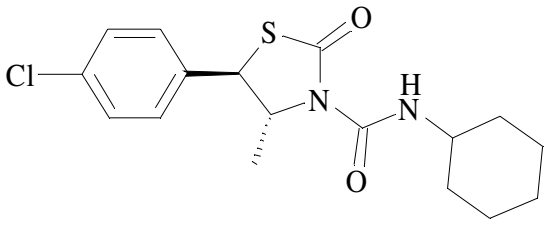
5.14 HEXYTHIAZOX (176)

RESIDUE AND ANALYTICAL ASPECTS

Hexythiazox is a non-systemic insecticide and miticide first evaluated by the 1991 JMPR and a number of times subsequently. It was recently reviewed for toxicology by the 2008 JMPR within the periodic review program of the CCPR. An ADI of 0–0.03 mg/kg bw was established. An ARfD was not considered necessary by the Meeting. In the 2009 JMPR hexythiazox is scheduled for periodic review for the residue section.

The Fortieth Session of the CCPR scheduled this compound for periodic evaluation by the 2009 JMPR (ALINORM 08/40/24, Appendix X). Information on GAPs was also provided by the Netherlands.



The following abbreviations are used for the metabolites discussed below:

hexythiazox	trans-5-(4-chlorophenyl)-N-cyclohexyl-4-methyl-2-oxo-3-thiazolidine-carboxamide
PT-1-2	tran-5-(4-chlorophenyl)-4-methyl-2-oxothiazolidine-3-carboxamide
PT-1-3	trans-5-(4-chlorophenyl)-4-methyl-2-oxothiazolidine
PT-1-4	trans-5-(4-chlorophenyl)-N-(cis/trans-3-hydroxycyclohexyl)-4-methyl-2-oxothiazolidine-3-carboxamide
PT-1-8	rans-5-(4-chlorophenyl)-N-(cis/trans-4-hydroxycyclohexyl)-4-methyl-2-oxothiazolidine-3-carboxamide
PT-1-10	trans-5-(4-chlorophenyl)-N-(3,4-dihydroxycyclohexyl)-4-methyl-2-oxothiazolidine-3-carboxamide

Animal metabolism

The Meeting received animal metabolism studies with ^{14}C-hexythiazox in rats, lactating goats and laying hens. Parent substance labelled in the 5-position of the thiazolidine ring was used in all of these studies. In general the metabolism of hexythiazox in animals is relatively limited. In all species the hydroxylation of the cyclohexane ring was the dominating biotransformation, resulting in the metabolites PT-1-4, PT-1-8 and PT-1-10. The cleavage of the amide bond was observed in rats only.

In the 2008 Evaluation for toxicology it was reported that in rats most of the administered radioactivity (60–90%) was excreted via the faeces. Depending on the dose level 10–20% (at 10 mg/kg bw dose) up to 65–70% (880 mg/kg bw dose) of the radioactivity was identified as unchanged parent substance. The highest concentrations of tissue residues were found in fat, adrenals, liver and ovaries; the main component in fat was hexythiazox. Metabolism of the absorbed dose was extensive, but most of the radioactive material was not attributed to specific metabolites. The main metabolic reactions identified were hydroxylation of the cyclohexane ring and cleavage of

the amide bond to the cyclohexane ring. The main identified metabolite was PT-1-8 (cis) representing approximately 10% of the administered radioactivity.

For lactating goats one animal was dosed with 46 mg per day (approx. 26 ppm or 1.16 mg/kg bw) for seven consecutive days. Most of the excretion of radioactivity was observed via faeces (56.2%) and urine (18.1%). In milk 0.3% of the administered dose (corresponding to approximately 0.1 mg/kg) was found. For the tissues liver was found with the highest TRR levels of 2.2 mg/kg. Kidney and fat contained 0.44 and 0.55 mg/kg, respectively. In muscle the lowest TRR levels of 0.11 mg/kg at maximum were measured. Identification of the radioactivity revealed unchanged parent hexythiazox as dominant residue in fat tissue and milk (61% TRR and 31% TRR, respectively). In liver, muscle and kidney hexythiazox was found at levels of 10% of the TRR or less. Most of the TRR was identified as PT-1-4 (cis) or PT-1-10 at levels up to 23% TRR and 36% TRR, respectively.

The metabolism of hexythiazox in laying hens was investigated using doses of 0.6 or 6 mg per animal per day for 6 consecutive days. In this case the highest residues were found in the eggs of the animals at levels of 0.5 mg/kg for the low dose group and 2.1 mg/kg for the high dosed animals. The highest residues in all tissues were detected in the liver, ranging from 0.14 mg/kg (low dose) up to 1.6 mg/kg (high dose). Kidney and fat tissues were in the same range of 0.06–0.07 mg/kg for the low dose group and 0.5 mg/kg for the high dose group. In muscle very low residues of 0.01 to 0.08 mg/kg were found. Identification of the radioactivity was conducted for eggs, liver and fat only. Eggs and liver gave very high unextracted residues in the range of 50% of the TRR. In the extracts the results were comparable to rats and lactating goats. In fat tissue most of the residue consisted of unchanged hexythiazox (48% of the TRR while in eggs and liver mainly hydroxylated metabolites (PT-1-8 and PT-1-10) were identified.

Plant metabolism

The Meeting received plant metabolism studies with [^{14}C]hexythiazox in apples, citrus, grapes, pears and tea. Parent substance labelled in the 5-position of the thiazolidine ring was used in all of these studies.

In general the biotransformation of hexythiazox is relatively slow. In most of the studies unchanged hexythiazox was the dominating residue found mainly on the surface. Following a period of three week a minor translocation into the plants of PT-1-2 and PT-1-3, the remaining cleavage products after removal of the cyclohexane ring, can be observed whereas parent hexythiazox remained nearly immobile.

