Bayer CropScience

Document Title

Summary of the residues in or on treated products, food and feed
Iodosulfuron-methyl-sodium + Mesosulfuron-methyl +Mefenpyr-diethyl
OD 42 (2+10+30 g/L)

Data Requirements

EU Regulation 1107/2009 & EU Regulation 284/2013
Document MCP
Section 8: Residues in or on treated products, food and feed

According to the guidance document, SANCO 10181/2013, for preparing dossiers for the approval of a chemical active substance

Date

2014-06-10

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Version history

Date	Data points containing amendments or additions[1] and brief description	Document identifier and version number

[1] It is suggested that applicants adopt a similar approach to showing revisions and version history as outlined in SANCO/10180/2013 Chapter 4 How to revise an Assessment Report

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Covers the point required in SANCO 10181/2013 format shown below

CP 8 RESIDUES IN OR ON TREATED PRODUCTS, FOOD OR FEED ....

In agreement with the Rapporteur Member State, the product dossier is submitted following the dRR format. All points required under the SANCO 10181/2013 are covered, although their naming might differ slightly.

IIIA 8.1 Stability of Residues

IIIA 8.1.1 Stability of residues during storage of samples

The stability of mesosulfuron-methyl derived residues upon deep frozen storage was investigated in various wheat matrices (shoot, straw and grain) for 40 months. The studies were submitted during the evaluation process and were considered adequate. Since Annex I inclusion, a new study has been generated with longer storage periods covered (40 months in wheat shoot and wheat straw).
They are summarised in Table 8.1.1-1 below:

Table 8.1.1-1 Summary of storage stability of mesosulfuron-methyl in wheat shoot, wheat straw, wheat grain

Active substance	Plant matrix	Stability	Storage conditions	Document No	Reference in AIR dossier
Mesosulfuron-methyl	Wheat Grain	Up to 1200 days	≤ -18°C	M-216176-01-1	KCA 6.1
	Wheat Straw			M-198612-04-1	KCA 6.1
	Wheat Shoot			M-198617-04-1	KCA 6.1

IIIA 8.1.2 Stability of residues in sample extracts

Relevant information on the stability of residues in the final or any intermediate extracts can be derived from the fortification experiments performed during sample analysis. Every analytical batch does contain at least one freshly fortified sample for concurrent recovery determination. The extracts of the fortified samples and of the study samples are handled and stored in parallel. If the recoveries in the fortified samples are within acceptable ranges, the stability of the sample extracts is considered as sufficiently proven.

IIIA 8.2 Supplementary studies on metabolism in plants or livestock

Metabolism, distribution and expression of residues were studied in plants and livestock with ^{14}C-labelled mesosulfuron-methyl.
The plant metabolism studies with ^{14}C-labelled mesosulfuron-methyl were performed in wheat and livestock. The study is presented in the MCA summary document on the active substance, Section 4, Point 6.1 and 6.2 and is summarised below:
-<u>Wheat:</u> The metabolism of mesosulfuron-methyl in wheat was investigated using both the U-phenyl-^{14}C-labelled and the 2-^{14}C-pyrimidyl-labelled active ingredients. The wheat plants were treated at a late tillering stage at rates between 10 g a.s./ha and 2 x 30 g a.s./ha. In order to avoid phytoxicity the compound was applied in a mixture with the safener mefenpyr-diethyl. The total radioactive residues at harvest were low, since even after treatment at the exaggerated rate of 2 x 30 g a.s./ha these residues did not exceed 0.0012 mg/kg in grain and 0.0457 mg/kg in straw. Besides the parent compound several metabolites were identified in straw. The same metabolites were detected in immature wheat plants, but with the parent compound accounting for a higher proportion of the total residue. Identification of the extractable residues in grain was not possible due to the extremely low concentration. All the metabolites detected in wheat were also found in animal metabolism studies.

The data from the original submission are regarded as being sufficient. No new studies are presented for the Annex I Renewal.

-Livestock: The livestock metabolism of mesosulfuron-methyl was investigated in a lactating cow and laying hens. U-^{14}C-phenyl-AE F130060 was orally administered at dose rates equivalent to 20.5 ppm (cow) and 10 ppm (hens). Mesosulfuron-methyl was shown to be rapidly and efficiently excreted. The levels of radioactive residues in eggs, milk and edible tissues were very low, thus indicating that there is no risk of accumulation of mesosulfuron-methyl residues in food of animal origin. The major identified residue component was parent mesosulfuron-methyl, with several cleavage and hydroxylation metabolites usually being present in lower amounts.

