 was identified at estimated levels of 0.6% and 3.3% of the TRR, respectively. The actual amounts were not measured in the TLC system used. No further metabolites were found.

For tomatoes the metabolism of lufenuron was investigated with [dichlorophenyl-$^{14}$C]-lufenuron only. Fruit bearing plants kept in a protected environment were treated with three sprayings equivalent to 0.03 kg ai/ha per application with one week intervals. Samples were collected directly after the first application and up to 28 DALA. In parallel 34µg lufenuron was directly injected into single fruits, which were sampled after 18 and 33 days.

Directly after the last foliar application, TRR levels in fruits were 1.2 mg eq/kg, degrading to 0.69 mg eq/kg after 28 days. TRR levels found in additional samples at 28 DAT were 0.47 mg eq/kg for leaves and 0.44 mg eq/kg in mature fruits. Newly developed green fruits had much lower total radioactive residues of 0.03 mg eq/kg. In all fruits receiving a foliar treatment > 89% of the residue was recovered in the surface wash. Unextracted residues were generally low (< 0.6% TRR).

The identification of the radioactivity (combined surface wash and extract) showed unchanged lufenuron as the major residue in fruits and leaves (93–98% TRR). Only in one fruit sample collected 28 DAT, minor amounts of CGA238277 (0.2% TRR, 0.0013 mg eq/kg) were found.

In mature fruits receiving a direct injection of lufenuron, the results from the extracts were comparable to foliar treated fruits. 90–95% of the radioactivity was identified as unchanged lufenuron. CGA238277 was identified in minor amounts up to 2% of the TRR. 5% of the TRR remained unextracted.

For cotton grown under glasshouse conditions the metabolism was investigated in two studies using [dichlorophenyl-$^{14}$C]-lufenuron or [difluorophenyl-$^{14}$C]-lufenuron.

For [dichlorophenyl-$^{14}$C]-lufenuron cotton plants received three foliar sprayings equivalent to 0.03 kg ai/ha each at 14 day interval, beginning at flowering. Sampling of leaves took place 1 hour, 1 day, 3 and 7 days after the first application and 14 days, 28 and 84 days (maturity) after the last application. In addition, four cotton plants received three stem injections (100 µg lufenuron each) made at 14-day intervals.

TRR levels found were up to 4.9 mg eq/kg in the leaves, < 0.001 mg eq/kg in seeds, 0.092 mg eq/kg in hulls and 0.001 mg eq/kg in green bolls. In leaves the amount of radioactivity in the surface wash decreased from 98% TRR after application 1 to 43% TRR at maturity (84 DALA).

The identification of the radioactivity (combined surface wash and extracts) showed 89–100% of the TRR as unchanged lufenuron. No metabolites were identified. In seeds and green bolls TRR levels were too low for further identification. Unextracted residues did not exceed 3.3% of the TRR.

The stem injection showed that most of the applied radioactivity remained at the injection site (81.2% AR). Minor translocation was observed into adjected stalks (13.3% AR) and leaves (1.6–3.9% AR). In all samples the unchanged parent was the only residue identified (~95–98% TRR).

For [difluorophenyl-$^{14}$C]-lufenuron the use pattern was comparable to the other label, but only the foliar treatment experiment was conducted. Samples of mature plant parts were collected 52 DALA.

TRR levels found were up to 5.95 mg eq/kg in leaves (52 DALA), 0.69 mg eq/kg in hulls and 0.003 mg eq/kg in seeds. In the leaves the surface wash contained most of the residue with 96% TRR directly after treatment and 49–58% TRR at maturity (52 DALA).

The identification again revealed unchanged lufenuron exclusively, representing >92% of the TRR in leaves and 79–83% TRR in other matrices. The TRR found in seeds was too low for identification. No further metabolites were detected.

Two confined rotational crop studies for lufenuron were submitted

In the first study [difluorophenyl-$^{14}$C]-lufenuron was applied under protected conditions to bare soil at a rate equivalent to 0.15 kg ai/ha. Lettuce, spring wheat, maize and carrots were planted in the treated soil 63 days after test substance application. The transfer of radioactivity into succeeding crops was very limited. In mature lettuce (126 d after treatment) the highest TRR level of 0.047 mg eq/kg was found. 53% of the TRR was identified as unchanged parent (0.025 mg/kg). In other matrices only wheat straw (0.023 mg eq/kg, 0.007 mg lufenuron/kg) and immature carrots roots (0.023 mg eq/kg, no identification conducted) showed total radioactive residues above 0.01 mg eq/kg. No further identification was conducted for these matrices. In soil samples, nearly the entire extracted radioactivity was attributed to lufenuron. No residue of CGA149772 or CGA149776 could be identified in any sample.