In the study on apples, leaves and fruits were treated by micro pipette at a rate equivalent to a concentration of 5 g ai/hL. Leaf samples were taken 0, 10, 21, 30, 60 and 91 days after the application and single fruit samples 10, 20, 30 and 59 days after the application. In the surface wash as well as in the extracts of the samples unchanged parent compound was the dominant residue accounting for 73.7–94.9% of the TRR. The leaf extracts contained additional metabolites at rates of 0.4–0.7% of TRR for PT-1-2, 0.5–2.5% TRR for cis-PT-1-8 (including conjugates) and 1.8–6.8% TRR for trans-PT-1-8 (including conjugates). In apple fruits traces of PT-1-2 and PT-1-8 (trans) were found in levels of less than 1.2% of the TRR.

For citrus fruits a similar methodology as for apples was used. The application rate was at a comparable concentration of 5.3 g ai/hL. Samples of treated and untreated citrus leaves and fruits were taken 7, 14, 30, 60 or 62 and 90 or 91 days after the application. In the surface wash and the peel extract the concentration of hexythiazox decreased from 98.1% down to 30.5% of the applied dose after 91 days. The only metabolite identified in the surface wash was PT-1-2 (up to 1.0% TRR), which was also found in the peel extract at higher amounts (up to 3.3% TRR). In the peel extract free and conjugated PT-1-4 (trans-2), PT-1-6 (trans-2), PT-1-8 (cis) and PT-1-8 (trans) were found. The conjugated form was always present in at least 2-fold higher amounts. In total PT-1-4 (trans-2), PT-1-6 (trans-2), PT-1-8 (cis) and PT-1-8 (trans) including conjugates were found in concentrations of up to 7.0%, 4.3% and 13.7% of the TRR, respectively.

Grapes were treated twice with an amount of 0.1 kg ai/ha of labelled hexythiazox each. Sampling of the leaves and fruits was conducted 21 days after the final application, but only the fruits were analysed for radioactive residues. In the fruits TRR of 0.233 mg/kg could be found. 62.9% of the TRR was located in the surface of the fruits and was released with the surface wash. Nearly all of the radioactivity coeluated with the parent reference compound. The fruit extract contained about 31.4% of the TRR in total. Hexythiazox was detected in all phases (5.0–6.3% TRR), but unidentified peaks were present in higher concentrations (up to 12.1% of the TRR). In the remainings, hydrolysed using NaOH 11.2%, the TRR were identified as PT-1-3. In this study no confirmation of the identity of metabolites via mass spectrometric methods was conducted.

In pears the leaves and fruits of the trees were also treated by micro pipette at a rate equivalent to a concentration of 5 g ai/hL. Leaf samples were taken 0, 5, 10, 20, 30, 60 and 90 days after the application and fruit samples 0, 5, 10, 20, 30 and 60 days after the application. In the surface wash as well as in the peel extract of the fruits hexythiazox was identified as the dominant residue amounting 64.6–95.0% of the TRR. The metabolites PT-1-2, PT-1-4 (trans-2) and the cis and trans isomers of PT-1-8 were identified in the fruits, but none at levels of more than 2.3% of the TRR.

In the leaves a comparable distribution of the radioactive residues was observed. Unchanged hexythiazox was dominant in the surface extract (93.1–44.6% of the TRR). In leaf tissue higher amounts of metabolites were found in comparison to the fruits. The metabolite PT-1-2 was found at low levels of 1.2% of the TRR. Most of the radioactivity found was identified as PT-1-8 (cis) and PT-1-8 (trans) in their conjugated forms at amounts of up to 4.3% and 9.2% of the TRR, respectively.

For tea the plants were treated once at a rate of 0.2 kg ai/ha. Leaf specimens were collected at 0, 7, 14 and 21 days after the treatment. The TRR in the tea leaves did not change with increasing PHI. In all of the samples TRR levels of 8.17 to 9.03 mg/kg, calculated as parent equivalents, were found. In comparison to the 0 day PHI results, more of the radioactivity was found in the extracts rather than the surface wash in the later samples (93.2% surface wash at PHI 0 down to 55.3% at PHI 21). The identification of the radioactivity revealed very limited degradation of the parent substance. In all samples hexythiazox was the dominant residue found at levels of at least 84.5% of the TRR. The only metabolites identified were PT-1-2 and PT-1-8 (trans), each at levels of less than 0.3% of the TRR.

Environmental fate in soil

Hexythiazox is degraded in soil quite rapidly with half-life rates of about one month. The main metabolites found in soil consisted of cleavage products of the parent molecule (PT-1-3 and PT-1-2). Under consideration of a rotational crop study using unlabelled material a significant uptake by follow crops is not expected.

For the environmental fate of hexythiazox in soil one study on the aerobic metabolism is available. Estimated aerobic soil metabolism half-lives for hexythiazox at 20 °C ranged from 32.1 to 35.2 days. After 153 days mineralisation and unextracted residues were in the range of 10–12.2% and 19.7–23% of the radioactivity, respectively.

The metabolite PT-1-9 was formed in the early stage of the study, reaching its maximum concentration of 10.1–14.4% of the applied radioactivity after 31 days. PT-1-2 and PT-1-3 were found in the later samples reaching a plateau after 90 days at individual amounts of 34.2–39.5% and 7.5–9.2% of the applied dose.

In addition to soil metabolism a field rotational crop study was submitted to the Meeting. Bare soil was treated at rates of 0.21 kg ai/ha and incorporated into the soil before planting. After 30, 120 and 240 days lettuce, mustard, radish, sorghum and wheat were planted as follow crops. Except for one sample each of radish tops (0.046 mg/kg) and sorghum stover (0.014 mg/kg) no hexythiazox residues above the LOQ of 0.01 mg/kg were found (sum of hexythiazox and all metabolites hydrolysable to PT-1-3, expressed as hexythiazox).

