# Dossier According to Directive 91/414/EEC

# TERPENOID BLEND (A-TERPINENE, P-CYMENE, D-LIMONENE) QRD 460

**Active substance for insect pest control developed from plant extract of** *Chenopodium ambrosioides* near *ambrosioides*

## DOCUMENT MII, Section 4

## METABOLISM AND RESIDUES DATA

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# 6 METABOLISM AND RESIDUES DATA

Terpenoid Blend (α-terpinene, p-cymene, and d-limonene) QRD 460 is a new active substance developed by AgraQuest Inc. based originally on the naturally occurring extract of the plant species *Chenopodium ambrosioides* near *ambrosioides* for use as an insecticide plant protection product.

To defend themselves against herbivores and pathogens, plants naturally release a variety of volatiles including various alcohols, terpenes and aromatic compounds. These volatiles can deter insects or other herbivores from feeding, can have direct toxic effects on pests, or they may be involved in recruiting predators and parasitoids in response to feeding damage (Ashour *et al*. 2010). They may also be used by the plants to attract pollinators, protect plants from disease, or they may be involved in interplant communication. As these properties have been known and observed for a very long time, it is a natural progression that three such terpenes, α-terpinene, p-cymene, and d-limonene, have been identified as candidates for biopesticidal use. In the original plant extract the three terpene compounds in combination are the source of insecticidal activity: as this naturally occurring combination is the key active moiety, they are considered and termed to be one active substance. This consideration was agreed at the DG SANCO Phytopharmaceutical Standing Committee meeting 26-27 November 2009 for QRD 420, which contains the same active substance as QRD 460.

The original plant extract (QRD 406) was registered by US EPA as a biopesticide in April 2008. The initial active substance and product was based on a plant extract of *Chenopodium ambrosioides* near *ambrosioides*. The essential oil was harvested from the plant biomass using steam distillation. Variability in growing conditions for the plants meant this active substance suffered from variability in the concentration of the three constituent active terpenes and so an alternative, QRD 460 was developed which is an optimized blend of the three terpenes that reflects the proportions found in the original plant extract QRD 406.

AgraQuest Inc. has submitted this application for approval of the new active substance QRD 460 and its product, QRD 452 respectively, for registration in the EU with ctgb Netherlands as the Rapporteur Member State. It is an insecticide for use on tomatoes and peppers in glasshouses and cucurbits in glasshouses and field at a maximum application rate of 1.523 kg a.s./ha up to 3 times with a 7 day interval between treatments.

**Table 6-1: EU Critical GAP for QRD 460 use on Tomatoes, Peppers and Cucurbits**

| Region | Outdoor/ Protected | Max. No. of Applications | Application Interval (days) | Max. Application | | Minimum PHI (days) |
|---|---|---|---|---|---|---|
| | | | | Rate (kg as/ha) | Water (L/ha) | |
| N EU | Protected | 3 | 7 | 0.381 – 1.523 | 400 - 1000 | 0 |
| S EU | Protected | 3 | 7 | 0.381 – 1.523 | 400 - 1000 | 0 |
| S EU | Outdoor | 3 | 7 | 0.762 – 1.523 | 400 - 1000 | 0 |

The mode of action of the product is considered non-toxic. Based on laboratory and field trial observations, the mechanism for controlling insect pests is considered to be through degradation of soft insect cuticles resulting in a disruption of insect mobility and respiration. This is considered to occur by direct contact and localized fumigant action. For further details, please refer to document MIII, Section 7, Point 6.

It is noteworthy that these terpenes, α-terpinene, p-cymene, and d-limonene, are commonly used as fragrances and flavourings (Joint FAO/WHO Expert Committee on Food Additives, & WHO Technical Report Series 928.). They are present in abundance in many herb plants, and are common in many other edible plants such as citrus fruits, tomatoes, celery and carrots, with various functions as secondary metabolites (Ashour, *et al*, (2010)). Consequently they are a ubiquitous part of both human and animals' natural diet and it is reasonable to expect regular contact with them in the environment without any concern.

All three terpenes are also found, to a greater or lesser extent, in the following EU registered or pending active substances: tea tree oil, thyme oil, orange oil, citronella, spearmint oil, and tagetes (marigold) oil.

Due to the chemical nature of the terpenes, they disperse rapidly via volatilization and leave little to no residues. This means that the standard EU registration approach for residue trials would be inappropriate and so a small number of specialised studies have been performed and presented here to characterise the activity of the QRD 460 active substance components and clearly demonstrate the lack of residues.

Three studies are presented here under Section 4 metabolism and residues, the storage stability of the residues samples under Point 6.1.1 (extracted from the study under Point 6.3.1), residues decline in tomatoes under Point 6.3.1, residues in mustard greens under Point 6.3.3 and residues in primrose under Point 6.3.4.

To aid evaluation of the dossier, the code designations are described so that it is clear which test substance was used for each study. All substances listed are considered substantially equivalent.

**Code Designations**

The various AgraQuest code designations that relate to the active substance, products and the submitted documents are as follows:

QRD 406 = *Chenopodium ambrosioides* near *ambrosioides* plant extract technical grade active ingredient (tgai) – consisting of the three terpenes as the active component plus plant derived impurities. Three terpenes comprise approximately 68% of QRD 406.

QRD 400 = formulated EC product with 25% plant extract (QRD 406) active ingredient, 75% other formulants (Also known as FACIN 25EC in some reports and registered in the USA as Requiem® 25EC and Metronome™.) The three terpenes in QRD 400 comprise approximately 17%.

QRD 420 = blended tgai using the three terpenes in the same concentrations as found in QRD 406 with plant derived impurities replaced with canola oil. The three terpenes comprise approximately 67% of QRD 420.

QRD 416 = formulated EC product with 25% blended (QRD 420) a.i., 75% other formulants (same formulants in the same concentrations as QRD 400). The three terpenes comprise approximately 16.75 % of QRD 416.

QRD 452 = QRD 416 – due to a code designation error, the product was re-coded as QRD 452. There are a few studies that reference QRD 416, but the composition is identical to QRD 452. (Also known and registered in the USA as Requiem® EC and Metronome™ EC). The concentration of the three terpenes in QRD 416 and QRD 452 is 16.75%.

QRD 460 = Blended tgai without canola oil. This contains only the three terpenes. The proportions of the three terpenes are essentially the same as the plant extract tgai minus plant derived impurities. So, less QRD 460 is required in Requiem® EC (QRD 452), 16.75% instead of 25%. The percentage of each terpene in QRD 452 and QRD 400 are the same.