In a second confined study conducted under field conditions [dichlorophenyl-$^{14}$C]-lufenuron was applied to bare soil once at a rate equivalent to 0.13 kg ai/ha. After different plant-back intervals (PBI) lettuce (PBI 76 d), winter wheat (PBI 126 d), sugar beets (PBI 306 days) and maize (PBI 331 d) were planted/sown and grown to maturity. TRR levels in all plant samples was between < 0.001 mg eq/kg and 0.004 mg eq/kg, which was too low for further identification.

In summary lufenuron is deposited on the plant surface and slowly adsorbed by leaves following direct treatment. On the surface and in plant tissue, the active substance is the only residue present in major amounts. Minor amounts of CGA238277 were identified in cabbage and tomato (up to 3.3% TRR). All plant metabolism studies for lufenuron were conducted under protected conditions. However, since lufenuron is not subject to photolysis the residue pattern in plants grown under field conditions is expected to be similar. Also, two of three studies were conducted with [dichlorophenyl-$^{14}$C]-lufenuron only. Since nearly the entire applied radioactivity was recovered as unchanged parent compound in these studies, no investigations with a second label are considered necessary.

For rotational crops the transfer of residues into succeeding crops from soil is very limited and mostly resulted in TRR levels too low for identification. In soil and in crop samples subject to identification parent lufenuron was the major residue. No further metabolites were identified.

***Animal metabolism***

Information was available on metabolism of lufenuron in laboratory animals, lactating goats and laying hens. Studies on rats, mice and dogs were evaluated by the WHO Core Assessment Group.

For lactating goats two studies were conducted involving daily administration of either $^{14}$C-difluorophenyl-labelled lufenuron at 5.4 ppm (0.135 mg/kg bw) or $^{14}$C-dichlorophenyl-lufenuron at 6.0 ppm (0.15 mg/kg bw) for ten consecutive days. The animals were slaughtered approximately 24h after the last dose.

The total recovery of the administered radioactivity was 95% for both labels. The majority of the radioactivity (73–74%) was found in the faeces. Radioactive residues in the edible tissues were 0.8–1.6% AR in muscle (0.038–0.08 mg eq/kg), 4.2–5.4% AR in fat (0.82–2.4 mg eq/kg), 0.28–0.3% AR in liver (0.37–0.42 mg eq/kg), 0.01–0.02% AR in kidney (0.11–0.12 mg eq/kg) and 5.8–6.8% AR in milk (up to 1.0 mg eq/kg). A plateau in milk was observed after approximately one week.

In tissues and milk unchanged parent was the only residue identified for both radiolabels, representing 73–94% of the TRR. The remaining radioactivity remained unresolved in the TLC-System used (6.6–19% TRR) or was not extracted from the sample (0.6–8.9% TRR).

Also for laying hens two studies were conducted involving daily administration of either $^{14}$C-difluorophenyl-labelled lufenuron at 3.4 ppm (2.6 mg/kg bw) or $^{14}$C-dichlorophenyl-lufenuron at 5.2 ppm (3.5 mg/kg bw) for fourteen consecutive days. The animals were slaughtered approximately 24h after the last dose.

The total recovery of the administered radioactivity was 75–79%. The majority of the radioactivity (54–62%) was found in the excreta. Radioactive residues in the edible tissues were 0.55–1.2% AR in lean meat (0.1–0.24 mg eq/kg), 5.1–9.9% AR in fat (7.2–13 mg eq/kg), 0.4–0.58% AR in liver (0.83–1.5 mg eq/kg), 0.07–0.09% AR in kidney (0.52–0.74 mg eq/kg) and 8.7–9.6% AR in eggs (up to 0.016 mg eq/kg in egg white and 8.5 mg eq/kg in egg yolk). In eggs a plateau was observed

after one week for $^{14}$C-difluorophenyl-lufenuron while residues for $^{14}$C-dichlorophenyl-lufenuron showed a slight increase until the end of dosing.