The data from the original submission are regarded as being sufficient. No new studies are presented for the Annex I Renewal.

IIIA 8.3 Supplementary residue trials (supervised field trials)

Mesosulfuron-methyl (AE F130060) is an herbicidal active substance. In 2009, the original Annex II dossier was submitted to France. In that dossier, uses on cereals were supported with residue trial data. Some new studies have since been conducted with mesosulfuron-methyl-containing formulations for use in European cereals, which is the "safe use" crop supported in the AIR3 process.

Table 8.3- 1: Worse case use pattern (GAPs) for the spray application of product IMS+MSM+MPR OD 42 containing formulations on cereals in Europe (Northern and Southern regions)

Crop	Member state or country	F / G or I	Formulation Conc. of as	Pests or group of pests controlled	Growth stage	Number	Water (L/ha)	Application (g as/ha)	PHI
Winter wheat	S-EU N-EU	F	Atlantis OD	Grassy and dicot weed species	BBCH 20-32 End of winter frost	1 per season	200-400	3 g IMS + 15 g MSM + 45 g MPR	Covered by normal vegetation period between last application and harvest

IIIA 8.3.1 Cereal

Supplementary trials: All supplementary trials have been presented in the active substance dossier.

Table 8.3- 2: Number and distribution of new residue trials conducted per geographical region on cereals(wheat, triticale, rye)

Formulation	Climatic zone, Countries	Formulation type	Year / No. of trials	Study number / Reference No.
Europe North				
AE F130060 02 WG13 A2*	Germany	WG13	1999 / 2	ER99ECN523 / M-199542-01-1 (b)
AE F130060 02 WG13 A2*	Northern France	WG13	1999 / 1	ER99ECN523 / M-199542-01-1 (b)
AE F115008 06 OD04 A1	Germany	OD42	2003 / 1	RA-2677/03 / M-227133-02-1 (c)
AE F115008 06 OD04 A1	Sweden	OD42	2003 / 1	RA-2677/03 / M-227133-02-1 (c)
AE F115008 06 OD04 A1	United Kingdom	OD42	2003 / 1	RA-2677/03 / M-227133-02-1 (c)
AE F115008 06 OD04 A1	Northern France	OD42	2003 / 1	RA-2677/03 / M-227133-02-1 (c)
Europe South				
AE F130060 02 WG13 A2*	France	WG13	1999 / 1	ER99ECN523 / M-199542-01-1 (b)
AE F115008 06 OD04 A1	Italy	OD42	2003 / 2	RA-2690/03 / M-227096-02-1 (c)
AE F115008 06 OD04 A1	France	OD42	2003 / 1	RA-2690/03 / M-227096-02-1 (c)

(b) Samples were analysed with the following analytical method: EM F08/99-0
(c) Samples were analysed with the following analytical method: 00815/M001
* with addition of external adjuvant

Conclusions

Northern Europe: Seven residue trials were conducted with two different formulation types (WG13 and OD42). The formulations were applied once at growth stage BBCH 32 to 49. Residues of mesosulfuron-methyl in shoot ranged from 0.15 to 0.90 mg/kg at the day of the application and declined to < 0.05 mg/kg by the second sampling (15 to 27 days after application). At harvest, residues of mesosulfuron-methyl at harvest were always lower than the respective LOQ in both wheat grain and wheat straw (LOQ grain: 0.01 mg/kg and LOQ straw: 0.05 mg/kg).

Southern Europe: Four residue trials were conducted with two different formulation types (WG13, and OD42). The formulations were applied once at growth stage BBCH 33 to 49. Residues of parent mesosulfuron-methyl in shoots ranged between 0.27 mg/kg and 0.66 mg/kg at the day of application. At harvest (48 to 58 days after application) residues were always less than the limit of quantification in the grain (0.01 mg/kg) and ranged between < 0.05 and 0.06 mg/kg in the straw (LOQ=0.05 mg/kg). In wheat grain at harvest, residues of mesosulfuron-methyl were always lower than the respective LOQ (LOQ grain: 0.01 mg/kg).

Results were comparable between Northern and Southern Europe. Residues of mesosulfuron-methyl in cereal grain, at harvest, were always lower than the limit of quantification.

