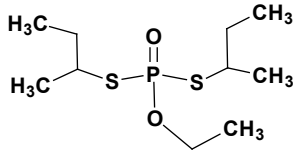
5.4 CADUSAFOS (174)

RESIDUE AND ANALYTICAL ASPECTS

Cadusafos is an organophosphate nematicide. It was evaluated by JMPR 1991(T, R), 1992(R). It was evaluated for toxicological review by JMPR in 2009 as the periodic re-evaluation. The ADI for cadusafos was established as 0–0.0005 mg/kg bw and acute reference dose was 0.001 mg/kg bw

Cadusafos was scheduled at the Forty-first Session of the CCPR (2009) for the periodic re-evaluation of residues by the 2010 JMPR.

Residue studies were submitted by the manufacturer to support the use of cadusafos in or on banana and potatoes.



Animal metabolism

The 2009 JMPR Meeting reviewed studies on the metabolism of ^{14}C-labelled cadusafos in rats. These studies showed that more than 80% of the administered dose was excreted within 24 hours, and more than 90% within 48 hours. Of the recovered radiolabel, 70–80% was found in the urine, 4–14% in the faeces, and 12–18% as CO_2. Cadusafos residues were widely distributed among rat organs, with a peak of 1.2% of the administered dose being found in the body at 7 days after dosing. Highest TRR concentrations were found in the liver, fat, kidney, and lungs. There was no evidence for accumulation of cadusafos residues in the body.

Cadusafos is extensively metabolized in rats. Metabolism proceeds by cleavage of one of the thio-butyl groups to give *sec*-butyl mercaptan and O-ethyl-S-(2-butyl) phosphorothioic acid, which can then be cleaved to S-(2-butyl) phosphorothioic acid or O-ethyl phosphorothioic acid. *Sec*-Butyl mercaptan is biotransformed to methyl *sec*-butyl sulfide, sulfoxide, and sulfone; and then to hydroxysulfones. Alternatively, *sec*-butyl mercaptan can be oxidized to butyl sulfonic acid, then ethyl and methyl sulfonic acid. CO_2 formation may proceed from *sec*-butyl mercaptan or from sulfonic acid. Carbon dioxide is incorporated into urea or other endogenous substances. No significant differences in the metabolic profile of cadusafos in male and female rats were reported.

No livestock metabolism studies were available for consideration since there are no relevant livestock feed items. Based on the results of the rat metabolism studies, cadusafos metabolism in animals consists of an initial hydrolysis reaction followed by a series of oxidation and/or methylation reactions to produce a variety of small, polar compounds.

Plant metabolism

Cadusafos metabolism studies were submitted on the following plants: banana, potato, corn, radish, and tomato. The studies on plant metabolism all involved applications to soil, consistent with intended use patterns. Cadusafos metabolism was relatively consistent in these matrices: hydrolytic cleavage followed by a series of oxidation reactions to give several small, polar compounds. In addition, conjugation with glucose was reported. The primary difference noted between plants was the extent of metabolism observed, with potato demonstrating the most extensive metabolism.

Banana

Two banana plants in the early fruiting stage were treated with [^{14}C]-cadusafos at the rate of 3.0 g ai per tree applied to the soil. Mature fruit and leaves from the plants were harvested and analysed. Initial combustion analysis indicated only low levels of total radioactive residue (TRR) in the fruit, 0.051 mg/kg in ripe pulp and 0.031 mg/kg in unripe pulp. Extraction and partition analysis of radiocarbon residue in ripe banana pulp and peel showed that the majority of the residue consisted of water-soluble polar metabolites with lower levels of organo-soluble metabolites. No parent chemical was detected in the ripe or unripe fruit (i.e., < 1 ppb), whereas 1 ppb of parent chemical was found in the leaf. The predominant residue identified in unripe pulp was methyl 2-butyl sulfone (36% TRR, 0.011 mg/kg). As bananas ripen to yellow, an additional oxidation step occurs resulting in hydroxy 2-butyl methylsulfone being the predominate metabolite observed in ripe pulp (52% TRR, 0.027 mg/kg).

Potato

Radio-labelled cadusafos was applied to soil in pots at a rate equivalent to 6 kg ai/ha. Potatoes were planted into the pots of treated soil and maintained in a greenhouse for 44 days, at which time they were moved to an outdoor screen house until maturity. The potatoes were harvested at normal maturity (160 days after treatment) and analysed. TRR levels of 0.69–0.70 mg/kg were found in potato tubers. Cadusafos undergoes initial hydrolysis to the transient butane-2-thiol, which undergoes a series of oxidations and methylations to yield a major product, hydroxy 2-butyl methylsulfone. This compound is further oxidized to two isomers of 1-carboxyhydroxyisopropylmethylsulfone, which, in conjugated form, represent the major metabolites in potato tubers (32–37% TRR, 0.22–0.25 mg/kg).