In tissues and eggs unchanged parent lufenuron was the predominant residue, representing 79–94% TRR in all matrices except egg white. For the difluorophenyl-label the cleavage product CGA149772 was the only metabolite detected, being present in egg white at 0.001 mg eq/kg (17.3% TRR). For the dichlorophenyl-label its counterpart CGA238277 was found in minor amounts in kidney (0.028 mg eq/kg, 5.3% TRR) and egg white (< 0.001 mg eq/kg, 7.0% TRR). The remaining radioactivity remained unresolved in the TLC-System used (3–42% TRR) or was not extracted from the sample (2–11% TRR).

In summary the metabolic degradation of lufenuron in livestock animals is very limited, showing parent as the predominant residue in all matrices. Minor amounts of the cleavage products CGA149772 and CGA238277 were found in poultry kidney and egg white.

***Methods of residue analysis***

The Meeting received analytical methods for the analysis of lufenuron in plant and animal matrices. The basic principle employs extraction by homogenisation with methanol or water and partitioning against hexane: ethyl ether (9:1,v:v). Clean-up is normally achieved by C18 solid-phase extraction. Residues are determined by liquid chromatography (LC) in combination with UV (255 nm) or tandem mass spectroscopy (MS/MS). Mass-transitions are m/z 509.1 → 326 for quantification and m/z 509→ 175 for confirmation. The methods submitted are suitable for measuring residues with a LOQ of 0.01 mg/kg in high water, high oil and high starch matrices while acidic matrices were validated with a LOQ of 0.02 mg/kg.

For animal matrices the analytical methods were comparable, however silica gel SPE was used for clean-up instead. Validated LOQs were 0.001 mg eq/kg for milk, 0.01 mg/kg for liver and kidney, 0.02 mg/kg for meat and 0.1 mg/kg for fat.

The application of multi-residue methods was tested with DFG S19 for both plant and animal matrices. The method was shown suitable with a general LOQ of 0.02 mg/kg for lufenuron.

***Stability of residues in stored analytical samples***

The Meeting received information on the storage stability of lufenuron in plant and animal matrices stored at -18°C.

In plant matrices with high water, high acid and high oil content parent lufenuron was stable for at least 24 months. High starch matrices were not tested.

In animal matrices (bovine tissues and milk) no significant degradation was observed within 9 months. No storage stability data were provided for poultry matrices and eggs.

***Definition of the residue***

The fate of lufenuron in plants was investigated after foliar application to tomatoes, cabbage and cotton. In all crop samples investigated unchanged lufenuron was the only major residue present, representing 79–100% TRR. The residue was mainly present as a surface residue. No significant transfer into untreated plant parts was observed.

In confined rotational crop studies the overall uptake of radioactivity was very limited. Only parent lufenuron could be detected in collected plant samples.

The Meeting concluded that lufenuron is the relevant residue in all plant matrices for compliance with MRLs and for dietary intake purposes. Analytical multi-residue methods are capable of measuring lufenuron in all plant matrices.

Livestock animal metabolism studies were conducted on lactating goats (5.4–6.0 ppm) and laying hens (3.4–5.2 ppm).

In both species unchanged parent lufenuron was the only residue identified in major amounts, representing 73–94% of the TRR in all matrices. In goat matrices and milk no other metabolites could be detected. In poultry matrices minor amounts of the cleavage products CGA149772 and CGA238277 were found, representing up to 17% TRR in egg white but at low levels (0.001 mg eq/kg) and 5.3% TRR in kidney (0.028 mg eq/kg). No further metabolites were found in poultry matrices or eggs.

The Meeting concluded that parent lufenuron is the relevant residue in all animal matrices for compliance with MRLs and for dietary intake purposes. Analytical multi-residue methods are capable of measuring lufenuron in all animal matrices.

In all species residue concentrations in fat tissues or egg yolk were at least one order of magnitude higher than in muscle tissues or egg white. The log $P_{ow}$ of lufenuron is 5.12. The Meeting decided that residues of lufenuron are fat soluble.

Definition of the residue for compliance with MRL and for dietary intake for plant and animal commodities: *lufenuron*

*The residue is fat-soluble.*

***Results of supervised residue trials on crops***

The Meeting received supervised trial data for applications of lufenuron on various vegetables crops as well as for soya beans, maize, sugarcane, cotton and coffee conducted in Brazil, China and Europe.