According to Article 12 of Regulation (EC) No 396/2005, the European Food Safety Authority (EFSA) has reviewed the Maximum Residue Levels (MRLs) currently established at European level for the pesticide active substance iodosulfuron-methyl-sodium. A reasoned Opinion on the review of the existing maximum residue levels (MRLs) for mesosulfuron-methyl was published in EFSA Journal 2012; 10(11):2976. To assess the magnitude of mesosulfuron-methyl residues resulting from critical GAPs chosen by EFSA (1x 20 g as/Ha; GS 32; PHI of 90 days), all trials reported in the PROFile including residue trials evaluated in the framework of the peer review were considered. A sufficient number of trials complying with the GAP was reported by the RMS France for the Northern outdoor GAP on wheat and rye. The number of residue trials supporting the Southern outdoor GAP was not compliant with the data requirements for these crops. However, the reduced number of residue trials was considered acceptable in this case because all results were below the LOQ and a no residue situation is expected in grains.

IIIA 8.4 Supplementary Livestock Feeding Studies

The cereal commodities likely to be fed to livestock consist of grain (which is fed to poultry, pigs and cattle) and straw (which is fed to cattle only). Use of mesosulfuron-methyl in cereal according to the recommended GAP is not likely to result in significant residues in any of these commodities. The calculated dietary burdens for different groups of cattle, swine and poultry do not exceed the trigger value of 0.004 mg/kg bw/day and are slightly above at 0.005 mg/kg bw/day for sheep rams/ewes and lambs only.

Furthermore livestock metabolism studies showed that mesosulfuron-methyl does not accumulate in eggs, milk or edible tissues. Therefore, no livestock feeding studies to investigate the residue levels of mesosulfuron-methyl in food of animal origin are required.

IIIA 8.4.1 Poultry

Please refer to IIIA 8.4.

IIIA 8.4.2 Lactating ruminants (goat or cow)

Please refer to IIIA 8.4.

IIIA 8.4.3 Pigs

Please refer to IIIA 8.4.

IIIA 8.4.4 Nature of residue in fish

No study was performed.

IIIA 8.5 Supplementary Studies on Industrial Processing and/or Household Preparation

The use of product IMS+MSM+MPR OD 42 in cereal according to the intended GAP does not result in significant residues (i.e. > 0.1 mg/kg) of mesosulfuron-methyl in grain at harvest, since the residues were below the limit of quantification in all trials.
Therefore, studies on industrial processing and/or household preparation are not necessary.

IIIA 8.5.1 Nature of residues

Please refer to IIIA 8.5.

IIIA 8.5.2 Distribution of the residue in peel/pulp

The distribution of the residue in peel and pulp is not relevant for the supported crops.

IIIA 8.5.3 Balance studies on a core set of representative processes

Please refer to IIIA 8.5.

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

Please refer to IIIA 8.5.

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

IIIA 8.5.4.2 Potable waters

IIIA 8.5.4.3 Irrigated crops

IIIA 8.6 Supplementary Studies for Residues in Representative Succeeding Crops

Confined crop rotation studies for mesosulfuron-methyl were performed using both the U-phenyl-^{14}C-labelled and the 2-^{14}C-pyrimidyl-labelled active ingredients. In both cases the substance was applied to bare soil at a rate of 15 g a.s./ha, with wheat, carrots, and spinach being planted 1, 4, and 12 months later. As expected, the spinach of the first re-cropping did not grow normally due to phytotoxicity. In the plants that however did develop, the total radioactive residues in the edible part were extremely low (maximum of 0.0016 mg/kg in wheat grain of the first re-cropping). The residues in the non-edible part of the plants were also low. The total residues in straw did not exceed 0.0219 mg/kg (in wheat of the first re-cropping). No residues at or above the limit of quantification (< 0.01 mg/kg) can be expected in succeeding crops.

IIIA 8.7 Proposed Residue Definition and Maximum Residue Levels

IIIA 8.7.1 Proposed residue definition

According to Article 12 of Regulation (EC) No 396/2005, the European Food Safety Authority (EFSA) has reviewed the Maximum Residue Levels (MRLs) currently established at European level for the pesticide active substance mesosulfuron-methyl. A reasoned opinion on the review of the existing maximum residue levels (MRLs) for mesosulfuron-methyl was published in EFSA Journal 2012; 10(11):2976.

Table 8.7.1- 1: Current proposed residue definitions

Matrices		Residue definition	Reference
Food of plant origin, cereals	Risk assessment and Monitoring	mesosulfuron-methyl	EFSA Journal 2012; 10(11):2976
Food of animal origin	Risk assessment and Monitoring	None, as no residue anticipated	

IIIA 8.7.2 Proposed maximum residue levels (MRLs)

According to the EFSA review, MRLs for the animal commodities are not required because animals are not expected to be exposed to significant levels of residues.