Maize

Metabolism of cadusafos was studied in corn (maize) using a 2 kg ai/ha treatment rate. The chemical was applied as a 20% granular formulation in bands to the soil. Corn plants were grown to maturity in the greenhouse. Plant samples were taken at 30 and 60-days post-treatment, at silage, and finally at maturity, i.e., grain and stover. TRR levels ranged from 0.85 mg/kg (cadusafos equivalents) in the 60-day post plant forage, to 2.87 mg/kg in the stover. Grain TRR levels were 0.23 mg/kg cadusafos equivalents found only in the mature (160 day) plant. Cadusafos is not stable in the plant and is degraded to more polar and water soluble metabolites. Specifically, analysis of the 30 day, 60 day, silage, and stover samples showed that cadusafos degrades to 2-butanesulfonic acid, hydroxy-2-butanesulfonic acid, and butanediols. S-2-butyl phosphorothioic acid was a minor metabolite in corn samples, while S,S-di-(2-butyl) phosphorodithioic acid was present only in the 30 and 60 day plant samples at less than 0.01 mg/kg. Further analysis of the organosoluble metabolites showed the presence of methyl 2-butyl sulfone, and hydroxy 2-butyl methylsulfone as minor components. Radiocarbon in the grain was analysed and was found to be primarily due to incorporation into glucose, indicating that the parent chemical undergoes a rapid and facile degradation in the corn plant.

Radish

Cadusafos was applied to soil at a rate of 9 kg ai/ha, and radish seeds were sown in the soil. At 50 days after treatment of [^{14}C]-cadusafos, mature radishes were harvested. The radishes were separated into the roots and the foliage for separate analysis. The recoveries of radioactivity in the root, foliage and soil accounted for 0.3%, 1.0% and 70.9% of the applied radioactivity, respectively. The total radioactive residues (TRRs) in the root, foliage and soil were 1.6 mg/kg, 5.0 mg/kg and 10.7 mg/kg equivalents of cadusafos, respectively.

The radish metabolism study showed that numerous compounds were detected in the extractable fractions from the root. There were no metabolites which were more than 4%TRR (0.07 mg/kg equivalent of cadusafos). The parent compound was detected at 0.8%TRR (0.014 mg/kg)

in the root. Numerous compounds were also detected in the extractable fractions from the foliage. All the metabolites were less than 10%TRR or 0.5 mg/kg except for methyl 2-butyl sulfone (19%TRR, 0.88 mg/kg). The parent compound was detected at 0.4% (0.018 mg/kg) in foliage. Many metabolites in the root and foliage were polar compounds which were found in the water-soluble fraction. In the soil no metabolite comprised more than 2%TRR.

Tomato

Radio-labelled cadusafos was applied by drip irrigation to the soil surface on two separate occasions at a total nominal rate of 6 kg ai/ha. The first application was made prior to transplanting at a rate of 4 kg ai/ha with a second 60 days later at 2 kg ai/ha. In tomato plants, cadusafos is metabolised via butane-2-thiol to butane-2-sulfonic acid and numerous minor metabolites and conjugates. Radioactive residues were mainly taken up via the roots into the shoots, whereas the uptake of residues into fruits was low. The TRR in edible tomato fruit ranged between 0.028 to 0.093 mg/kg. Tomatoes were separated into pomace and juice fractions and analysed. It was observed that the major part of the radioactivity (up to 95%) found in the fruits was present in tomato juice. Analyses of the tomato juice samples showed up to 22 radioactive fractions in addition to the parent compound. All fractions were below 10% TRR, except one fraction, likely consisting of several compounds characterized as conjugates, found in green tomatoes. However, none of the radioactive fractions exceeded 0.010 mg/kg in tomato fruit. The major part of the radioactive residue was shown to be conjugated to sugars.

Environmental fate in soil

The degradation of radio-labelled cadusafos in aerobic conditions was investigated in silt loam and sandy loam soils in the US, and in clay loam and silt loam soils in Germany and Spain. The estimated time to 50% degradation (DT_{50}) ranged from 11–62 days in the reported studies. These studies showed that cadusafos has a relatively short estimated half-life in soil.

To investigate the possible photodegradation of cadusafos in soil, sandy loam soil samples were exposed to natural sunlight (11 hour photo periods per day) following treatment with radio-labelled cadusafos at approximately 1 mg/kg and analysed at standard intervals up to 30 days. After 30 days, only 1% of the applied cadusafos was found to have degraded into three compounds. The slow photochemical degradation is in line with the low UV/visible absorbance of cadusafos. Thus, cadusafos may be considered a photolytically-stable compound.