No confined study on rotational crops was submitted to the Meeting. Given that cleavage of the molecule is the only significant transformation step observed in soil metabolism studies and the results of the analysis of all residues hydrolysable to PT-1-3 in the unlabelled study, the Meeting considered the residue situation in rotational crops to have been investigated sufficiently.

Methods of residue analysis

The Meeting received information on analytical methods for the determination of hexythiazox in plant and animal matrices.

In the methods hexythiazox is extracted with methanol and the partitioned into n-hexane. After partition between n-hexane and acetonitrile, the acetonitrile layer is concentrated to dryness. The residue is cleaned-up by Florisil PR Column chromatography and a C18 solid phase extraction column. Hexythiazox is determined by HPLC-UV at 225 nm. The LOQ was 0.05 mg/kg for all plant matrices. Analytical recovery data were satisfactory for hexythiazox in plant commodities. Residue methods were tested by independent laboratories unfamiliar with the analysis and were found to have satisfactory recoveries and no background interferences.

In supervised field trials an additional method was described measuring the total residue of hexythiazox including metabolites after hydrolysis with 0.1N NaOH into PT-1-3. The separation and detection of PT-1-3 is achieved via HPLC-UV. This method is applicable to plant and animal matrices, but no studies including validation data for animal material were submitted. In the corresponding field trials LOQs of 0.02 mg/kg were achieved.

For animal matrices the samples are extracted with methanol (muscle, kidney, liver and eggs) or acetone (milk and fat). The extract was then liquid/liquid partitioned, evaporated to dryness and hydrolysed with sodium hydroxide solution. After further cleaned up on a silica gel column PT-1-3 was determined by reversed phase HPLC and UV detection at 225 nm. The LOQ achieved in the validations was 0.05 mg/kg for all matrices.

Although no data on analytical multi-residue method for plant commodities were submitted to Meeting it is noted that hexythiazox parent substance is validated within the QuEChERS-Multimethod.

Stability of residues in stored analytical samples

Information was received on the freezer storage stability of hexythiazox residues in plant commodities.

The storage stability of hexythiazox was investigated in one study including homogenated samples with a fortification level of 0.5 or 1.0 mg/kg (strawberry, cucumber, water melon, grape, green pepper, mandarin orange pulp and whole fruits, pears and apples) as well as treated field samples, which were chopped instead of macerated (cucumber, strawberry, tea, Chinese citron peel and pulp and mandarin orange peel and pulp). All samples were stored at –30 °C for a period of one month up to 13 months, analysed for hexythiazox and compared to the nominal level of fortification. Expect for homogenised grapes (63% recovery) all samples were stable and gave recoveries of at least 70% of the initial dose.

For the storage stability of hexythiazox in animal commodities no data on the storage stability was submitted to the Meeting. Under consideration of a residue definition for hexythiazox involving all metabolites containing the PT-1-3-moiety, it was concluded by the Meeting that theoretical breakdown products of hexythiazox are also measured by the analytical method. In view of this estimation of the “total residue” further data on the storage stability of hexythiazox residues is not considered necessary.

Definition of the residue

The residue following use of hexythiazox on crops is predominantly unchanged hexythiazox. After 30 days at least 70% of the radioactivity was identified as parent substance mainly located on the plant surface. At higher PHI of 60 to 90 days 30% to 60% of the radioactivity was still present as hexythiazox. Metabolites identified were mainly hydroxylated at the cyclohexane ring (PT-1-4, PT-1-8 and PT-1-10), followed by cleavage and removal of the cyclohexane-ring forming PT-1-2 in amounts of less than 4% of the TRR after up to 90 days. The combined quantities of PT-1-4, PT-1-8 and PT-1-10 were at levels of less than 10% of the hexythiazox levels in all samples analysed. In summary at all sampling dates most of the residue was identified as unchanged hexythiazox parent located on the surface.

The hydroxyl-metabolites (PT-1-4 and PT-1-8) are not mutagenic in bacteria and are of low acute toxicity (oral LD_{50} > 5000 mg/kg bw). These metabolites, together with PT-1-10 are formed in rats. Although there are no repeat dose toxicity studies on these compounds, it is considered realistic to assume them to have similar toxicity to hexythiazox.

In soil, degradation of hexythiazox is dominated by a cleavage resulting mainly in PT-1-2. The uptake from the soil observed in field rotation studies is very limited, showing most residues below 0.01 mg/kg (measured as PT-1-3 after hydrolytic extraction). Only in radish tops (0.046 mg/kg) and sorghum stover (0.012 mg/kg) total hexythiazox residues, determined as PT-1-3 for analysis, were found above the LOQ of 0.01 mg/kg after 30 days.

Metabolite PT-1-3 is of greater acute toxicity than hexythiazox, while it is not mutagenic in bacteria there are no data on its toxicity after repeat dosing.

Following normal solvent extraction no PT-1-3 was identified in metabolism studies.

The Meeting was aware that according to the hydrolysis study, using aqueous buffer solutions parent hexythiazox in sterilised food commodities might be subject to a transformation into PT-1-3 to a certain extent. Quantitative data representing realistic processing conditions are not available, since all information is based on residues converted to PT-1-3 for analysis. In general the Meeting expects the contribution to dietary intake to be small in comparison to the overall intake.

The Meeting concluded parent hexythiazox is a representative marker for hexythiazox residues in all plant commodities and decided to set the residue definition for enforcement purposes in plant commodities to be parent hexythiazox only.