*Cucumber*

Lufenuron is registered in Spain for cucumbers under protected conditions at rates of 2 × 0.1 kg ai/ha with a PHI of 7 days. Supervised field trials from France, Greece and Spain according to this GAP and at rates up to +50% higher were submitted.

In protected cucumbers residues of lufenuron following GAP treatment (±25%) were (n=4): 0.01, 0.02, 0.06, 0.06 mg/kg.

The Meeting concluded that four supervised trials on cucumber approximating GAP are insufficient for an evaluation and decided to explore the proportionality approach using trials at +50% GAP rate. Since some of the trials according to GAP were also conducted at slightly elevated rates, all data are proportionally adjusted to the Spanish GAP rate of 0.1 kg ai/ha:

In protected cucumbers treated with 0.1 kg ai/ha lufenuron residues were (no scaling factor): 0.06 mg/kg.

In protected cucumbers treated with 0.11 kg ai/ha lufenuron residues were (scaling factor 0.91): 0.018 mg/kg (0.91×0.02 mg/kg).

In protected cucumbers treated with 0.12 kg ai/ha lufenuron residues were (scaling factor 0.83): 0.0083 and 0.05 mg/kg (0.83×0.01 mg/kg and 0.83×0.06 mg/kg).

In protected cucumbers treated with 0.15 kg ai/ha lufenuron residues were (scaling factor 0.66): 0.013(3), 0.02(3), 0.026 mg/kg (0.66×0.02 mg/kg(3), 0.66×0.03 mg/kg(3) and 0.66×0.04. mg/kg)

The combined total dataset for lufenuron in protected cucumbers was (n=11): 0.0083, 0.013(3), 0.018, 0.02(3), 0.026, 0.05 and 0.06 mg/kg.

The Meeting estimated a maximum residues level of 0.09 mg/kg and a STMR of 0.02 mg/kg for lufenuron in cucumber.

*Melons, except watermelons*

Lufenuron is registered in Spain for melons under protected conditions at rates of 3 × 0.1 kg ai/ha with a PHI of 7 days. Supervised field trials from Spain according to this GAP were submitted.

All samples were segmented and in some trials already separated into pulp and peel in the field, which is against the current Codex sampling procedure. However, lufenuron was not metabolized in plant metabolism studies, even after direct injection into tomato fruits. In addition simulated hydrolysis indicated no degradation at pH 7 or lower, which is representive of fruits and vegetables. The Meeting therefore concluded that segmentation of samples in the field did not influence the magnitude of residues. The Meeting also noted that no contamination of melon pulp with peel residues during separation occurred and decided to use the data for its assessment.

Some trials submitted involved a last sampling at 3 DALA which is shorter than the PHI of the Spanish GAP of 7 days. In plant metabolism studies lufenuron was a surface residue not subject to degradation or metabolism. Also, melons near maturity have already finalized their growth and are only subject to ripening. Therefore the Meeting concluded that no different residue populations have to be expected for melons within the last week before harvest when sampled at 3 or 7 DALA and decided to take samples collected after three days also into account for the assessment. This conclusion is supported by several decline studies from 0 to 10 DALA, indicating no constant decrease of the residue concentration but the usual sampling variation within the results.

In protected melons (whole fruits) residues of lufenuron were (n=6): 0.02, 0.03, 0.06, 0.09, 0.13, 0.19 mg/kg.

In the corresponding pulp samples, if measured, residues of lufenuron were (n=4): < 0.02(4) mg/kg.

For melon, except watermelons, the Meeting estimated a maximum residues level of 0.4 mg/kg, based on whole melon fruits, except watermelons and an STMR of 0.02 mg/kg, based on pulp data.

*Peppers, sweet*

Lufenuron is registered in Spain for sweet peppers under protected conditions at rates of 3 × 0.1 kg ai/ha with a PHI of 7 days. Supervised field trials on sweet peppers from Greece, Italy and Spain according to this GAP were submitted.

In protected sweet peppers residues of lufenuron following GAP treatment (±25%) were (n=6): 0.08, 0.13, 0.13, 0.17, 0.18 and 0.54 mg/kg.

The Meeting estimated a maximum residues level of 0.8 mg/kg and an STMR of 0.15 mg/kg for lufenuron in sweet peppers.