# IIA 6.1 Stability of residues

## IIA 6.1.1 Stability of residues during storage of samples

| | |
|---|---|
| **Report:** | IIA 6.1.1/01. [redacted] RL; [redacted] WB (2005). Raw Agricultural Commodity (RAC) Residue Decline of FACIN 25% EC Applied to Tomato, Analytical Phase. Wildlife International, Ltd. Project ID 44815A001, **Reported as Appendix III** of [redacted] DR (2005). Raw Agricultural Commodity (RAC) Residue Decline of FACIN 25% EC Applied to Tomato. Landis International, Inc. Project ID 44815A001 |

**Guidelines**

EPA Guideline OPPTS No. 860.1500

**GLP**

Signed and dated GLP and Quality Assurance statements were provided.

There were no deviations considered to compromise the scientific validity of the study.

**Executive Summary**

A study to demonstrate the stability of α-terpinene, p-cymene and d-limonene residues in tomato was conducted during 2004.

Stability of residues under freezer conditions was assessed by fortification of untreated tomato matrix at a concentration of 0.0500 mg as/Kg for of α-terpinene, p-cymene and d-limonene. Control samples of tomato were fortified and analysed following freezer storage at three intervals (Days 0, 14 and 28). The analysis set consisted of control and two samples fortified at 0.0500 mg as/Kg with each analyte. Stored samples were retained in the same freezer as field samples. Analysis comprised GC separation followed by MS detection. Residues of α-terpinene, p-cymene and d-limonene did not show any indication of significant degradation under freezer conditions for at least 28 days. The maximum storage interval for field-harvested samples was 27 days.

# I. MATERIALS AND METHODS

## A. MATERIALS

### A1. Test Materials

| Test Material | α-terpinene | ρ-cymene | d-limonene |
|---|---|---|---|
| Batch No. | 054088/1 | 11119LA | 016151/1 |
| Purity | 97.1% | 99.4% | 99.9% |

### A2. Test Commodities

The test commodity used was tomato matrix.

### A3. Test Facility

This study was performed at [redacted].

## B. STUDY DESIGN AND METHODS

### B1. Test Procedure

Control samples of tomato were fortified and analysed following freezer storage at three intervals (Days 0, 14 and 28). The analysis set consisted of control and two samples fortified at 0.0500 mg as/Kg with each analyte. Stored samples were retained in the same freezer as field samples.

### B1. Analytical Procedures

GC separation followed by MS detection.

# II. RESULTS AND DISCUSSION

Recoveries of residues of α-terpinene, p-cymene and d-limonene are shown in table 6.1.1-3.

**Table 6.1.1-3: Stability of α-terpinene, p-cymene and d-limonene in Tomato extract following Freezer Storage**

| Sample Preparation Day | Sample Analysis Day | Measured Concentration (mg as/Kg) | | | Percent recovered (%) | | |
|---|---|---|---|---|---|---|---|
| | | α-terpinene | p-cymene | d-limonene | α-terpinene | p-cymene | d-limonene |
| 0 | 0 | 0.0528 | 0.0495 | 0.0482 | 106 | 99.0 | 96.3 |
| | | 0.0483 | 0.0488 | 0.0426 | 96.6 | 97.6 | 85.2 |
| 0 | 14 | 0.0377 | 0.0377 | 0.0330 | 75.3 | 75.3 | 65.9 |
| | | 0.0350 | 0.0421 | 0.0368 | 69.9 | 84.3 | 73.6 |
| 14 | 14 | 0.0519 | 0.0468 | 0.0409 | 104 | 93.7 | 81.8 |
| | | 0.0474 | 0.0479 | 0.0405 | 94.7 | 95.9 | 81.0 |
| 0 | 28 | 0.0338 | 0.0365 | 0.0342 | 67.7 | 73.0 | 68.3 |
| | | 0.0360 | 0.0381 | 0.0495 | 72.1 | 76.1 | 99.0 |
| 28 | 28 | 0.0471 | 0.0434 | 0.0386 | 94.3 | 86.7 | 77.1 |
| | | 0.0451 | 0.0440 | 0.0385 | 90.3 | 87.9 | 77.0 |

## III. CONCLUSIONS

Residues of α-terpinene, p-cymene and d-limonene did not show any indication of significant degradation under freezer conditions for at least 28 days. The maximum storage interval for field-harvested samples was 27 days.

The three constituent molecules in QRD 460, α-terpinene, p-cymene and d-limonene, readily volatilise as explained under point 6.3, and have been shown to be non-detectable on leaf surfaces 10 minutes after application; therefore, it is proposed that no additional residue trials for any further crops be required.

## IIA 6.1.2 Stability of residues in sample extracts

Not relevant for the studies presented.

# IIA 6.2 Metabolism, distribution and expression of residues

**Background information**

The plant from which the original extract was derived, *Chenopodium ambrosioides* near *ambrosioides,* is a common plant in the US, Mexico, and Central America and is used as a spice and herb in cooking. This plant and many others, contain the three terpenes identified in the active substance QRD 460. As such, these terpenes are naturally occurring and commonly found in citrus fruits, nutmeg and celery, caraway and mint, thyme and many other edible plants.

In more detail, α-terpinene, p-cymene and d-limonene, are three structurally similar hydrocarbons that are classified as monoterpenes. Monoterpenes are a class of terpenes that consist of two connected isoprene units and have a molecular formula of $C_{10}H_{16}$. Biochemical modifications such as oxidation or rearrangement produce the related monoterpenoids. α-Terpinene and d-limonene are classical monoterpenes having the molecular formula $C_{10}H_{16}$, whereas p-cymene with a molecular formula of $C_{10}H_{14}$ is technically considered to be a related monoterpenoid.

Reviewing the literature, α-terpinene has been isolated from cardamon and marjoram oils, and from other natural sources, including carrots, blackberries, and raspberries ([redacted], 2011).

p-Cymene is a constituent of a number of essential oils, most commonly the oil of cumin and thyme, and in other natural sources such as carrots, tomatoes, potatoes, and raspberries.

d-Limonene takes its name from the lemon (*Citrus limonum)*, as the rind of the lemon, like other citrus fruits, contains considerable amounts of this compound, which contributes to their odour. Limonene is a chiral molecule, and biological sources produce just one enantiomer; the principal industrial source, citrus fruit, contains d-limonene ((+)-limonene), which is the (*R*)-enantiomer. d-Limonene is usually obtained commercially by extraction from orange peel with liquid $CO_2$ and has a wide and varied number of uses in fragrances, cleaning agents, food stuffs, flavourings, pesticides, etc.

From a literature review, a summary table of the amounts found and the references to which they correspond is presented below in Table 6.2-1 ([redacted] 2011).

Natural levels of α-terpinene were found up to 0.1 mg/kg, of ρ-cymene up to 0.2 mg/kg, and of d-limonene up to 30 g/kg (note the change in units) and these are from a small selection of references found where quantitative measurements were made. Levels of d-limonene in citrus far exceed the highest human exposure values anticipated from the proposed pesticide use of QRD 460. For this reason, it would be reasonable to conclude that running the usual consumer risk models or performing additional residue testing on crops is not necessary.