For dietary intake assessment the toxicological significant metabolites PT-1-4, PT-1-8 and PT-1-10, also identified in the rat, amounted in sum less than 10% of the TRR according to the results of metabolism studies using radiolabelled material. No data on the ratio between hexythiazox and all residues converted to PT-1-3 under field conditions were submitted. The plant specific metabolite PT-1-3 was not identified in any sample in plant metabolism studies and the Meeting considered it to be an analytical artefact. Although the low share of PT-1-4, PT-1-8 and PT-1-10 would not suggest an inclusion into the residue definition for risk assessment purposes of plant commodities normally, the Meeting acknowledged that no data besides metabolism studies are available to confirm this assumption. Taking into account a possible deviations in the rate of metabolisation under field conditions, the Meeting agreed to define the residue definition for intake purposes as “sum of hexythiazox and all metabolites containing the trans-5-(4-chlorophenyl)-4-methyl-2-oxothiazolidine-moiety (PT-1-3), expressed as hexythiazox” to cover all of the residue of toxicological concern.

In animals hexythiazox is also hydroxylated at various positions of the cyclohexane ring. A cleavage into PT-1-3 was not observed. In fatty tissues, milk and eggs hexythiazox was the dominant residue. Watery matrices like liver, kidney and muscle mainly contained a mixture of hydroxylated metabolites. Residues found in fatty tissues of goats and laying hens were by a factor of 5 to 8 times higher in comparison to muscle. For milk (skim milk ↔ cream) and eggs (egg white ↔ egg yolk)

higher residues of total PT-1-3 were found in the fat, based on the livestock feeding studies submitted. Due to overall low residues a ratio could not be estimated.

For animal matrices the metabolism results in a higher percentage of hydrolysed metabolites with hexythiazox being found at very low levels or even below the LOQ. In addition, no analytical methods for the parent substance alone are available, as well as livestock feeding studies analysed for single substances instead of the total residues determined as PT-1-3. In view of these factors the Meeting concluded that the residue definition (for risk assessment and enforcement) for hexythiazox in animal matrices is sum of hexythiazox including all metabolites hydrolysable to PT-1-3, expressed as hexythiazox. The residue is considered as fat soluble.

Definition of the residue (for compliance with MRLs) for plant commodities: *hexythiazox*

Definition of the residue (for estimation of dietary intake) for plant commodities: *sum of hexythiazox and all metabolites containing the trans-5-(4-chlorophenyl)-4-methyl-2-oxothiazolidine-moiety (PT-1-3), expressed as hexythiazox*

Definition of the residue (for compliance with MRLs and for estimation of dietary intake) for animal commodities: *sum of hexythiazox and all metabolites containing the trans-5-(4-chlorophenyl)-4-methyl-2-oxothiazolidine-moiety (PT-1-3), expressed as hexythiazox*

The residue is fat-soluble.

Results of supervised residue trials on crops

The Meeting received supervised residue trials data for hexythiazox on citrus (grapefruit, lemons, mandarins and oranges), almonds, pecan, apples, pears, stone fruit (cherries, nectarines, peaches and plums), blackberries, grapes, raspberries, strawberries, dates, tomatoes, cucumbers, melons, sweet corn, fresh beans, succulent beans, dry beans, cotton, hops and corn.

In trials where duplicate field samples from replicated or unreplicated plots were taken at each sampling time and analysed separately, the sample with higher residues was taken as the best estimate of the residue from the plot. Supervised field trials conducted with different formulations at identical varieties, locations and dates were not considered as independent. The highest result according to the corresponding GAP was selected in these cases.

Labels (or translation of labels) were available from the Netherlands and USA describing the registered uses of hexythiazox.

The NAFTA calculator was used as a tool in the estimation of the maximum residue level from the selected residue data set obtained from trials conducted according to GAP. As a first step, the Meeting reviewed all relevant factors related to each data set in arriving at a best estimate of the maximum residue level using expert judgement. Then, the NAFTA calculator was employed. If the statistical calculation spreadsheet suggested a different value from that recommended by the JMPR, a brief explanation of the deviation was supplied. Some common factors that may lead to rejection of the statistical estimate include when the number of data points in a data set is < 15 or when there are a large number of values < LOQ.

Citrus fruits

Hexythiazox is registered in the USA for use on citrus fruits at a rate of 1 × 0.2 kg ai/ha with a PHI of 28 days. Supervised residue trials conducted in the US on grapefruits, lemons and oranges according to this GAP were submitted.

For whole grapefruits residues were (n=6): < 0.05, < 0.05, 0.05, 0.06, 0.16 and 0.18 mg/kg. The distribution between pulp and whole fruits was not measured.

In whole lemons fruits residues were (n=5): 0.06, 0.1, 0.15, 0.2 and 0.29 mg/kg. The distribution between pulp and whole fruits was not measured.

For whole oranges residues were (n=6): < 0.05, 0.06, 0.11, 0.11, 0.12 and 0.2 mg/kg. The distribution between pulp and whole fruits was not measured.

For mandarins and oranges additional field trials conducted in Southern Europe were submitted, but no corresponding GAP is available. Since these trials contained analytical results for whole fruits and pulp, the data from day 14 is used to estimate the residue ratio between both matrices. Individual ratios were (n=5) < 0.56, < 0.63, < 0.71, < 0.83 and < 0.83. Additional trials are available, but no residues above the LOQ were found in whole fruits as well as in citrus pulp. The Meeting estimated a factor of 0.7 for the ratio of residues between whole citrus fruits and citrus pulp.

The Kruskal-Wallis-Test for grapefruits, lemons and oranges (residues below the LOQ were treated as residues at the LOQ) indicated that the residue populations were not significantly different and may be combined.

The Meeting decided to combine the US data for grapefruits, lemons and oranges for the whole group of citrus fruits, resulting in residues of < 0.05(3), 0.05, 0.06(3), 0.1, 0.11, 0.11, 0.12, 0.15, 0.16, 0.18, 0.2, 0.2 and 0.29 mg/kg for the whole fruits (n=17). Under consideration of the ratio of 0.7 between the residues in whole fruits and citrus pulp an STMR value of 0.077 mg/kg was estimated by the Meeting.