*Tomato*

Lufenuron is registered in Spain for tomatoes under protected conditions at rates of 3 × 0.1 kg ai/ha with a PHI of 7 days. Supervised field trials on tomatoes from Greece, Spain and Switzerland according to this GAP were submitted.

In protected tomatoes residues of lufenuron following GAP treatment were (n=13): 0.02, 0.04, 0.04, 0.05, 0.06, 0.08(4), 0.09, 0.1, 0.11 and 0.24 mg/kg.

The Meeting estimated a maximum residues level of 0.4 mg/kg and an STMR of 0.08 mg/kg for lufenuron in tomatoes.

*Sweet corn*

The Meeting received supervised field trail information on sweet corn, however no corresponding GAP was made available to the Meeting and therefore no recommendation was made.

*Soya beans*

Lufenuron is registered in Brazil for soya beans at maximum rates of 2 × 0.02 kg ai/ha with a PHI of 35 days. Supervised field trials on soya beans from Brazil at exaggerated rates (3.8 times higher) and a higher number of treatments (four instead of two) were submitted.

In soya beans residues of lufenuron after exaggerated treatment were (n=3): < 0.01(3) mg/kg

The Meeting concluded that under consideration of the exaggerated treatment regime involved, the seeds being protected by the pod during applications and the non-systemic properties of the active substance observed in plant metabolism studies, no finite residue following treatment at GAP rate have to be expected. The Meeting estimated a maximum residues level of 0.01* mg/kg and an STMR of 0 mg/kg for lufenuron in soya beans (dry).

*Potatoes*

Lufenuron is registered in Brazil for potatoes at rates of 4 × 0.04 kg ai/ha with a PHI of 14 days. Supervised field trials from Brazil matching the GAP were submitted.

In potato tubers residues of lufenuron after treatment according to GAP were (n=4): < 0.01(4) mg/kg

Taking into account the non-systemic properties of the active substance, the Meeting concluded that residues in tuber above the LOQ are unlikely to occur and estimated a maximum residues level of 0.01* mg/kg and an STMR of 0.01 mg/kg for lufenuron in potatoes.

*Maize*

Lufenuron is registered in Brazil for maize at maximum rates of 2 × 0.01 kg ai/ha with a PHI of 35 days. All supervised field trials on maize submitted were sampled at significantly longer DAT intervals than the PHI.

The Meeting concluded that the data submitted for lufenuron in maize is insufficient for a recommendation.

*Sugar cane*

Lufenuron is registered in Brazil for sugar cane at rates of 2 × 0.02 kg ai/ha with a PHI of 14 days. Supervised field trials from Brazil matching the GAP were submitted.

In sugar cane residues of lufenuron after treatment according to GAP were (n=4): < 0.01 and 0.02(3) mg/kg

The Meeting concluded that the data submitted for lufenuron in sugar cane is insufficient for a recommendation.

*Cotton*

Lufenuron is registered in China for cotton at rates of 2 × 0.045 kg ai/ha with a PHI of 28 days. Supervised field trials from China according to this GAP were submitted, however the trial description did not included information on the stage of boll opening for cotton plants.

In cotton seeds residues of lufenuron after treatment according to GAP were (n=4): < 0.05(4) mg/kg

The Meeting concluded that the stage of boll opening is a sensitive parameter for residues following foliar application. Without this type of information, a set of four field trials in not considered sufficient for estimating maximum residue levels in cotton seed. Supportive information from plant metabolism studies cannot be taken into account as the active substance was applied before boll opening in these studies.

*Coffee*

Lufenuron is registered in Brazil for coffee at rates of 2 × 0.04 kg ai/ha with a PHI of 7 days. Supervised field trials from Brazil matching the GAP were submitted.

In coffee beans (dry processed) residues of lufenuron after treatment according to GAP were (n=4): < 0.01(3) and 0.01 mg/kg

The Meeting concluded that the data submitted for lufenuron in coffee is insufficient for a recommendation.

### *Fate of residues during processing*

The Meeting received information on the hydrolysis of radio-labelled lufenuron as well as processing studies using unlabelled material in tomatoes.

In a hydrolysis study using [dichlorophenyl-$^{14}$C]-lufenuron or [difluorophenyl-$^{14}$C]-lufenuron, typical processing conditions were simulated (pH 4,5 and 6 with 90°C, 100°C and 120°C for 20, 60 and 20 minutes). No significant degradation of the parent was observed. For pH5 with 100°C for 60min a minor formation of CGA224443 and CGA149772 (up to 6.9% of the applied radioactivity) was observed.