Buffered aqueous solutions (pH 5, 7 and 9) containing approximately 3 mg/L of radio-labelled cadusafos were analysed for hydrolysis at intervals up to 34 days. Cadusafos was stable at pH 5 and 7 during the 34-day study period. At pH 9, slow hydrolysis was observed. Cadusafos may be considered a hydrolytically-stable compound.

Rotational crops

No rotational crop studies were submitted for review. For rotated crops there would be no expectation of residues remaining in the soil following early season applications as cadusafos has a relatively short estimated half-life in soil.

Methods of analysis

The Meeting received description and validation data for a single-residue analytical method for cadusafos in samples of plant origin. The method is based on extraction with a methanol/water mixture, gravity filtering though glass wool and partitioning with methylene chloride, followed by liquid-liquid extraction using water and dichloromethane and an additional clean-up on an alumina column. The organic phase was filtered through anhydrous sodium sulfate, concentrated and taken up with hexane. Further clean up was achieved using silicagel SEP PAK cartridges and eluting

cadusafos with 25% ethyl acetate in hexane. Quantitative determination of the active substance was performed using gas chromatography and a flame photometric detector operating in phosphorous mode.

The method was validated for banana, potato, melon, green beans, strawberry and peppers with a LOQ of 0.005 mg/kg (0.001 mg/kg for banana). Method recoveries ranged from 80–94% for banana pulp and 87–94% for potatoes, with RSDs < 10%. The method was used in the supervised trials on plant commodities evaluated by this Meeting (banana and potato) with concurrent recoveries within the range of 70–110% and RSD < 10%.

Adequate single-residue methods exist for both gathering data in supervised trials and for monitoring and enforcing cadusafos MRLs in the matrices validated. No information regarding the recovery of cadusafos through multiresidue methods was submitted. However, organophosphate compounds are generally amenable to analysis by multiresidue methods and the Pesticide Data Programme of the United States Department of Agriculture has reported monitoring results for cadusafos residues in banana samples.

Stability of pesticide residues in stored analytical samples

The Meeting received information on the stability of cadusafos in freezer-stored samples of banana, potato, and corn. The results show that cadusafos was stable under freezer-storage conditions during the tested storage interval of 14–15 months, which covers the storage intervals in the supervised trials evaluated by this Meeting.

Definition of the residue

The plant metabolism studies indicate that significant portions of cadusafos are oxidized and then converted to the corresponding conjugates in plant matrices. However, due to the lower toxicity of the polar conjugates formed, the Meeting concluded that the residue definition for plant commodities for purposes of enforcement is cadusafos. The Meeting also concluded that for purposes of dietary intake considerations, the residue definition is cadusafos alone. This determination is consistent with conclusions of the 2009 JMPR, which listed cadusafos as the only toxicologically significant compound in plants, animals, and the environment.

The octanol-water partition coefficient of cadusafos (log K_{OW} = 3.9) implies that cadusafos is likely to be fat soluble. The Meeting determined there was insufficient information available to reach a conclusion regarding the fat solubility of cadusafos in livestock commodities.

Results of supervised trials on crops

The Meeting received results from supervised trials with cadusafos on banana and potato. All results on relevant commodities in trials conducted according to GAP were less than the method LOQ. Consequently, it was not suitable to use the NAFTA calculator to estimate the maximum residue levels. Instead, maximum residue estimation was based on the method LOQ.

Banana

The Meeting received results from supervised trials with cadusafos used on bananas in Australia, Costa Rica (n = 6), Ecuador, Guatemala, Honduras (n = 2), Ivory Coast (n = 2), Martinique, Mexico, and Philippines (n = 2). The GAP in all these countries (except Ecuador: 2 × 2 g ai/plant) specifies two soil applications at a rate of 3 g ai/plant, or three applications at a rate of 2 g ai/plant, for a total rate of 6 g ai/plant per year, with no retreatment interval (RTI) or pre-harvest interval (PHI) given.

The trials reported cadusafos residues in banana peel and pulp samples over a wide range of PHIs and at several treatment rates. The LOQ for all trials was 0.005 mg/kg except for the trial conducted in the Philippines, where the LOQ was 0.02 mg/kg.

All banana pulp samples had residues < 0.005 mg/kg, except for the Philippines trial, where < 0.02 mg/kg was reported. Similarly, all peel samples were < 0.005 mg/kg, except for the Martinique trial which reported detectable cadusafos levels in peel samples harvested at several PHIs, including a maximum level of 0.022 mg/kg at a 0-day PHI following a single application of 6 g ai/plant; and one trial from Costa Rica where a two peel samples had cadusafos residues at 0.005 mg/kg.