The Meeting confirmed the previous recommendation on a maximum residue level for hexythiazox in citrus fruits of 0.5 mg/kg (whole fruit) and estimated an STMR value for hexythiazox in citrus fruit of 0.077 mg/kg (pulp).

The value derived from use of the NAFTA calculator of 0.45 mg/kg (95/99 95th percentile) was in good agreement with the estimate of 0.5 mg/kg made by the Meeting (after rounding up to one significant figure).

Pome fruit

For pome fruit hexythiazox is registered in the USA at rates of 1 × 0.2 kg ai/ha with a PHI of 28 days. Supervised residue trials conducted in the US on apples and pears according to this GAP were submitted.

For apples residues were (n=15): 0.05, 0.05, 0.08, 0.08, 0.09(3), 0.11, 0.11, 0.12, 0.15, 0.16, 0.2, 0.21 and 0.21 mg/kg.

In pears residues were (n=6): 0.06, 0.06, 0.1, 0.11 and 0.16 mg/kg.

Based on the results for apples the Meeting estimated a maximum residue level and an STMR value for hexythiazox in pome fruits of 0.4 and 0.11 mg/kg, respectively.

The value derived from use of the NAFTA calculator of 0.35 mg/kg was in good agreement with the estimate of 0.4 mg/kg made by the Meeting (after rounding up to one figure (NAFTA 95/99 95th percentile)).

The Meeting withdraws its previous recommendations of maximum residue levels of 0.5 mg/kg for hexythiazox in apples and pears.

Stone fruit

Hexythiazox is registered on stone fruit in the USA with an application rate of 1 × 0.2 kg ai/ha with a PHI of 28 days. Supervised residue trials conducted in the US on cherries, nectarines and peaches according to this GAP were submitted.

For cherries residues were (n=4): 0.04, 0.06, 0.08 and 0.12 mg/kg.

For nectarines residues were (n=3): 0.05, 0.05 and 0.09 mg/kg.

For peaches residues were (n=3): 0.09, 0.09 and 0.18 mg/kg.

Additional trials on plums and other stone fruit were submitted, but the PHI of 7 days was below the registered GAP in the US.

The Meeting decided to combine the data for nectarines and peaches treated according to US GAP , resulting in residues of 0.05, 0.05, 0.09(3) and 0.18 mg/kg (n=6).

Considering the supportive data for cherries the Meeting estimated a maximum residue level and an STMR value for hexythiazox in stone fruits of 0.3 and 0.09 mg/kg, respectively.

The value derived from use of the NAFTA calculator was 0.3 mg/kg, which agreed with the maximum residue level of 0.3 mg/kg estimated by the current Meeting.

The Meeting withdraws its previous recommendations of maximum residue levels for hexythiazox of 1 mg/kg in cherries, 1 mg/kg in peaches and 0.2 mg/kg in plums (including prunes).

Currants (red, white)

Hexythiazox is registered in the USA on currants at a rate of 0.21 kg ai/ha with a PHI of 3 days. Supervised residue trials submitted on blackberries and raspberries were conducted with an application rate of 0.42 kg ai/ha with a PHI of 21 days.

The Meeting noted that the data from USA does not match GAP and can not be used for a maximum residue level estimation. The Meeting withdraws its previous recommendations for currants (red, white) of 0.2 mg/kg.

Grapes

For grapes hexythiazox is registered in the USA at a rate of 1 × 0.2 kg ai/ha with a PHI of 28 days. Corresponding supervised residues trials were conducted according to the maximum GAP with two formulations in the US.

For grapes residues were (n=12): 0.04, 0.04, 0.05, 0.13, 0.13, 0.19, 0.21, 0.22, 0.24, 0.31, 0.31 and 0.48 mg/kg.

Additional supervised field trials were submitted for Europe, but no corresponding GAPs are available.

The Meeting confirms its previous recommendation of a maximum residue level of 1 mg/kg and estimated an STMR value for hexythiazox in grapes of 0.2 mg/kg.

An estimate of 1 mg/kg, derived from the use of the NAFTA calculator, was in agreement with the maximum residue level estimated by the current Meeting.

Strawberries

Hexythiazox is registered in the USA on strawberries at a rate of 0.21 kg ai/ha with a PHI of 3 days. Corresponding supervised residues trials were conducted according to the maximum GAP with two formulations in the US. Residues found in strawberries were (n=3): 0.13, 0.17 and 0.3 mg/kg.

The Meeting noted that the data from USA for strawberries, representing a major crop, were not sufficient for a maximum residue level estimation. The Meeting withdraws its previous recommendation for strawberries of 0.5 mg/kg.

Dates

In dates hexythiazox is used according to US GAP with an application rate of 0.21 kg ai/ha and a PHI of 90 days. Corresponding supervised residues trials were conducted according to the maximum GAP in the US. Residues found in dates were (n=3): 0.11, 0.26 and 0.63 mg/kg.

The Meeting estimated a maximum residue level and an STMR value for hexythiazox in dates of 2 and 0.26 mg/kg, respectively.

An estimate of 2 mg/kg, derived from the use of the NAFTA calculator, was in agreement with the maximum residue level estimated by the current Meeting.

Tomatoes

For protected tomatoes hexythiazox is registered in the Netherlands with an application rate of 1 × 0.08 kg ai/ha (0.005 kg ai/hL) with a PHI of 3 days. Supervised residue trials on protected tomatoes corresponding to the maximum GAP are available from France and Italy. Residues found in the fruits were (n=8): < 0.05(6), 0.05 and 0.05 mg/kg.

The Meeting confirmed the maximum residue level for hexythiazox in tomatoes of 0.1 mg/kg and estimated an STMR value of 0.05 mg/kg.

Statistical calculations were not conducted, as the majority of reported residue levels were below the LOQ.