The fate of lufenuron residues has been examined simulating household and commercial processing of tomatoes. Estimated processing factors for the commodities considered at this Meeting are summarised below.

| Raw commodity | Processed commodity | Lufenuron | | |
|---|---|---|---|---|
| | | Individual processing factors | Mean or best estimate processing factor | STMR-P in mg/kg |
| Tomato (STMR: 0.08 mg/kg) | Juice, raw | <0.17, 0.17 | 0.17 | 0.014 |
| | Puree | 0.79, 0.83, 0.86,0.9 | 0.85 | 0.068 |
| | Paste | 0.83, 1.1 | 0.97 | 0.078 |
| | Canned/preserve | <0.17(4) | 0.17 | 0.014 |
| | pomace, wet | 7.9, 7.9, 8.6, 9.7 | 8.3 | 0.66 |

### *Residues in animal commodities*

*Farm animal feeding studies*

The Meeting received feeding studies involving lufenuron on lactating cows and steers.

Three groups of lactating cows were dosed daily at levels of 0.82, 4.3 and 8.6 ppm in the diet for 28 consecutive days. Milk was collected throughout the whole study and tissues were collected on day 29 within 24 hrs after the last dose.

In milk residues of lufenuron were 0.16 mg/kg, 0.99 mg/kg and 2.5 mg/kg for the low, middle and high dose group, respectively. Skim milk and cream were analysed individually, showing residues of 0.006, 0.038 and 0.054 mg/kg for skim milk and 3.1, 24 and 32 mg/kg for cream.

In tissues mean concentrations of lufenuron with increasing dose rate were 0.03, 0.17 and 0.43 mg/kg in muscle, 0.06, 0.37 and 0.77 mg/kg in liver, 0.03, 0.22 and 0.36 mg/kg in kidney and 0.73, 4.5 and 8.0 mg/kg in fat.

In the steer study three groups of Angus steers were dosed 0.02 or 1 ppm in the diet for 28 consecutive days. Animals were sacrificed 24h after the last administrations (day 28).

Mean lufenuron residues in the low and high-dose animals were < 0.01 and < 0.01 mg/kg in muscle, < 0.01 and 0.023 mg/kg in liver, < 0.01 and 0.026 mg/kg in kidney and 0.036 and 0.23 mg/kg in fat, respectively.

*Estimated maximum and mean dietary burdens of livestock and animal commodities maximum residue levels*

Dietary burden calculations for beef cattle, dairy cattle, broilers and laying poultry are presented in Annex 6. The calculations were made according to the livestock diets from US-Canada, EU, Australia and Japan in the OECD Table (Annex 6 of the 2006 JMPR Report).

| | Livestock dietary burden, lufenuron, ppm of dry matter diet | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | US-Canada | | EU | | Australia | | Japan | |
| | max. | mean | max. | mean | max. | mean | max. | mean |
| Beef cattle | 0.02 | 0.02 | 0.34 | 0.34 | 0.02 | 0.02 | none | none |
| Dairy cattle | 0.02 | 0.02 | 0.34 [a] | 0.34 [b] | 0.02 | 0.02 | none | none |
| Poultry - broiler | none | none | 0.01 | 0.01 | none | none | none | none |
| Poultry - layer | none | none | 0.01 [c] | 0.01 [d] | none | none | none | none |

[a] Highest maximum beef or dairy cattle burden suitable for MRL estimates for mammalian meat and milk

[b] Highest mean beef or dairy cattle burden suitable for STMR estimates for mammalian meat and milk

[c] Highest maximum broiler or laying hen burden suitable for MRL estimates for poultry products and eggs

[d] Highest mean broiler or laying hen burden suitable for STMR estimates for poultry products and eggs

none - no relevant feed items

### *Animal commodities maximum residue levels*

For beef and dairy cattle a maximum and mean dietary burden of 0.34 ppm was estimated. Two feeding studies on lactating cows and steers were submitted. Since no accumulation of residues in steers compared to dairy cows was observed, the Meeting decided to base its recommendations for mammalian products on the lactating cow feeding study, generally showing higher residues at identical intake levels.

