Document Title

Tier 2 Summary of the Metabolism and Residues Data on the Plant Protection Product for

Spirotetramat 150 g/L OD
Material No.: 06424376

valid also for the Plant Protection Product

Spirotetramat 240 g/L SC
Material No.: 06424384

Data Requirements

Directive 91/414/EEC
Annex IIIA
Section 4, Point 8
Document M

According to OECD format guidance for industry data submissions on plant protection products and their active substances

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Author(s)

[redacted]

Bayer CropScience

OWNERSHIP STATEMENT

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IIIA1 8 Metabolism and Residues Data on the Plant Protection Product

The OECD dossier containing residue data for the active substance spirotetramat (BYI 08330) and the formulations spirotetramat OD 150 and SC 240 will be submitted jointly to AGES as Rapporteur Member State on behalf of the EU-Commission, EPA-USA and PMRA for Canada. As it is a Joint Review, in which the agencies involved share the workload, the residue data for both, NAFTA and EU have been jointly presented in the Annex II dossier, with the aim to come to mutually agreed MRLs and Import Tolerances in the EU and in the NAFTA region.

All data related to metabolism and residue data is presented in section 4, Point 6 of the Annex II dossier.

IIIA1 8.1 Stability of residues

IIIA1 8.1.1 Stability of residues during storage of samples

Please refer to Annex Point KIIA 6.1.1

IIIA1 8.1.2 Stability of residues in sample extracts

Please refer to Annex Point KIIA 6.1.2

IIIA1 8.2 Supplementary studies on metabolism in plants or livestock

No supplementary studies conducted. Please refer to Dossier Points KIIA 6.2.1, KIIA 6.2.2, KIIA 6.2.3 and MIIA

IIIA1 8.3 Supplementary residue trials (supervised field trials)

Please refer to Annex Point KIIA 6.3.1 for the supervised field residue trials conducted in the EU and to Annex Point 6.3.2 for the supervised field trials conducted in the USA.

IIIA1 8.3.1 Residue Trials EU, crop 1 – 21 (citrus - hop)

Please refer to Annex Point IIIA1 8.3

IIIA1 8.3.2 Residue Trials USA ,crop group 1 - 11 (brassica vegetables – tree nuts))

Please refer to Annex Point IIIA1 8.3

IIIA1 8.4 Supplementary livestock feeding studies

Please refer to Annex Points KIIA 6.4.1, KIIA 6.4.2 and to Annex Point MIIA

IIIA1 8.4.1 Poultry

Please refer to Annex Point IIIA 1.8.4

IIIA1 8.4.2 Lactating ruminants (goat or cow)

Please refer to Annex Point IIIA 1.8.4

IIIA1 8.4.3 Pigs

Please refer to Annex Point IIIA 1.8.4

IIIA1 8.4.4 Nature of residue in fish

Not required by Directive 91/414/EEC

IIIA1 8.5 Supp. studies on industrial processing and/or household preparation

Please refer to Annex Point KIIA 6.5

IIIA1 8.5.1 Nature of residues

Please refer to Annex Point KIIA 6.5.1

IIIA1 8.5.2 Distribution of the residue in peel/pulp

Please refer to Annex Point KIIA 6.5.2 and Annex point MIIA

IIIA1 8.5.3 Balance studies on a core set of representative processes

Please refer to Annex Point KIIA 6.5.3

IIIA1 8.5.4 Follow-up studies; potable waters; irrigated crops

Not applicable

IIIA1 8.5.4.1 Follow-up studies to determine concentration or dilution factors

Please refer to Annex Point KIIA 6.5.4

IIIA1 8.5.4.2 Potable waters

Not required by Directive 91/414/EEC.

IIIA1 8.5.4.3 Irrigated crops

Not required by Directive 91/414/EEC.

IIIA1 8.6 Supplementary studies for residues in representative succeeding crops

Please refer to Annex Point KIIA 6.6

IIIA1 8.7 Proposed residue definition and maximum residue levels

This Point is addressed in the tier 2 summary under Dossier Point MIIA, section 4, Point 6 "Metabolism and Residues Data for Spirotetramat (BYI 08330), (Spirotetramat 150 g/L OD, material no.: 06424376 and Spirotetramat 140 g/L SC, material no.: 06424384).