Egg plant

Hexythiazox is registered in the Netherlands for protected eggplants with an application rate of 1 × 0.08 kg ai/ha (0.005 kg ai/hL) with a PHI of 3 days. No supervised residue trials on eggplants were submitted to the Meeting.

The Meeting decided that tomatoes can be extrapolated to eggplants. Based on the residue data for tomatoes the Meeting estimated a maximum residue level and an STMR value for hexythiazox in eggplants of 0.1 and 0.05 mg/kg, respectively.

Sweet corn

For sweet corn supervised residue trials were submitted to the Meeting although no corresponding GAP is available.

The Meeting concluded that maximum residue levels on sweet corn could not be estimated without a corresponding GAP.

Fruiting vegetables, Cucurbits (except watermelon)

For cucumbers hexythiazox is registered in the Netherlands for field and glasshouse use with an application rate of 1 × 0.08 kg ai/ha (0.005 kg ai/hL) with a PHI of 3 days. Supervised residue trials on protected cucumbers corresponding to the maximum GAP are available from Italy, Spain and the Netherlands. Residues found in the fruits were (n=8): < 0.05(8) mg/kg.

Hexythiazox is registered in the Netherlands for protected melons (except water melons) with an application rate of 1 × 0.08 kg ai/ha (0.005 kg ai/hL) with a PHI of 3 days. Supervised residue trials on protected melons corresponding to the maximum GAP are available from France, Spain and the Netherlands.

Residues found in melon whole fruits were (n=8): < 0.05(8) mg/kg.

Residues found in melon pulp were (n=8): < 0.05(8) mg/kg.

Hexythiazox is registered in the Netherlands for protected summer squash with an application rate of 1 × 0.08 kg ai/ha (0.005 kg ai/hL) with a PHI of 3 days. No supervised residue trials on squashes were submitted to the Meeting.

Hexythiazox is registered in the Netherlands for protected winter squash with an application rate of 1 × 0.08 kg ai/ha (0.005 kg ai/hL) with a PHI of 3 days. No supervised residue trials on squashes were submitted to the Meeting.

The Meeting decided that data for cucumbers can be extrapolated to summer squash and data for melons to winter squash. Based on the identical residue data for protected cucumbers and melons the Meeting estimated a maximum residue level and an STMR value for hexythiazox in fruiting vegetables, cucurbits expect water melons of 0.05 and 0.05 mg/kg, respectively.

Statistical calculations were not possible, since all reported residue levels were below the LOQ.

The Meeting withdraws its previous recommendation of maximum residue levels of 0.1 mg/kg for hexythiazox in cucumbers.

Common beans (pods and/or immature seeds)

For common beans (pods and/or immature seeds) supervised residue trials were submitted to the Meeting although no corresponding GAP is available.

The Meeting withdraws its previous recommendation of maximum residue levels of 0.5 mg/kg for hexythiazox in common beans (pods and/or immature seeds).

Pulses

For pulses supervised residue trials were submitted to the Meeting although no corresponding GAP is available.

The Meeting concluded that maximum residue levels on pulses could not be estimated without corresponding GAP.

Maize

Hexythiazox is registered in maize in the USA with an application rate of 1 × 0.2 kg ai/ha with a PHI of 45 days. Supervised residue trials conducted in the US were available using one application at rates of 0.21 or 1.1 kg ai/ha and PHIs of 79 up to 110 days, which did not match the US GAP.

The Meeting noted that the data from USA did not match GAP for maize and could not be used to estimate a maximum residue level.

Tree nuts

In tree nuts hexythiazox is registered in the USA at a rate of 1 × 0.2 kg ai/ha with a PHI of 28 days. Supervised field trials were conducted in the US at rates of 0.25 kg ai/ha up to 0.42 kg ai/ha on almonds and pecan with a PHI of 28 and 29 days. For almonds residues were (n=2): < 0.02 and < 0.02 mg/kg. In pecans residues of < 0.02(5) mg/kg were found.

The Meeting estimated a maximum residue level based on the LOQ of the analytical method for hexythiazox parent of 0.05(*) mg/kg. Under consideration of the non-systemic properties the Meeting estimated an STMR value of 0 mg/kg for hexythiazox in tree nuts.

Statistical calculations were not possible, as all reported residue levels were below the LOQ.

Cotton

For cotton hexythiazox is registered in the USA (California only) at a rate 1 × 0.17 kg ai/ha with a PHI of 35 days. Supervised field trials from the US were submitted involving two applications in an

2–3 months interval with 0.17 to 0.21 kg ai/ha each and a PHI of 28–35 days. Residues found in the ginned seeds were (n=3): 0.07, 0.1 and 0.1 mg/kg.

The Meeting noted that the data from USA for cotton were not sufficient for a maximum residue level estimation.

Hops

Hexythiazox is registered in the USA for hops with an application rate of 1 × 0.21 kg ai/ha without a specified PHI. In one supervised field trials according to GAP residues in hops were (n=1): 1.9 mg/kg

The Meeting noted that the data for hops from USA was insufficient for a maximum residue level estimation and withdraws its previous recommendation of 2 mg/kg for hexythiazox in dry hops.

Almond hulls

In almonds hexythiazox is registered in the USA at a rate of 1 × 0.2 kg ai/ha with a PHI of 28 days. Supervised field trials were conducted in the US at rates of 0.25 kg ai/ha on almonds with a PHI of 28 days. For almond hulls residues were (n=2): 1.2 and 1.4 mg/kg.

The Meeting noted that the data for almond hulls from USA was insufficient for a maximum residue level estimation.

Cotton gin trash

For cotton hexythiazox is registered in the USA at a rate 1 × 0.17 kg ai/ha with a PHI of 35 days. Supervised field trials from the US were submitted involving two applications in an 2–3 months interval with 0.17 to 0.21 kg ai/ha each and a PHI of 28 days. Residues found in gin trash were (n=3): 1.5, 1.6 and 2.3 mg/kg.