| Lufenuron feeding study | Feed level | Total residue | | | | |
|---|---|---|---|---|---|---|
| | (ppm) | (mg/kg) in milk | (mg/kg) in muscle | (mg/kg) in kidney | (mg/kg) in liver | (mg/kg) in fat |
| Maximum residue level: dairy cattle | | | | | | |
| Feeding study (HR for each dose group, except for milk) | 0.82 | 0.16 (cream: 3.1) | 0.04 | 0.04 | 0.07 | 1.2 |
| Dietary burden and residue estimate | 0.34 | 0.066 (cream: 1.2) | 0.017 | 0.017 | 0.029 | 0.5 |
| STMR dairy cattle | | | | | | |
| Feeding study (Mean for each dose group) | 0.82 | 0.16 (cream: 3.1) | 0.03 | 0.03 | 0.06 | 0.73 |
| Dietary burden and residue estimate | 0.34 | 0.066 (cream: 1.2) | 0.012 | 0.012 | 0.025 | 0.3 |

The Meeting estimated STMR values of 0.012 mg/kg for muscle, 0.025 mg/kg for edible offal (based on liver) and 0.3 for fat. Corresponding maximum residue levels were estimated at 0.04 mg/kg for edible offal, mammalian (based on liver) and 0.7 mg/kg for meat (based on the fat) and mammalian fat.

For milk, an STMR and a MRL of 0.066 mg/kg and 0.1 mg/kg were estimated, respectively. Based on the data for cream, the Meeting also estimated an STMR and MRL of 1.2 mg/kg and 2 mg/kg for lufenuron in milk fat, respectively.

For poultry a maximum and mean dietary burden of 0.01 ppm was estimated. No farm animal feeding studies were provided for poultry. Therefore the Meeting decided to make its recommendations based on the $^{14}$C-difluorophenyl-labelled poultry metabolism study which showed higher residues than the corresponding $^{14}$C-dichlorophenyl-labelled experiment.

| Lufenuron feeding study | Feed level | Total residue | | | | |
|---|---|---|---|---|---|---|
| | (ppm) | (mg/kg) in eggs | (mg/kg) in muscle | (mg/kg) in kidney | (mg/kg) in liver | (mg/kg) in fat |
| Mean and maximum residue level: poultry | | | | | | |
| $^{14}$C-difluorophenyl-labelled metabolism study | 3.4 | 2.5 [a] | 0.196 | 0.588 | 1.34 | 9.15 |
| Dietary burden and residue estimate | 0.01 | 0.01 | 0.0006 | 0.0017 | 0.004 | 0.027 |

[a] In the metabolism study egg white and egg yolk were analysed separately. To estimate residues in whole eggs, an average ratio of 65% egg white and 35% egg yolk was taken into account: 0.65 × 0.003 mg eq/kg in egg white + 0.35 × 7.18 mg eq/kg in egg yolk = 2.5 mg eq/kg in whole eggs

The Meeting estimated STMR values of 0.01 mg/kg for eggs, 0.0006 mg/kg for poultry meat, 0.004 mg/kg for poultry edible offal of (based on liver) and 0.027 mg/kg for poultry fat. Corresponding maximum residue levels for lufenuron were estimated at 0.02 mg/kg for eggs, poultry meat and edible offal of and at 0.04 mg/kg for poultry fat.

## RECOMMENDATIONS

On the basis of the data from supervised trials, the Meeting concluded that the residue levels listed in Annex 1 were suitable for estimating maximum residue limits and for IEDI assessment.

Definition of the residue for compliance with MRL and for dietary intake purposes for plant and animal commodities: *Lufenuron*

## FURTHER WORK OR INFORMATION

- Poultry feeding study

## DIETARY RISK ASSESSMENT

### *Long-term intake*

The evaluation of lufenuron has resulted in recommendations for MRLs and STMRs for raw and processed commodities. The International Estimated Daily Intakes for the 17 GEMS/Food cluster diets, based on this years estimated STMRs, were in the range 0–4% of the maximum ADI of 0.02 mg/kg bw. The results are shown in Annex 3 to the 2015 Report.

The Meeting concluded that the long-term intake of residues of lufenuron from uses that have been considered by the JMPR is unlikely to present a public health concern.

### *Short-term intake*

For short-term intake, an ARfD was considered unnecessary. The Meeting concluded that the short-term intake of lufenuron residues from uses considered by the Meeting is unlikely to present a public health concern.