Please refer also to KIIA 6.7.

IIIA1 8.7.1 Proposed residue definition

This Point is addressed in the tier 2 summary under Dossier Point MIIA, section 4, Point 6 "Metabolism and Residues Data for Spirotetramat (BYI 08330), (Spirotetramat 150 g/L OD, material no.: 06424376 and Spirotetramat 140 g/L SC, material no.: 06424384).

Please refer also to KIIA 6.7.1

IIIA1 8.7.2 Proposed maximum residue levels (MRLs)

This Point is addressed in the tier 2 summary under Dossier Point MIIA, section 4, Point 6 "Metabolism and Residues Data for Spirotetramat (BYI 08330), (Spirotetramat 150 g/L OD, material no.: 06424376 and Spirotetramat 140 g/L SC, material no.: 06424384)

Please refer also to KIIA 6.7.2

IIIA1 8.8 Proposed pre-harvest intervals, re-entry or withholding periods

This Point is addressed in the tier 2 summary under Dossier Point MIIA, section 4, Point 6 "Metabolism and Residues Data for Spirotetramat (BYI 08330), (Spirotetramat 150 g/L OD, material no.: 06424376 and Spirotetramat 140 g/L SC, material no.: 06424384). It is also addressed in Annex Point MIIIA1, section 1, points 3 and 4, Further Information.

Please refer also to KIIA 6.8

IIIA1 8.8.1 Pre-harvest interval (in days) for each relevant crop

Please refer to Annex Point KIIA 6.8.1 and MIIIA1, section 1, point 3 and 4, Further Information.

IIIA1 8.8.2 Re-entry period (in days) for livestock, to areas to be grazed

Please refer to Annex Point MIIIA1, section 1, points 3 and 4, Further Information.

IIIA1 8.8.3 Re-entry period for man to crops, buildings or spaces treated

Please refer to Annex Point MIIIA1, section 1, points 3 and 4, Further Information.

IIIA1 8.8.4 Withholding period (in days) for animal feedingstuffs

Please refer to Annex Point MIIIA1, section 1, points 3 and 4, Further Information.

IIIA1 8.8.5 Waiting period before sowing or planting crop to be protected

Please refer to Annex Point MIIIA1, section 1, points 3 and 4, Further Information.

IIIA1 8.8.6 Waiting period between application and handling treated products

Please refer to Annex Point MIIIA1, section 1, points 3 and 4, Further Information.

IIIA1 8.8.7 Waiting period (in days) before sowing or planting succeeding crops

Please refer to Annex Point MIIIA1, section 1, points 3 and 4, Further Information.

IIIA1 8.9 Other/special studies

No other or special studies as those compiled in the dossier have been conducted or have been considered to be necessary or triggered.

IIIA1 8.10 Estimation of exposure through diet and other mean

Please refer to Annex Point KIIA 6.9

IIIA1 8.10.1 TMDI calculations

Please refer to Annex Point KIIA 6.9.1 and MIIA

IIIA1 8.10.2 NEDI calculations

Please refer to Annex Point KIIA 6.9.2 and MIIA

IIIA1 8.10.3 NESTI calculations

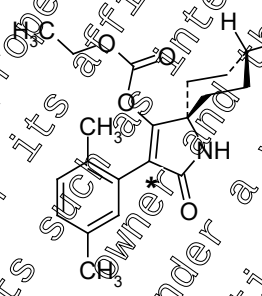
Please refer to Annex Point KIIA 6.9.3 and MIIA

IIIA1 8.11 Summary and evaluation of residue behaviour

Plant metabolism

Target crops

The metabolism of BYI08330 was investigated in apple, cotton, lettuce, and potato with the azaspirodecenyl-3-^{14}C label.