The Meeting noted that the data from USA for cotton gin trash was insufficient to give any recommendation.

Maize forage

Hexythiazox is registered for use in maize in the USA with an application rate of 1 × 0.2 kg ai/ha and a PHI of 45 days. Supervised residue trials conducted in the US were available using one application at a rate of 0.21 kg ai/ha with a PHI of 44 to 49 days. Residues found in maize forage were (n=5): 0.13, 0.58, 0.91, 1.1 and 1.7 mg/kg.

The Meeting estimated an STMR value and a highest residue value for hexythiazox in maize forage of 0.91 and 1.7 mg/kg, respectively.

Maize stover

For maize stover, hexythiazox is registered in the USA with an application rate of 1 × 0.2 kg ai/ha with a PHI of 45 days. Supervised residue trials conducted in the US, using one application at rates of 0.21 kg ai/ha with a PHI of 79 up to 110 days, did not match the US GAP.

The Meeting noted that as the data from the USA did not match GAP for maize it could not be used for a recommendation.

Fate of residues during processing

The Meeting received information on the fate of hexythiazox residues during processing of oranges, grapes, plums and cotton seeds. Also information was provided on hydrolysis studies with hexythiazox to assist with identification of the nature of the residue during processing. Processing

factors presented below have been calculated for hexythiazox for all commodities relevant to trade and/or the dietary intake estimation. Further data on processed commodities are presented in the evaluation for this active substance.

Hexythiazox was stable at pH4, 80 °C for 20 minutes and pH5, 100 °C for 60 minutes, simulating pasteurisation and cooking of commodities. Under simulated sterilisation conditions (pH6, 120 °C for 20 minutes) hexythiazox degraded into PT-1-3, leaving only half of the initial concentration in the test solutions.

Raw agricultural commodity (RAC)	Processed commodity	Calculated processing factors	Median or best estimate [a]
Oranges	Juice	< 0.05, < 0.07, 0.22, 0.26, 0.3	0.22
	Marmalade	0.11, 0.14, 0.27	0.14
	Pulp, dry	1.8, 2.7	2.3
Grapes	Wine, red	< 0.02, < 0.1	< 0.06
	Wine, white	< 0.02, < 0.09	< 0.06
	Juice, red	0.08, 0.75	0.42
	Juice, white	< 0.02, 0.14	0.08
	Raisins	0.52, 1.4, 1.7, 3.3	1.6
	Pomace, wet	3.4, 16.6	10
Plums	Prunes, dried	4.8, 5	4.9

[a] processing factors presented are based on the total residue hydrolysable to PT1-3

Oranges were processed into juice, marmalade and dry pulp. Processing factors were 0.22, 0.14 and 2.3, respectively. Based on the median residue of 0.11 mg/kg for whole citrus fruits, STMR-P values for hexythiazox residues were 0.024 mg/kg in orange juice, 0.015 mg/kg in marmalade and 0.25 mg/kg in dry pulp.

Grapes were processed into red and white wine, red and white juice, raisins and wet pomace. Processing factors were < 0.06 for wine (red and white combined), 0.42 for juice (based on red juice), 1.6 for raisins and 10 for wet grape pomace. Based on the STMR value of 0.2 mg/kg for grapes STMR-P values for hexythiazox were 0.01 mg/kg for wine (red and white), 0.084 mg/kg for grape juice, 0.32 mg/kg for raisins and 2 mg/kg for wet pomace.

Based on the average dry-matter content of grape pomace, wet of 15% the Meeting estimated a maximum residue level of 15 mg/kg for grape pomace, dry.

Plums were processed into prunes, resulting in a processing factor of 4.9. Based on the STMR of 0.09 mg/kg for stone fruit a STMR-P value of 0.44 mg/kg for dried prunes was estimated.

Based on the highest residue of 0.18 mg/kg for stone fruit and the processing factor of 4.9 for dried prunes, the Meeting estimated a maximum residue level of 1 mg/kg and an STMR-P value of 0.44 mg/kg for hexythiazox in dried prunes.

Residues in animal commodities

Livestock dietary burden

The Meeting received lactating dairy cow and laying hens feeding studies which provided information on likely residues resulting in animal commodities, milk and eggs from hexythiazox residues in the animal diet.

Lactating dairy cows

In a study two lactating cows were dosed over a period of 14 consecutive days with hexythiazox at rates of 12 mg or 120 mg per animal and day. Milk was collected over the whole study period. After the dosage period the animals were kept 8 days for withdrawal before being sacrificed. Samples of fat, muscle, kidney and liver were taken for analysis. All samples were analysed for the sum of hexythiazox and its metabolites, determined as PT-1-3. In none of the samples residues above the limit of quantification of 0.05 mg/kg were found.

In a second study twelve lactating Holstein cows were divided into four groups receiving doses of 0, 5, 15 or 50 ppm hexythiazox for a period of 28 consecutive days. One animal of each dose group was kept for an additional withdrawal period of 7 days. During the whole period of time samples of milk were collected. After the withdrawal period the animals were sacrificed and samples of fat, liver, kidney and muscle were taken. All samples were analysed for the sum of hexythiazox and its metabolites, determined as PT-1-3. In the groups receiving doses of 0, 5 or 15 ppm per day, no residues above the LOQ of 0.01 mg/kg were found in any sample expect liver (0.06 mg/kg), kidney (0.01 mg/kg) and renal/omental fat (0.01 mg/kg). For the dose group 50 ppm residues in milk were slightly above the LOQ (< 0.01–0.02 mg/kg). The separation into skim milk and cream revealed that most of the residue is found in the fat fraction. No residues above the LOQ of 0.01 mg/kg were found in skim milk, while in cream levels ranging from 0.02 to 0.1 mg/kg were found. Highest residues were found in the liver, going up to 0.186 mg/kg in the 50 ppm dose group.