**Table 6.2-1. Naturally occurring residues of d-Limonene, p-Cymene and α-Terpinene in Crops**

| Crop | Terpene | Residue (mg/kg [ppm]) |
|---|---|---|
| Orange Carrots[1] | α-terpinene<br>p-cymene<br>limonene | 0.010 ± 0.001<br>0.057 ± 0.014<br>0.236 ± 0.039 |
| Purple Carrots[1] | α-terpinene<br>p-cymene<br>limonene | 0.002 ± 0.001<br>0.017 ± 0.008<br>0.066 ± 0.008 |
| Yellow Carrots[1] | α-terpinene<br>p-cymene<br>limonene | 0.020 ± 0.004<br>0.004 ± 0.001<br>0.049 ± 0.007 |
| White Carrots[1] | α-terpinene<br>p-cymene<br>limonene | 0.116 ± 0.028<br>0.209 ± 0.068<br>0.638 ± 0.073 |
| Strawberries[2] | Limonene | 0.0013 ± 0.005 (Chandler cultivar)<br>0.0007 ± 0.0003 (Sweet Charlie cultivar) |
| Tomatoes[3] | p-cymene<br>p-cymene<br>p-cymene<br>p-cymene<br>p-cymene | 0.001 ± 0.001 (Moneyberg cultivar)<br>0.002 ± 0.001 (Motelle cultivar)<br>0.006 ± 0.005 (Mogeor cultivar)<br>0.010 ± 0.005 (Monalbo cultivar)<br>0.007 ± 0.004 (Pitenza cultivar) |
| Potatoes[4] | p-cymene<br>limonene<br>limonene<br>limonene | 0.0024 (in flowering stage)<br>0.0096 (in sprouting stage)<br>0.0096 (foliage in tuberization stage)<br>0.0216 (in flowering stage) |
| Blackberries[5] | α-terpinene<br>limonene | 0.008 ± 0.0002 to 0.063 ± 0.001 (various cultivars)<br>0 to 0.352 ± 0.003 (various cultivars) |
| Red Raspberries[5] | α-terpinene | 0.034 ± 0.004 to 0.080 ± 0.010 (Meeker cultivar) |
| Red Raspberries[6] | α-terpinene<br>p-cymene<br>limonene | 0.004 ± 0.003 to 0.025 ± 0.005<br>0.014 ± 0.001 to 0.024 ± 0.003<br>0.002 ± 0.0001 – 0.0004 |
| Apples (Fuji)[7] | d-limonene | 0.0008 to 0.0017 |
| Sweet Cherries[8] | Limonene | 0.001 to 0.0042 (12 different cultivars) |
| Lemon[9,10] | d-limonene | 13,384 |
| Grapefruit[9,10] | d-limonene | 10,873 |

| | | |
|---|---|---|
| Orange[9,10] | d-limonene | 4,063 |

[1-10] These references are given in [redacted], 2011 listed in references

For the crops on which QRD 460 has been tested (presented here as the "untreated" sample), low natural levels have been detected, but these are clearly variable:

**Tomato (p55 of report)**
Untreated – sampled (one value each) at 0 and 6 hrs and 1 day

| | α-terpinene (mg/kg) | p-cymene (mg/kg) | d-limonene (mg/kg) |
|---|---|---|---|
| 0 hrs | <LOQ | <LOQ | <LOQ |
| 6 hrs | <LOQ | <LOQ | 0.0213 |
| 1 day | <LOQ | <LOQ | 0.0122 |

**Mustard Greens (p20 of report)**
Untreated had one rep for each 'PHI' 0, 1 and 4 hrs (the treatments had 2 reps)

| | α-terpinene (mg/kg) | p-cymene (mg/kg) | d-limonene (mg/kg) |
|---|---|---|---|
| 0 hrs | <0.05 | 0.05 | <0.05 |
| 1 hrs | <0.05 | 0.13 | 0.10 |
| 4 hrs | <0.05 | 0.09 | <0.05 |

The three terpenes were not detected in the primrose trial untreated samples.

**Metabolism of Terpenoid blend (α-terpinene, ρ-cymene, d- limonene) QRD 460**

QRD 460 active substance is a mixture of three terpenes: α-terpinene, p-cymene, and d-limonene. The chemical structures of terpenes are simple and their key properties are that they readily volatilise into air where they breakdown in a relatively short time and are not soluble in water. Their metabolism and residue behaviour are directly influenced by these properties.

The metabolism of, QRD 460 has not been explicitly investigated using the standard study protocols because the three terpenes are well known, naturally occurring constituents of many fruits and herbs and other edible plants. Therefore humans and the environment are constantly exposed to them naturally via food, medicine and essential oils and cultivation and via the natural environment at levels far exceeding the potential exposure levels from the proposed plant protection use.

As such, any metabolism and distribution of α-terpinene, ρ-cymene and d- limonene in plants forms the natural and normal part of plant growth and development, contributing much to the aromatics of numerous citrus fruits, herbs and spices. Their metabolism is considered not to be relevant because, in general terms, exposure is not going to be as a result of the application as a plant protection product.

When QRD 460 is applied to plants, it may trigger plant defence responses but it is not yet clear that it enters them so breakdown in the usual pattern is not expected. The activity of QRD 460 and its product is closer to a type of localized fumigant that after application volatilizes rapidly ([redacted], (2011) Fate of d-Limonene, α-Terpinene and p-Cymene in Air, Soil and Water, Unpublished) from the surface of the treated plant leaving little or no residue. This is confirmed in the studies presented here under Point 6.3 where no residue of α-terpinene, ρ-cymene and d-limonene could be detected on or in the plants to which it was applied, between 1-24 hours after application. Therefore it is reasonable to conclude that further exploration of the metabolism in plants with respect to the plant protection use of QRD 460 is unnecessary.

The volatilization mechanism of dispersal and lack of environmental residues is discussed in further detail in Annex II, Section 5, Point 7, the Environmental Fate section.

## IIA 6.2.1 Metabolism in plants

After application of the diluted product containing QRD 460, the three terpenes rapidly volatilize from the surface of the plants. This process was demonstrated in the studies summarized under Point 6.3.

The results of a residue decline study, Point 6.3.3, performed for AgraQuest Inc. with the QRD 452 product and QRD 400 showed that residues of the three QRD 460 terpene components declined to non-detectable levels within one hour after foliar application on mustard greens at 2.9 kg a.s./ha (QRD 400) and 2.69 kg a.s./ha (QRD 452) which is above the maximum proposed EU application rate of 1.523 kg a.s./ha. The product was applied three times at specified intervals and the plants were sampled at 0, 1, and 4 hours after the third application. The rates applied are greater than the maximum use rate for the EU, but are considered representative for the purposes of this submission..