BYI08330 was applied to the plants by spraying. Unchanged parent compound was the major residue in apple fruits and leaves, cotton lint, lettuce, and potato leaves. BYI08330-enol was the most prominent compound in cotton seeds and potato tubers. Significant percentages (>10% of TRR) of BYI08330-enol-glc, BYI08330-ketohydroxy, and BYI08330-mono-hydroxy were detected in at least one RAC of the metabolism studies.

The structures and chemical names of the active substance and of all metabolites are summarised in the list of metabolites which is a part of the Annex II dossier. This list gives an overview on metabolites and where they were identified (e.g. in sprayed target crops, confined rotational crops, rat, goat, laying hen or environmental fate studies). Individual quantifications of BYI08330 and of metabolites are given in tables in section 6.2.1.

The parent compound BYI08330 and the metabolites BYI08330-enol, BYI08330-enol-glc, BYI08330-ketohydroxy, and BYI08330-mono-hydroxy are proposed as relevant residue for dietary risk assessment and were included in the plant residue method.

Succeeding crops (confined rotational crops)

The metabolism of BYI08330 was also investigated in confined rotational crops (spring wheat, Swiss chard and turnips) using the same radiolabel as for the target plant metabolism studies. The metabolism in rotational crops was investigated following spray application of BYI08330 onto bare soil (day 0) with an application rate of 406 g/ha. Crops of the first, second and third rotation were sown at day 30, day 135 and day 260, respectively. Representative immature and mature plant samples were analysed. The Total Radioactive Residues (TRRs) were highest in wheat straw of the first rotation(0.998 mg/kg) followed by wheat hay (0.384 mg/kg), turnip leaves (0.123 mg/kg), Swiss chard (0.078 mg/kg), wheat

grain (0.026 mg/kg), wheat forage (0.024 mg/kg), and turnip roots (0.021 mg/kg). A significant decline of TRRs from the first to the third rotation was observed in all RACs. Only wheat hay and wheat straw showed residues > 0.01 mg a.i. equiv./kg in the third rotation. The lowest residues were generally detected in the edible matrices wheat grain and turnip roots, followed by Swiss chard.
Parent compound could not be detected in any sample. Significant metabolites (> 10% of the TRR) in the first and second rotation were: BYI08330-ketohydroxy, BYI08330-desmethyl-ketohydroxy-Glc (two isomers), BYI08330-desmethyl-ketohydroxy-Glc-MA (two isomers), BYI08330-desmethyl-di-hydroxy-Glc,BYI08330-desmethyl-di-hydroxy-Glc-MA, and BYI08330-di-hydroxy. Other identified metabolites were of minor importance.
Since a major part of the residues were represented by conjugates, plant extracts were subjected to acidic hydrolysis to cleave the conjugates and to simplify the metabolic profiles for analysis of residues. BYI08330-desmethyl-di-hydroxy, BYI08330-ketohydroxy-alcohol, and BYI08330-desmethyl-ketohydroxy were identified as the major constituents of the residues after hydrolysis.

The residue analytical method for rotated crops quantifies the parent compound BYI08330 and the metabolite BYI08330-ketohydroxy by direct analysis of extracts. The compounds BYI08330-desmethyl-di-hydroxy, BYI08330-ketohydroxy-alcohol, and BYI08330-desmethyl-ketohydroxy were determined after acidic hydrolysis.

Animal metabolism

The metabolism of BYI08330 was investigated in the rat (described in section 3 point 5), laying hen and goat using the same radiolabel as for the plant metabolism studies.
Laying hens were dosed for 14 consecutive days with 1.01 mg a.i./kg bw (12.86 ppm in the diet) and sacrificed 24 hours after the last administration. A plateau level of residues in the eggs was reached after ca. 7 days. TRR values in eggs and edible materials were very low in the range of 0.003 to 0.017 mg/kg. Despite the very low TRR values, high rates for extraction and identification were achieved.
No parent compound could be detected in any sample. BYI08330-enol was the predominant component of the residues in eggs, muscle, and liver accounting for 50 – 84 % of the total radioactive residue in these materials. The most prominent metabolite (57% of TRR) detected in fat at a very low absolute level of 0.002 mg/kg was characterised as a conjugate. BYI08330-enol-GA was a significant metabolite in liver and was included in the animal residue method. Individual quantifications of BYI08330 related residues are given in tables in section 6.2.2 (poultry).