Laying hens

For laying hens the animals were separated into four groups receiving doses of 0, 5, 15 or 50 ppm hexythiazox for 28 consecutive days. Each group consisted of four subgroups with four animals each. For each dose group one subgroup was kept 7 additional days for withdrawal. During the whole period of time eggs were collected. At the end of the dose period the animals were sacrificed and samples of fat, muscle, liver and kidney were taken. All samples were analysed for the sum of hexythiazox and its metabolites, determined as PT-1-3. In eggs residues were found in all dose groups ranging from < 0.01 to 0.058 mg/kg for the 5 ppm group up to 0.03 to 0.36 mg/kg for the 50 ppm group. A separate analysis of egg white and egg yolk on day 20 reveals higher residues in the yolk by a factor of 1.7 to 2.5. In muscle no residues above the LOQ of 0.01 mg/kg could be detected. Highest residues in the tissues were found in liver and fat. Residues were 0.03 mg/kg and 0.05 mg/kg for the 5ppm group, 0.07 mg/kg and 0.08 mg/kg for the 15ppm group and 0.12 mg/kg and 0.17 mg/kg for the 50 ppm group, respectively.

Estimated maximum and mean dietary burdens of livestock

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 and Australia in the OECD Table (Annex 6 of the 2006 JMPR Report).

	Livestock dietary burden, hexythiazox, ppm of dry matter diet					
	US-Canada		EU		Australia	
	max.	mean	max.	mean	max.	mean
Beef cattle	1.7	0.9	3.5	1.9	6.1[a]	4.5[b]
Dairy cattle	2.2	1.2	3.0	1.4	6.1	4.5
Poultry—broiler	0	0	0	0	0	0

	Livestock dietary burden, hexythiazox, ppm of dry matter diet					
	US-Canada		EU		Australia	
	max.	mean	max.	mean	max.	mean
Poultry—layer	0	0	0.4[c]	0.2[d]	0	0

[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 layer poultry burden suitable for MRL estimates for poultry meat and eggs

[d] Highest mean broiler or layer poultry burden suitable for MRL estimates for poultry meat and eggs

Animal commodities, MRL estimation

In the table below, dietary burdens are shown in round brackets (), feeding levels and residue concentrations from the feeding studies are shown in square brackets [] and estimated concentrations related to the dietary burden are shown without brackets.

Dietary burden (ppm) Feeding level [ppm]	Milk/Eggs	Muscle	Liver	Kidney	Fat
HR	mean	highest	highest	highest	highest
HR beef or dairy cattle (6.1) [5, 15]	Milk 0.01 [< 0.01, < 0.01]	0 [< 0.01, < 0.01]	0.03 [< 0.01, 0.09]	0.02 [0.02, 0.02]	0.01 [< 0.01, 0.01]
HR laying hens (0.4) [5]	Eggs 0.004 [0.05]	0 [< 0.01]	0.002 [0.03]	0.01 [< 0.01]	0.004 [0.05]
STMR	mean	mean	mean	mean	mean
STMR beef or dairy cattle (4.5) [5, 15]	Milk 0.01 [< 0.01, < 0.01]	0 [< 0.01, < 0.01]	0.01 [< 0.01, 0.06]	0.01 [0.01, 0.01]	0.01 [< 0.01, 0.01]
STMR laying hens (0.2) [5]	Eggs 0.002 [0.05]	0 [< 0.01]	0.001 [0.02]	0.01 [< 0.01]	0.002 [0.05]

In lactating cows as well as in laying hens no residues above the LOQ of 0.05 mg/kg for the analytical method for enforcement purposes were estimated. The Meeting estimated maximum residue levels for mammalian meat (fat), eggs, milk, milk fat, edible offal (mammalian) and poultry edible offal of 0.05 mg/kg. For poultry meat (fat) the Meeting estimated a maximum residue level of 0.05(*) mg/kg.

The Meeting estimated an STMR value for hexythiazox in whole milk of 0.01 mg/kg. The separation of skim milk and cream was conducted for the 50ppm dose group revealing residues up to 0.1 mg/kg in the fat. Under consideration of the maximum dietary burden of 5.7 ppm the Meeting also estimated an STMR value of 0.01 mg/kg for hexythiazox in milk fat.

The residue arising from a dietary burden of 5.7 ppm was 0.01 mg/kg in the fat. Since the target tissue for hexythiazox residues in animal tissues is fat, the Meeting estimated an STMR value of 0.01 mg/kg for mammalian meat (fat basis). For mammalian meat (muscle) the Meeting estimated an STMR value of 0 mg/kg.

In kidney and liver the Meeting estimated STMR values 0.01 mg/kg, respectively.

For eggs the Meeting estimated an STMR value of 0.002 mg/kg. In poultry tissues STMR values were estimated at levels of 0.01 mg/kg for poultry edible offal of, 0.002 mg/kg for poultry meat (fat) and 0 mg/kg for poultry meat (muscle).

DIETARY RISK ASSESSMENT

Long-term intake

The evaluation of hexythiazox resulted in recommendations for MRLs and STMR values for raw and processed commodities. Where data on consumption were available for the listed food commodities, dietary intakes were calculated for the 13 GEMS/Food Consumption Cluster Diets. The results are shown in Annex 3.

The IEDIs in the thirteen Cluster Diets, based on the estimated STMRs were 0–2% of the maximum ADI (0.03 mg/kg bw). The Meeting concluded that the long-term intake of residues of hexythiazox from uses that have been considered by the JMPR is unlikely to present a public health concern.

Short-term intake

The 2008 JMPR decided that an ARfD is unnecessary. The Meeting therefore concluded that the short-term intake of hexythiazox residues is unlikely to present a public health concern.