This finding was similar to the results of a residue decline study, Point 6.3.4, conducted by AgraQuest Inc. with the original plant extract based product (QRD 400) which showed that residues of the three major terpene components declined to non-detectable levels within 10 minutes of 3 foliar applications on primrose at a rate much greater than the proposed EU rate. Plants were sampled at intervals after each application. Consistent results were obtained after each application. Essentially, by the time the leaves had dried, there was no detectable residual product. Thus, the potential for any post-application oral exposure is virtually non-existent and supports a case that exposure to residual product should be of minimal concern and that the plant protection product does not enter plants in any significant fashion and therefore does not breakdown inside them via the usually assumed pathways.

Results of the primrose study are consistent with and supported by a third residue decline study conducted with QRD 400 on tomatoes, Point 6.3.1. The tomato study demonstrated rapid dissipation of the three terpenes at 0, 3, 6, 12, and 24 hr post-treatment. All constituents were less than the limit of quantitation (<LOQ) of 0.01 mg/kg at all time intervals. The product was applied four times using an application rate of 2.01 kg a.s./ha which is above the highest rate proposed in the EU.

In summary, results of the primrose, tomato and mustard green studies demonstrate that multiple applications of the formulated product QRD 452 or the original plant extract product at rates greater than the highest proposed EU rate resulted in NO detection of residues even shortly after application and no accumulation of residues over multiple applications.

No residues of the product are expected to occur at the time of harvest because the active substance is volatile and dissipates soon after application. Data from residue studies clearly demonstrates that the active substance is not detectable shortly after application, regardless of the rate or number of multiple applications applied, and as such will not be present or detectable at the time of harvest.

On this basis, it can be proposed that no meaningful residues remains on the plant material after application of the QRD 460 product and so it is not expected for QRD 460 to be effectively available to metabolise in plants from the proposed crop protection use.

Due to its ubiquitous nature, rapid volatilization from the plant surface, and the lack of residue ([redacted], 2011), no metabolism study has been performed and it is proposed that, due to the known presence of the three terpenes in many edible plants, further investigation of the metabolism of QRD 460 for plant protection use would not bring any further benefit to the consumer risk assessment.

It is also proposed that it would not be appropriate to set an MRL as all QRD 460 constituents are commonly occurring in many herbs and edible plants and are widely eaten by humans. The plant protection use of QRD 460 adds no significant residue exposure to that from other natural food sources of exposure.

## Expression of residues

As all three terpenes in the active substance QRD 460 are naturally occurring in a broad assortment of edible plants, have been shown to dissipate rapidly in the environment via volatilization, and studies have shown that the plant protection use of the active substance leave little to no residue shortly after application, it is reasonable to conclude that the expression of residues does not warrant further consideration.

## IIA 6.2.2 Poultry

Not relevant as no residue exposure from the plant protection use of QRD 460.

## IIA 6.2.3 Lactating ruminants (goat or cow)

Not relevant as no residue exposure from the plant protection use of QRD 460.

## IIA 6.2.4 Pigs

Not relevant as no residue exposure from the plant protection use of QRD 460.

## IIA 6.2.5 Nature of residue in fish

Not relevant as no residue exposure from the plant protection use of QRD 460.

## IIA 6.2.6 Chemical identity (emphasis on impurities of residual concern)

Not relevant as no residues or impurities identified shortly after application from the plant protection use of QRD 460.

## IIA 6.3 Residue trials

Crop residue trials have not been conducted in Europe. However, data are available from two GLP compliant trials conducted in California, one on outdoor grown tomatoes, the second on outdoor grown mustard greens. In addition supporting data are presented from a study with primrose conducted according to the principles of GLP but unaudited. Further, it is well known that these three terpenes rapidly volatilise ([redacted], 2011) and break down in air, which makes analytical detection after spray application difficult.

Results of the primrose, tomato and mustard green studies demonstrate that multiple applications of QRD 452 or the original plant extract product, resulted in no detectable residues even shortly after application and no accumulation of residues over multiple applications.

No detectable residues of the product are expected after application or at the time of harvest because the active substance is volatile and dissipates soon after application. Data from the available residue studies clearly demonstrate that the active substance is not detectable shortly after application and as such will not be present at the time of harvest. It is therefore concluded that it is not necessary to conduct any further standard crop residues trials on tomato and pepper or other crops.

Future crops on which QRD 460 may be applied should also be exempted from the need for specific residue studies.

## IIA 6.3.1 Residues in Tomatoes

QRD 460 is intended for use on tomatoes grown as outdoor and protected crops in Europe.

**Table 6.3.1-1: EU Critical GAPs for QRD 460 use on Tomatoes**

| Region | Outdoor/ Protected | Max. No. of Applications | Application Interval (days) | Max. Application | | Minimum PHI (days) |
|---|---|---|---|---|---|---|
| | | | | Rate (kg as/ha) | Water (L/ha) | |
| N EU | Protected | 3 | 7 | 0.381 – 1.523 | 400 - 1000 | 0 |
| S EU | Protected | 3 | 7 | 0.381 – 1.523 | 400 - 1000 | 0 |
| S EU | Outdoor | 3 | 7 | 0.381 – 1.523 | 400 - 1000 | 0 |

Residue trials on tomatoes have not been conducted in Europe. However, data are available from a trial conducted on outdoor grown tomatoes in California. The trial was conducted using 'FACIN 25EC', also known as QRD 400. The composition of QRD 400 is essentially the same as QRD 452 with respect to the three active substance terpenes and hence results generated using QRD 400 can be considered to be substantially similar to QRD 452. Full compositional details for both formulations can be found in Document J as this information is confidential.

**Table 6.3.1–2: Report Reference for Residue Trial on Tomatoes**

| Annex Pt. | Number | Author/s | Trial Year | Report Title |
|---|---|---|---|---|
| IIA 6.3.1/01 | (1 of 1) | [redacted] DR | 2005 | Raw Agricultural Commodity (RAC) Residue Decline of FACIN 25% EC Applied to Tomato. Landis International, Inc. Report No. 44815A001 |

**Guidelines**

US EPA Guideline: OPPTS 860.1500

**GLP**

Trial (field and analytical phases) was carried out according to the principles of GLP.

The results from this trial are summarised in Table 6.3.1-3 below.