Based on the submitted trials reflecting the GAP, the Meeting estimated a maximum residue level for cadusafos in banana of 0.01 mg/kg to confirm the previous recommendation of 0.01 mg/kg, an STMR of 0.005 mg/kg and an HR of 0.005 mg/kg.

The recommendations are supported by monitoring data results from the USDA's Pesticide Data Programme (PDP), which reported no detects in 1393 samples analysed in the years 2001 and 2002, when the LOQ ranged from 0.005 – 0.025 mg/kg, and no detects in 532 samples analysed in the years 2006 and 2007, when the LOQ was 0.005 mg/kg.

Potato

The Meeting received results from supervised trials with cadusafos used on potato in Brazil, Mexico (3), Spain (3), and Greece (2).

The GAP of Brazil for potato specifies 3 kg ai/ha, 1 application, with a 90-day PHI. One trial in Brazil was conducted at the GAP, including a double rate treatment. Cadusafos residues were < 0.02 mg/kg in both cases.

The GAP of Mexico for potatoes specifies 5 kg ai/ha, 1 application, and a 144-day PHI. Two trials in Mexico were conducted at the GAP rate; a third trial conducted in Mexico reported a PHI of 193 days and, therefore, was not according to GAP. There were two trials conducted in Spain at a double rate. A third Spanish trial reported a residue level of 0.03 mg/kg; however, the PHI was only 88 days in this trial. As no GAP was submitted from Spain or Greece, trials conducted in those countries were not considered further for maximum residue level estimations. At the Mexico GAP, cadusafos residues were: < 0.005 and 0.008 mg/kg.

The Meeting determined that insufficient residue data were available to estimate a maximum residue level for potato. The Meeting therefore agreed to withdraw its previous maximum residue level recommendation of 0.02 mg/kg for potato.

Fate of residues during processing

The Meeting received processing studies for potato. The residue definition recommended for plant commodities will suffice for processed plant commodities (parent only).

The processing (or transfer) factors derived from the processing studies are summarized in the table below. The factors are the ratio of the total residue in the processed commodity divided by the total residue in the raw agricultural commodity (RAC).

Processing (Transfer) factors from the processing of raw agricultural commodities (RACs) with field-incurred residues from foliar treatment with cadusafos

RAC	Processed Commodity	Processing Factor [a]
Potato	Peel [b]	0.6, 0.33, 0.5 Mean: 0.48
	Peeled potato [c]	< 0.5,< 0.2,< 0.33, < 0.25 Mean: < 0.2
	Boiled potato [d]	< 0.5,< 0.2,< 0.33, < 0.25 Mean: < 0. 2

[a] Each value represents a separate study. The processing factor is the ratio of the total residue in the processed item divided by the total residue in the RAC.

[b] Peels were from boiled potatoes. In one trial with raw peels, a PF of 7.5 was determined.

[c] Potato with no peel after boiling.

[d] Boiled potato with peel.

No maximum residue level recommendations were appropriate for processed potato commodities.

Estimated maximum and mean dietary burdens of farm animals

There are no cattle or poultry feed items resulting from the RACs for which the 2010 Meeting made maximum residue level recommendations, and hence, no need to calculated dietary burden levels for farm animals.

Animal commodity maximum residue levels

A bovine feeding study was not provided. However, there are no cattle feed items resulting from the RACs for which the 2010 Meeting made maximum residue level recommendations, and hence, no need to recommend maximum residue levels for ruminant commodities.

A poultry feeding study was not provided. However, as there are no poultry feed items resulting from the RACs which the 2010 Meeting evaluated, recommendations for maximum residue levels for poultry commodities were unnecessary.

DIETARY RISK ASSESSMENT

Long-term intake

The evaluation of cadusafos has resulted in recommendations for MRLs and STMRs for bananas. Bananas were included at the appropriate level in the dietary intake calculations. The International Estimated Daily Intakes (IEDI) for the 13 GEMS/Food regional diets, based on the banana STMR were in the range 0–1% of the maximum ADI of 0.0005 mg/kg bw.

The Meeting concluded that the long-term intake of residues of cadusafos from its use on bananas was unlikely to present a public health concern.

Short-term intake

The International Estimated Short-Term Intake (IESTI) for cadusafos was calculated for bananas. The short term intake of bananas represented 20% of the ARfD of 0.001 mg/kg bw for the general population, and 40% of the ARfD of 0.001 mg/kg bw for children $\leq$ 6 years. Accordingly, the Meeting concluded that the short-term intake of residues of cadusafos from its use on bananas was unlikely to present a public health concern.