The nature of residues in milk and foodstuff originating from ruminants was investigated with a lactating goat. The goat was dosed for four consecutive days with 2.22 mg a.i./kg bw (73.03 ppm in the diet) and sacrificed 24 hours after the last administration.
A plateau level of residues in milk was reached within the study period. TRR values in milk and edible materials were low in the range of 0.003 to 0.184 mg/kg. Despite the very low TRR values, high rates for extraction and identification were achieved.
No parent compound could be detected in any sample. In milk, muscle, fat, and kidney, BYI08330-enol was the predominant component of the residues accounting for 49 – 78 % of the total radioactive residue. BYI08330-enol-GA was the predominant compound in liver (37 % of TRR) and was also detected in relevant portions in milk (24 % of TRR), fat (19 % of TRR), and kidney (14 % of TRR). Other

metabolites were only detected at low levels (< 10 % of TRR) in foodstuff originating from ruminants. Individual quantifications of BYI08330 related residues are given in tables in section 6.2.3 (goat).

Parent compound BYI08330 as well as the metabolites BYI08330-enol and BYI08330-enol-GA are proposed as relevant residue for dietary risk assessment and were included in the animal residue method.

Supervised residue trials were conducted in Europe and the USA to support the use of BYI08330 as a spray application in citrus, lettuce, pome fruit, stone fruit, grapes, strawberries, brassica vegetables, fruiting vegetables and cucurbits, beans, onions and hops in Europe and in citrus, leafy vegetables, pome fruit, stone fruit, tree nuts, grapes, fruiting vegetables and cucurbits, brassica vegetables, potatoes and hops in the USA.

The deep freezer storage stability of BYI08330, BYI08330-enol, BYI08330-ketohydroxy, BYI08330-monohydroxy and BYI08330-enol-glucoside was investigated in tomato fruit and paste, potato tuber, climbing French beans, lettuce, almond nutmeat, orange juice and prunes. The storage period was 5 months for orange juice and prunes, 12 months for tomato paste and 18 month for all other commodities. The total residue of BYI08330 (the sum of BYI08330 and its 4 metabolites) and BYI08330-ketohydroxy, BYI08330-monohydroxy and BYI08330-enol-glucoside were the stable during deep freezer storage for the tested periods in all matrices. Residues of BYI08330-enol were stable in tomato fruit and paste and in almond nutmeat. In beans, lettuce and potato tuber a small part of the BYI08330 (9-27 %) was degraded to BYI08330-ketohydroxy during storage at -18°C for 18 months.

As relevant residue in plants for enforcement and MRL setting the sum of BYI08330 and BYI08330-enol expressed as BYI08330 is proposed. The MRLs proposed for the different crops are summarized in Table 6.11.1-1.

Table 6.11.1-1: MRLs proposed for plant commodities

USA Crop/Crop Group	Crop	Proposed MRL	USA Crop/Crop Group	Crop	Proposed MRL
Leafy Vegetables	Crop group US	**5**	**Brassica - Head and Stem**	Crop group US	**3**
	Lettuce, head and leaf	**5**		Broccoli/Cauliflower	**3**
Pome Fruit	Crop group	**0.5**		Head Cabbage	**3**
Stone Fruit	Crop group US	**2**		Brussels sprouts	**0.2** (EU)
	Peach/apricot/nectarine	**2**		Kohlrabi	**2** (EU)-
	Plum	**2**	**Leafy Brassica**	Crop Group	**1** (EU) **16** (US)
	Cherry	**2**	**Legume Vegetables**	Beans/peas with pod	**1**
Grape	Grape, wine and table grape	**1**	**Potato**		**1**
Strawberry	strawberry	**0.5**	**Tree Nuts**	Crop Group	**0.5**
Bulb Vegetables	Onion	**0.3**	**Hops**	Hop (dried cones)	**10**