**Table 6.3.1-3: Residues of α-terpinene, p-cymene and d-limonene in/on tomato Treated with FACIN 25% EC**

| GLP and Trial Details | Crop (variety) | Region/Country | Application Rate (g as/ha) | Growth Stage at Application | PHI (h – hours d -days) | Crop Part | Residue (mg/kg) | | | Recovery Data |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | α-terpinene | p-cymene | d-limonene | |
| 860.1500-04-448-15B-01 | Tomato (Ace 55 VF) | California/USA | 2010 | (1) | 0 h | Fruit | <LOQ | <LOQ | 0.0179 | 81.5%, 86.6% and 71.9% for α-terpinene, p-cymene and d-limonene at 0.01 ppm fortication.<br><br>98.5%, 95.7% and 95.1% for α-terpinene, p-cymene and d-limonene at 0.100 ppm fortication. |
| | | | 2010 | (2) | 0 h | | <LOQ | <LOQ | <LOQ | |
| | | | 2010 | (3) | 3 h | | <LOQ | <LOQ | 0.0100 | |
| | | | 2010 | (4) | 6 h | | <LOQ | <LOQ | <LOQ | |
| | | | | | 10 h | | <LOQ | <LOQ | <LOQ | |
| | | | | | 1 d | | <LOQ | <LOQ | 0.0136 | |
| | | | | | 1 d | | <LOQ | <LOQ | 0.0108 | |
| | | | | | 2 d | | NA | NA | NA | |
| | | | | | 3 d | | NA | NA | NA | |
| | | | | | 5 d | | NA | NA | NA | |
| | | | | | 7 d | | NA | NA | NA | |
| | | | | | 9 d | | NA | NA | NA | |
| | | | | | 11 d | | NA | NA | NA | |
| | | | | | 14 d | | NA | NA | NA | |

(1) 20% of fruits show typical fully ripe colour
(2) 20% of fruits show typical fully ripe colour
(3) 25% of fruits show typical fully ripe colour
(4) 25-30% of fruits show typical fully ripe colour
NA Not Analysed

**Materials and Methods**

Four foliar applications of FACIN 25EC were made to the treated plot at a target rate of 2.010 kg as/Ha (814 g as/A), resulting in a total seasonal application of 8.04 kg as/Ha (3256 g as/A) and using an application volume of 483 ± 22.47 L/ha (43 ± 2 Gallons per Acre). The interval between applications was 5 days and samples were collected for analysis immediately after the last application (once spray deposits had dried) and at 3, 6 and 10 hours and 1, 2, 3, 5, 7, 9, 11 and 14 days after the last application (DALT).

Samples were shipped frozen and analysed within 27 days. Following extraction α-terpinene, p-cymene and d-limonene, residues were quantified after GC separation by MS detection. A limit of quantitation (LOQ) of 0.01 mg/kg was determined for each of the three compounds.

**Findings**

No terpenes were detected in any non-treated samples except for d-limonene which was seen in various non-treated as well as some treated samples. This terpene presence was due to background levels of d-limonene present in tomatoes since it was seen in some (but not all) non-treated as well as in some treated samples at or near the LOQ. Other than naturally occurring d-limonene, there were no residues of the active substance (α-terpinene, p-cymene or d-limonene) found in any sample attributable to the test substance.

**Conclusion**

Residue trials on tomatoes have not been conducted in Europe. However, data are available from a trial conducted on outdoor grown tomatoes in California. This trial demonstrates that no residues will be detected following application of QRD 452, even when sampled immediately following application. Therefore, it is not necessary to conduct the full set of residues trials usually required to establish an MRL.

## IIA 6.3.2 Residues in Peppers

**Table 6.3.2-1: EU Critical GAPs for QRD 460 use on Peppers**

| Region | Outdoor/ Protected | Max. No. of Applications | Application Interval (days) | Max. Application | | Minimum PHI (days) |
|---|---|---|---|---|---|---|
| | | | | Rate (kg as/ha) | Water (L/ha) | |
| N EU | Protected | 3 | 7 | 0.381 – 1.523 | 400 - 1000 | 0 |
| S EU | Protected | 3 | 7 | 0.381 – 1.523 | 400 - 1000 | 0 |
| S EU | Outdoor | 3 | 7 | 0.381 – 1.523 | 400 - 1000 | 0 |

The GAP for peppers is the same as that for tomatoes.

Residue trials on peppers have not been conducted in Europe. However, data are available from a trial conducted on outdoor grown tomatoes in California and tomato trials may be extrapolated to cover peppers. This trial demonstrates that no residues, apart from naturally occurring levels of α-terpinene, p-cymene or d-limonene will be detected following application of QRD 452 even when sampled immediately following application. Therefore it is not necessary to conduct the full set of residues trials usually required. See Annex point IIA 6.3.1 above for details.

## IIA 6.3.3 Residues in Mustard Greens

This study was conducted to provide residue data for insecticide products containing a proprietary mixture of terpene compounds on mustard greens to support registration requirements. The trial was conducted with QRD 400 and QRD 416 which contain equivalent amounts of the three terpenes to QRD 452. Full compositional details are included in Document J as this information is confidential.

**Table 6.3.3-1: Report Reference for Residue Trial on Mustard Greens**

| Annex Pt. | Number | Author/s | Trial Year | Report Title |
|---|---|---|---|---|
| IIA 6.3.3/01 | (1 of 1) | [redacted] JM, [redacted] M | 2007 | QRD 400/QRD 416: Residue levels of Terpenes in Mustard Greens from a Trial Conducted in California during 2007. SynTech Research, Inc. Report/Study No. 77SRU07R-1 |

**Guidelines**

US EPA Guideline: OPPTS 860.1500

**GLP**

The trial (field and analytical phases) was carried out according to the principles of GLP.

**Materials and Methods**

Three separate applications of QRD 400 or QRD 416 were made to the crop at 10 and 5 days before harvest and at harvest. Both formulations are emulsifiable concentrates containing equivalent concentrations of the three terpenes and were applied at rates of 2914.21 g as/ha (2.6 lb as/A) for QRD 400 and 2690.03 g as/ha (2.4 lb as/A) for QRD 416. Duplicate samples of mustard greens were collected at 0, 1 and 4 hours after the last treatment and were kept frozen for 26 days until analysis. Samples were analysed with a GC/MS method. The residue method had an LOQ of 0.05 mg/kg.

The results from this trial are summarised in Tables 6.3.3-2 and 6.3.3-3 below.