Table 8.7.2- 1: Current MRLs established by EFSA

Commodity	MRL (mg/kg)	Reference
Rye grain	0.01*	EFSA Journal 2012; 10(11):2976
Wheat grain	0.01*	

* indicates that the MRL is set at the limit of analytical quantification

IIIA 8.8 Proposed Pre-Harvest Intervals, Re-Entry or Withholding Periods

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

It is not necessary to define a pre-harvest interval. Instead, the pre-harvest interval is given by the growing period between the growth stage at treatment and harvest.

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

Product IMS+MSM+MPR OD 42 is not intended for use in areas where livestock animals may be grazed. Therefore no re-entry period needs to be proposed.

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

The product is intended for use in cereal. Re-entry in treated fields is generally not necessary. Also, the product is applied early post-emergence on very young plants. Thus, dermal exposure to persons entering a treated field is negligible. No use in buildings is intended. Therefore no re-entry period needs to be proposed.

IIIA 8.8.4 Withholding period (in days) for animal feedingstuffs

The cereal commodities fed to livestock consist of grain and straw harvested at normal maturity. The highest residue levels of mesosulfuron-methyl likely to be present in these commodities were taken into account when proposing MRL values for these substances in food of animal origin (refer to point 8.7.2). No other cereal commodity is usually fed to livestock. Therefore it is not necessary to define a withholding period for animal feeding stuff.

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

The product is always applied after sowing the cereals to be protected. Therefore there is no need to define a waiting period between last application and sowing or planting the crops to be protected.

IIIA 8.8.6 Waiting period between application and handling treated products

Handling of treated cereals is generally not required before harvest, which is always done mechanically. Furthermore, the residue levels in grain are low. Therefore there is no need to define a waiting period between application and handling treated products. It is covered by the vegetation period of the crop.

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

No measurable residues are expected in succeeding crops for mesosulfuron-methyl. Therefore there is no need to define a waiting period before sowing or planting succeeding crops.

IIIA 8.9 Other/Special Studies

The active substance summary for mesosulfuron-methyl sufficiently addresses aspects of the residue situation that might arise from the use of product IMS+MSM+MPR OD 42. Therefore, other special studies are not needed.

IIIA 8.10 Estimation of Exposure Through Diet and Other Means

The ADI and ARfD for the active substance mesosulfuron-methyl contained in IMS+MSM+MPR OD 42 are summarised in the table below.

Toxicological endpoints for mesosulfuron-methyl

Compound	Endpoint	Value (mg/kg bw)	Study	Safety factor	Reference
Mesosulfuron-methyl	Acceptable Daily Intake (ADI)	1	Mouse oncogenicity study	100	SANCO/10298/2003-Final 25 June 2004
	Acute Reference Dose (ARfD)	No value proposed as mesosulfuron-methyl is not acutely toxic			

IIIA 8.10.1 TMDI calculations

In order to evaluate the potential chronic exposure to mesosulfuron-methyl residues through the diet, the Theoretical Maximum Dietary Intakes (TMDI) was estimated using the EFSA PRIMo model (revision 2). For the evaluation of the chronic exposure the model uses 5 WHO diets relevant to the EU and 22 national diets from 13 different EU Member States.

TMDI calculation was performed using the MRLs given in Table 8.10.1-1.

Table 8.10.1- 1 : input values used for TMDI calculation of mesosulfuron-methyl

Commodity	Chronic risk assessment		
	Input value (mg/kg)	Comment	Origin of the MRL
Rye grain	0.01*	Rye grain	EFSA Journal 2012; 10(11):2976
Wheat grain	0.01*	Wheat grain	

As shown in Table 8.10.1- 2, the highest TMDI calculated for mesosulfuron-methyl represented less than 1% of the ADI, which denotes considerable margins of safety.

Table 8.10.1- 2: Highest TMDI calculated for mesosulfuron-methyl according to the EFSA model

Compound	EFSA model Highest TMDI (%ADI)	Highest contributor	
		MS diet	Commodity / group of commodities
Mesosulfuron-methyl	0.01	WHO Cluster diet B	cereals

Acute Reference Dose (ARfD) and Dietary Exposure Calculation

No ARfD was allocated. On the basis of its toxicological profile, mesosulfuron-methyl is considered unlikely to present an acute hazard.

IIIA 8.10.2 NEDI calculations

Since the TMDI calculation for mesosulfuron-methyl demonstrate a considerable margin of safety, it was not deemed necessary to perform NEDI calculations in order to refine the dietary risk assessment.

IIIA 8.10.3 NESTI calculations

Mesosulfuron-methyl is characterised by low acute toxicity and it was not deemed necessary to set or propose an ARfD for these compounds. It is, therefore, not relevant to perform NESTI calculations.