Fruiting Vegetables	Crop group US	**1**	**Processed products** (US only)		
	Tomato	**1**		Orange oil	**4**
	Pepper	**1**		Potato flakes	**2.5**
Cucurbits	Crop Group US	**0.2**		Raisins	**2.5**
	Cucumber	**0.2**		Tomato dried	**2.5**
	Melon	**0.2**			
	Squash	**0.2**			

A cattle feeding study was conducted. Residues in animal commodities were very low. No MRLs were proposed for commodities, in which no residues were found in the feeding study even at the 10x overdose. The proposed MRLs are summarized in Table 6.11.1-2.

Table 6.11.1-2: MRLs proposed for animal commodities

Commodity	Proposed MRL (mg/kg)	Commodity	Harmonised MRL/tolerance (mg/kg)
Cattle meat	**0.01**	**Hog liver**	**0.01**
Cattle fat	**0.01**	**Hog meat by-products, except liver**	**0.02**
Cattle liver	**0.01**	**Sheep meat**	**0.01**
Cattle meat by-products except liver	**0.02**	**Sheep fat**	**0.01**
Goat meat	**0.01**	**Sheep liver**	**0.01**
Goat fat	**0.01**	**Sheep meat by-products, except liver**	**0.02**
Goat liver	**0.01**	**Horse meat**	**0.01**
Goat meat by-products, except liver	**0.02**	**Horse fat**	**0.01**
Hog meat	**0.01**	**Horse liver**	**0.01**
Hog fat	**0.01**	**Horse meat by-products, except liver**	**0.02**

Results of the confined **rotational crop** study showed that no residues of the individual compounds are to be expected in edible parts of field crops. No field rotational crop studies were deemed necessary according to European Guidelines.
Residues in the feed items wheat hay and straw exceeded 10% of the TRR. Therefore limited rotational crops studies in the field were conducted in the USA. In these trials all individual BYI08330 analyte residues were less than the LOQ. The results support an 'immediate' or 30-day plant back interval for all rotational crops in the USA following the use of BYI08330 on a target crop.

An acute reference dose (ARfD) of 1 mg/kg and an acceptable daily intake (ADI) of 0.132 mg/kg was derived for BYI08330 from results of acute and chronic toxicity testing.
The calculation of the theoretical maximum daily intake (TMDI) was performed according to the GEMS/Food Consumption Cluster Diet (2006) and the PSD Ten Consumer Model (2006), using residues levels in the different crops at the proposed MRLs. Depending on the model used and on the consumer group the estimated worst case intake of residues of BYI08330 ranged between 5 and 18 % of the ADI.

The national estimated short term intake (NESTI) was calculated according to PSD´s acute intake guidance based on intake data of 10 consumer groups using residue levels at the respective MRLs. The potential intake of BYI08330 residues did not exceed 18 % of the ARfD for any crop and consumer group.

For the US, assessments were conducted to evaluate the potential risks due to acute and chronic dietary exposure of the entire U.S. population and selected population subgroups to residues of BYI08330. By adding drinking water estimates based on PRZM/EXAMS calculations to DEEM-FCID the aggregate dietary (food plus drinking water) exposure and the resulting risk from BYI08330 was determined. The acute and chronic assessments were conducted using Exponent Inc.'s DEEM-FCID™ software. Consumption data used in this program were taken from USDA's CSFII, 1994-1996, 1998. The BYI08330 aggregate acute dietary analysis indicated that the most highly exposed population subgroup was children (1-2 yrs) with an exposure equal to 8.1% of the acute population adjusted dose (aPAD) at the 99.9th percentile. Acute exposure of the overall U.S. population was 3.3% of the aPAD. The BYI08330 aggregate chronic dietary analysis indicated that chronic exposure to BYI08330 residues is very low with the overall U.S. population and all population subgroups having exposure less than 1% of the cPAD.

Hence, residues of BYI08330 in edible commodities are not expected to impose an acute or chronic risk to the consumer.