**Table 6.3.3-2: Residues of α-terpinene, p-cymene and d-limonene in/on Mustard Greens Treated with QRD 400**

| GLP and Trial Details | Crop (variety) | Region/Country | Application Rate (g as/ha) | Growth Stage at Application | PHI (h – hours) | Crop Part | Residue (mg/kg) | | | Recovery Data |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | α-terpinene | p-cymene | d-limonene | |
| Study No. 77SRU07R-1 | Mustard Greens (Florida Broadleaf) | California/USA | 2914.21<br>2914.21<br>2914.21<br>2914.21 | Not Reported | 0 h<br>0 h<br>1 h<br>1 h<br>4 h<br>4 h | Leaves | 6.17<br>0.81<br><0.05<br><0.05<br><0.05<br><0.05 | 7.86<br>1.41<br><0.05<br><0.05<br><0.05<br><0.05 | 6.43<br>1.13<br>0.06<br>0.05<br><0.05<br><0.05 | Average recoveries 73% α-terpinene, 91% p-cymene, 99% d-limonene (for fortification levels 0.00, 0.05, 0.10 and 30.0 mg/kg) |

**Table 6.3.3-3: Residues of α-terpinene, p-cymene and d-limonene in/on Mustard Greens Treated with QRD 416**

| GLP and Trial Details | Crop (variety) | Region/Country | Application Rate (g as/ha) | Growth Stage at Application | PHI (h – hours) | Crop Part | Residue (mg/kg) | | | Recovery Data |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | α-terpinene | p-cymene | d-limonene | |
| Study No. 77SRU07R-1 | Mustard Greens | California/USA | 2690.03<br>2690.03<br>2690.03<br>2690.03 | Not Reported | 0 h<br>0 h<br>1 h<br>1 h<br>4 h<br>4 h | Leaves | 2.80<br>1.00<br><0.05<br><0.05<br><0.05<br><0.05 | 2.41<br>0.96<br><0.05<br><0.05<br><0.05<br><0.05 | 2.06<br>0.82<br><0.05<br><0.05<br><0.05<br><0.05 | Average recoveries 73% α-terpinene, 91% p-cymene, 99% d-limonene (for fortification levels 0.00, 0.05, 0.10 and 30.0 mg/kg) |

**Findings**

The individual terpene levels ranged from 6.17 to 7.86 mg/kg immediately following the third application of QRD 400 and from 2.06 to 2.80 for QRD 416. The residues showed very rapid dissipation to <0.05 mg/kg (LOQ of the method) at 1 and 4 hours after the last application except for one sample at 1 hour that contained 0.06 mg/kg of d-limonene.

**Conclusion**

Residues of the three terpene components declined to non-detectable levels within one hour after foliar application of QRD 400 or QRD 416 on Mustard Greens.

## IIA 6.3.4 Residues in Primrose

This study was conducted to obtain original data supporting the use of FACIN 25% EC on greenhouse grown ornamental plants and other crops. Specifically the study is designed to provide data on residue levels for the time period from zero to three hours following application.

**Table 6.3.4-1: Report Reference for Residue Trial on Primrose (*Primula acaulis*)**

| Annex Pt. | Number | Author/s | Trial Year | Report Title |
|---|---|---|---|---|
| IIA 6.3.4/01 | (1 of 1) | [redacted] J. et al. | 2007 | Persistence of FACIN 25% EC on Primrose (Primula acaulis) AgraQuest Study No. AQ 07-020. |

**Guidelines**

US EPA Guideline: OPPTS 860.1500

**GLP**

The trial (field and analytical phases) was carried out according to the principles of GLP but was not audited.

**Materials and Methods**

Three consecutive foliar applications of FACIN 25% EC were made on a five-day interval. Greenhouse-grown Primula acaulis (Primrose) were sprayed at a rate equal to 4% FACIN 25% EC, in 100 gallons of water per acre (equivalent to 3,785 L as/A or 9.35 L as/ha). Immediately following each of the spray applications, primrose plants were removed from the spray chamber and leaf samples were harvested. In addition to time zero collections, leaf disks were collected five, 15, and 30 minutes after spraying. Additional samples were collected one, three, and 24 hours after treatment. Leaf samples consisted of six leaf disks removed from sprayed leaves using a 1.4 cm diameter brass cork borer. Six leaf disks were added to 1.8ml of acetonitrile in brown glass vials with Teflon closures. Three replicates were collected for each time point during each spray event. Leaf disk harvest was initiated at the determined time point and completed in less than two minutes. Leaf samples were stored at 4ºC for less than a week until analyzed.

Three terpenes, α-terpinene, ρ-cymene and d-limonene and the internal standard 4-terpineol were quantified using gas chromatography. A limit of quantitation (LOQ) of 1.0 µg/ml (parts per million = ppm) was determined for each of the three compounds. The estimated limit of detection (LOD) for all three compounds was ~0.01µg/ml, each.

In contrast, similar plants and spray methods were used to evaluate the persistence of Lannate WP® insecticide (Methomyl; S-Methyl-N-[(methylcarbamoyl)oxy] thioacetamide). Residues of this product were detected.

**Table 6.3.4-2: Residues of α-terpinene, p-cymene and d-limonene in/on Primrose (*Primula acaulis*) Treated with FACIN 25% EC**

| GLP and Trial Details | Crop (variety) | Region/ Country | Application Rate (L as/ha) | Growth Stage at Application | PHI (m – mins, h – hours) | Crop Part | Residue (µg/ml)# | | | Recovery Data |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | α-terpinene | p-cymene | d-limonene | |
| AQ 07-020 | Primrose (Garden Music, ColorSpot) | Protected study, California/USA | Treatment 1 9.35 | 6-12 leaves | 0 m | Leaves | 6.58 | 8.08 | 5.22 | Recovery of residues from leaf disks, fortified and stored cold, did not show any significant degradation of analyte at 4º C. |
| | | | | | 5 m | | 0.82 | 2.94 | 0.81 | |
| | | | | | 15 m | | 0.00 | 0.00 | 0.06 | |
| | | | | | 30 m | | 0.33 | 0.45 | 0.31 | |
| | | | | | 1.5 h | | 0.00 | 0.00 | 0.00 | |
| | | | | | 3 h | | 0.00 | 0.00 | 0.00 | |
| | | | | | 24 h | | 0.00 | 0.00 | 0.00 | |
| | | | Treatment 2 9.35 | | 0 m | | 4.76 | 5.76 | 3.06 | |
| | | | | | 5 m | | 1.60 | 2.24 | 1.12 | |
| | | | | | 15 m | | 0.00 | 0.00 | 0.00 | |
| | | | | | 30 m | | 0.00 | 0.00 | 0.00 | |
| | | | | | 1.5 h | | 0.00 | 0.00 | 0.00 | |
| | | | | | 3 h | | 0.00 | 0.00 | 0.00 | |
| | | | | | 24 h | | 0.00 | 0.00 | 0.00 | |
| | | | Treatment 3 9.35 | | 0 m | | 3.57 | 3.65 | 2.57 | |
| | | | | | 5 m | | 0.40 | 0.33 | 0.32 | |
| | | | | | 15 m | | 0.00 | 0.00 | 0.00 | |
| | | | | | 30 m | | 0.00 | 0.00 | 0.00 | |
| | | | | | 1.5 h | | 0.00 | 0.00 | 0.00 | |
| | | | | | 3 h | | 0.00 | 0.00 | 0.00 | |
| | | | | | 24 h | | 0.00 | 0.00 | 0.00 | |

**# Average of three replicates**

**Findings**

Residual FACIN 25% EC disappeared quickly from all of the treated leaf surfaces. Significant terpene residues were only detected from the leaf samples collected immediately following spray deposition, and in the samples collected five minutes after the spray event.

In contrast, over the course of three sprays on a five day interval, the active ingredient in Lannate was shown to accumulate on (in) the primrose leaf samples.

**Conclusion**

Since there was no significant residual FACIN detected at any sampling interval beyond five minutes, standard decline curves were not calculated. Given that this greenhouse test was performed using deposition rates significantly higher than those proposed for the intended uses of QRD 460 / QRD 452 in the EU, the accumulation of terpene residue should be of no concern on foliage.

## IIA 6.3.5 Residues in Cucurbits

**Table 6.3.2-1: EU Critical GAPs for QRD 460 use on Cucurbits (Melon and Cucumber)**

| Region | Outdoor/ Protected | Max. No. of Applications | Application Interval (days) | Max. Application | | Minimum PHI (days) |
|---|---|---|---|---|---|---|
| | | | | Rate (kg as/ha) | Water (L/ha) | |
| S EU | Protected | 3 | 7 | 0.762 – 1.523 | 400 - 1000 | 0 |
| S EU | Outdoor | 3 | 7 | 0.762 – 1.523 | 400 - 1000 | 0 |

The GAP for cucurbits does not exceed that for tomatoes or peppers and is very similar.

Residue trials on curcubits have not been conducted in Europe.

As data available from a trial conducted on outdoor grown tomatoes in California demonstrates that no residues, apart from naturally occurring levels of α-terpinene, p-cymene or d-limonene will be detected following application of QRD 452, even when sampled immediately following application, therefore it is not necessary to conduct the full set of residues trials usually required. See Annex point IIA 6.3.1 above for details.

## IIA 6.4 Livestock feeding studies

As all three terpenes in terpenoid blend (α-terpinene, p-cymene, d-limonene) QRD 460 are naturally occurring and dissipate rapidly in the environment primarily by volatilization, and available studies clearly demonstrate no residue left in the crops shortly after application, no livestock feeding studies are triggered.

### IIA 6.4.1 Poultry

No livestock feeding studies are triggered.

### IIA 6.4.2 Lactating ruminants (goat or cow)

No livestock feeding studies are triggered.

### IIA 6.4.3 Pigs

No livestock feeding studies are triggered.

### IIA 6.4.4 Fish

No fish studies are triggered.

## IIA 6.5 Effects of industrial processing and/or household preparation (representative processing situations)

Not relevant because there are no detectable residues in crops where the QRD 460 product has been applied. Therefore, no studies have been conducted.

### IIA 6.5.1 The nature of residue

As there are no detectable residues in crops where the QRD 460 product has been applied for plant protection use, it is proposed that QRD 460 be exempted from the need for MRLs and so the nature of the residue does not warrant further consideration.

### IIA 6.5.2 Distribution of the residue in peel/pulp

Not relevant because there are no detectable residues in crops where the QRD 460 product has been applied. Therefore, no studies have been conducted.

### IIA 6.5.3 Residue levels - balance studies on a core set of representative processes

Not relevant because there are no detectable residues in crops where the QRD 460 product has been applied. Therefore, no studies have been conducted.

### IIA 6.5.4 Residue levels - follow-up studies to determine concentration or dilution factors

Not relevant because there are no detectable residues in crops where the QRD 460 product has been applied. Therefore, no studies have been conducted.

## IIA 6.6 Residues in succeeding crops

Not relevant because there are no detectable residues in crops where the QRD 460 product has been applied. Therefore, no consequent effects are expected on succeeding crops and no studies have been conducted.

### IIA 6.6.1 Theoretical consideration of the nature and level of the residue

As there are no detectable residues in crops where the QRD 460 product has been applied for plant protection use, it is proposed that QRD 460 be exempted from the need for MRLs and so the nature of the residue does not warrant further consideration.

### IIA 6.6.2 Metabolism and distribution studies on representative crops

In those crops where QRD 460 terpenes naturally occur, the metabolism and catabolism is part of the natural cycle of these compounds within plants and the plant protection use proposed does not contribute to this cycle.

Where the terpene exposure is only as a result of application of the QRD 460 product for plant protection use, they volatilise so rapidly that no detectable residues were found shortly after application and so no meaningful absorption is expected.

It is proposed that no metabolism studies be required for QRD 460 for the proposed use and future crop extensions of use.

### IIA 6.6.3 Field trials on representative crops

Not relevant for QRD 460 as explained under Point 6.6.2. MRL exemption is supported.

## IIA 6.7 Proposed residue definition and maximum residue levels

Due to the fact that all three terpenes in QRD 460 active substance are naturally occurring and dissipate rapidly in the environment by volatilization (see Section 5, Environmental Fate), and that the studies available clearly demonstrate there are no detectable residues left in the crops shortly after application, no residue definition is proposed and QRD 460 should be exempted from the need for MRLs.

As stated previously, the components of QRD 460 are present in a multitude of fruits, vegetables, herbs, spices, and other foods and beverages. Although the levels are relatively low, the general public is exposed to these components through ingestion, dermal contact, and inhalation on a daily basis. According to a 2005 World Health Organization (WHO) report on food additives, the per capita daily consumption of the three main components of QRD 460 as <u>food additives</u> in the US and Europe, respectively, are as follows: d-limonene, 12.76 mg and 39.307 mg; p-cymene, 0.472 mg and 1.085 mg; α-terpinene, 0.093 mg and 0.032 mg.

d-limonene was given an ADI, “not specified” classification due to the absence of meaningful toxicity, while all three terpenes were given “No safety concern” for current estimated intake values from food. The establishment of an acceptable daily intake expressed in numerical form was not deemed necessary. Exposure from the plant protection use described here does not contribute in any significant way to these existing exposure levels.

This conclusion is in line with other essential oil type or plant derived plant protection active substances in the EU and also consistent with other non-EU Regulatory Authorities decisions on this active substance.

### IIA 6.7.1 Proposed residue definition

No residue definition is proposed for QRD 460.

### IIA 6.7.2 Proposed maximum residue levels (MRLs) and justification of the acceptability of the levels proposed, including details of statistical analyses used

None proposed.

## IIA 6.8 Proposed pre-harvest intervals, re-entry intervals or withholding periods to minimize residues in crops, plants, plant products, treated areas or spaces and a justification for each proposal

### IIA 6.8.1 Pre-harvest interval (in days) for each relevant crop

It is proposed that the pre-harvest interval should be zero days. This is based on the rapid degradation of the active moiety and the lack of any detectable residue on plants, shortly after application.

### IIA 6.8.2 Re-entry period (in days) for livestock, to areas to be grazed

No re-entry period for livestock is required for the glass house use proposed for QRD 460. For outdoor use, none is required as the product dissipates rapidly with no detectable residues shortly after application.

## IIA 6.8.3 Re-entry period (in hours or days) for man to crops, buildings or spaces treated

As exposure to the terpenes contained in QRD 460 is part of the normal human experience via smell, taste and touch (products containing them include laundry detergents, fragrances, fruit, vegetables and herbs), and they have been shown to dissipate rapidly from treated plants, it is reasonable to conclude that no, or minimal, re-entry restrictions to limit exposure to the plant protection use of QRD 460 are necessary.

## IIA 6.8.4 Withholding period (in days) for animal feeding stuffs

Not relevant for QRD 460 as not applied to animal feedstuffs.

## IIA 6.8.5 Waiting period (in days) between last application and sowing or planting the crop to be protected

No waiting period is required as no effect expected based on the rapid degradation of the active moiety and the lack of any detectable residue on plants, shortly after application.

## IIA 6.8.6 Waiting period (in days) between application and handling treated products

No waiting period is required as no effect expected based on the rapid degradation of the active moiety and the lack of any detectable residue on plants, shortly after application.

## IIA 6.8.7 Waiting period (in days) between last application and sowing or planting succeeding crops

No waiting period is required as no effect expected based on the rapid degradation of the active moiety and the lack of any detectable residue on plants, shortly after application.

## IIA 6.9 Estimation of the potential and actual exposure through diet and other means

No calculations are offered because, as demonstrated from the residue trials the lack of detectable residues, therefore exposure, obviate any consumer risk and support the exemption from the requirement to establish MRLs from the plant protection use of QRD 460.

As humans have been historically exposed to the three terpene constituents of QRD 460 from natural and other sources, that is, from eating, smelling and touching the edible plants in which they occur; from cooking with the herbs and ingredients containing them as flavourings; and from their use as fragrances in a large number of household items, it is unlikely that the use of the active substance QRD 460 for plant protection will add significantly to this natural exposure.

The components of QRD 460 are naturally occurring in a multitude of fruits, vegetables, herbs, spices, and other foods and beverages. Although the levels are relatively low, the general public is exposed to these components through ingestion, dermal contact, and inhalation on a daily basis. According to a 2005 World Health Organization (WHO) report on food additives, the per capita daily consumption of the three main components of QRD 460 as food additives in the US and Europe, respectively, are as follows: d-limonene, 12.76 mg and 39.307 mg; p-cymene, 0.472 mg and 1.085 mg; α-terpinene, 0.093 mg and 0.032 mg.

The Scientific Panel on food additives, flavourings, processing aids and materials in contact with food (AFC) reported MSDI (Maximised Survey-derived Daily Intakes) values for p-cymene of 0.926 mg/capita/day, α-terpinene of 0.027 mg/capita/day and d-limonene of 33.542 mg/capita/day. All were considered of no safety concern at the estimated levels of intake. In the EU, JECFA considered d-limonene poses no safety concerns at the estimated current intakes in Europe. The establishment of an acceptable daily intake expressed in numerical form was not deemed necessary.

In conclusion, use of plant protection products containing QRD 460 will not contribute to dietary exposure of these terpene components and it is therefore not relevant to establish an ADI for QRD 460.

This is consistent with the regulatory situation in the US where the EPA granted exemption from the requirement for a tolerance (40 CFR 180.1296) based on absence of detectable residue and resultant lack of oral exposure to all populations.

It is notable than when pesticide active substances are formulated to form end-use products, a safety evaluation of the co-formulants is conducted and if those co-formulants are also on an approved list of food additives, then they are considered safe and acceptable for the pesticide use. This should give further reassurance that in the case of QRD 460 all three of the active moieties are listed as food additives approved for consumption.

The plant protection use is insignificant in comparison to other natural, historic and ongoing exposure to consumers from which there is no evidence of harm, as also concluded in the WHO evaluations above. Therefore further consideration of the exposure levels from the pesticidal use of QRD 460 constituents is not warranted.

## IIA 6.9.1 TMDI calculations

Not relevant to exposure from QRD 460 as no residues detected.

## IIA 6.9.2 NEDI calculations

Not relevant to exposure from QRD 460 as no residues detected.

## IIA 6.9.3 NESTI calculations

Not relevant to exposure from QRD 460 as no residues detected.

# IIA 6.10 Other/special studies

Not relevant to exposure from QRD 460 as no residues detected.

# IIA 6.11 Summary and evaluation of residue behaviour; Reasonable grounds in support of the petition

## IIA 6.11.1 Summary and evaluation of residue behaviour

Crop residue trials have not been conducted in Europe. However, data are available from two GLP compliant trials conducted in California, one on outdoor grown tomatoes, the second on outdoor grown mustard greens. In addition supporting data are presented from a study with primrose conducted according to the principles of GLP but unaudited. Further, it is well known that these three terpenes rapidly volatilise ([redacted], (2011) and break down in air, which makes analytical detection after spray application difficult.

Results of the primrose, tomato and mustard green studies demonstrate that multiple applications of QRD 460 or the original plant extract product resulted in no detectable residues even shortly after application at rates higher than those proposed for the EU and no accumulation of residues over multiple applications.

As a result of this data, and the fact that all three terpenes are naturally occurring in many plant species, it was reasonable to conclude that plant metabolism studies with the active substance was not necessary. Data presented clearly show natural occurrence of the terpenes in QRD 460 is ubiquitous and the plant protection use does not appear to contribute in any meaningful way. In addition, the active substance is not expected to enter the plants after application to any significant degree, therefore, it is not available to be metabolised in plants from this proposed pesticide use.

Due to the fact that all three terpenes in the QRD 460 active substance are naturally occurring, have been shown to dissipate rapidly in the environment by volatilization (see Section 5, Environmental Fate), and that the available studies clearly demonstrate there is no meaningful residue on crops shortly after application, no residue definition is proposed and QRD 460 should be exempted from the need for MRLs.

An ADI is not appropriate due to the safe profile of QRD 460, so it is reasonable to conclude that the standard consumer risk model is not necessary. Values identified from the WHO/FAO assessment of the three terpene components of QRD 460 as food additives further support that exposure from the proposed plant protection use is negligible.

Future crops on which QRD 460 may be applied should also be exempted from the need for specific residue studies.

## IIA 6.11.2 Reasonable grounds in support of the petition

No metabolism studies or further residue studies are required to conclude that the consumer risk from the plant protection use of QRD 460 gives negligible concern and is acceptable.

Exposure to humans from natural and other sources of the three constituent terpenes has been a reality for centuries and no concern is raised about their toxicity or exposure effects from known studies or anecdotal evidence.

Due to the lack of residues detected after application of the QRD 460 product, it is proposed that QRD 460 be exempted from the need to set MRLs.

## References

| Annex point/ reference number | Author(s) | Year | Title<br>Sponsor/Source<br>Test Facility, Report No<br>GLP or GEP status (where relevant),<br>Published or Not | Data Protection Claimed<br><br>Y/N | Owner<br><br>AQ = AgraQuest |
|---|---|---|---|---|---|
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