# FINAL REGISTRATION REPORT

## Part B

## Section 10

## Assessment of the relevance of metabolites in groundwater

Detailed summary of the risk assessment

---

Product code: **102000025743**

Product name(s): **Foramsulfuron + Thiencarbazone-methyl OD 80 (50+30 g/L)**

(Active substance(s))

---

**Central Zone**

**Zonal Rapporteur Member State: Poland**

**CORE ASSESSMENT**

**(Re-Authorisation)**

---

Applicant: **Bayer Crop Science Division**

Submission date: **31/08/2020**

MS Finalisation date: **06/2021; 12/2021**

# Version history

| When | What |
|---|---|
| 31/08/2020 | Original Bayer Crop Science document (Regulation 1107/2009 - Art. 43)<br>Foramsulfuron |
| June 2021 | Assessment by the expert |
| December 2021 | Final version prepared by zRMS after Commenting period |
| | |

# OECD Statement on Confidentiality

The summaries and evaluations contained in this monograph or review report may be based on unpublished proprietary data submitted for the purpose of the assessment undertaken by the regulatory authority that prepared it. Other registration authorities should not grant, amend, or renew a registration on the basis of the summaries and evaluation of unpublished proprietary data contained in this Monograph or review report unless they have received the data on which the summaries and evaluation are based, either:

- From the owner of the data; or
- From a second party that has obtained permission from the owner of the data for this purpose or, alternatively, the applicant has received permission from the data owner that the summaries and evaluation contained in this Monograph or review report may be used in lieu of the data; or
- Following expiry of any period of exclusive use, by offering – in certain jurisdictions – mandatory compensation;

unless the period of protection of the proprietary data concerned has expired.

Applicants wishing to avail of information in this Monograph or review report should seek advice from the regulatory authority to which application is made concerning the requirements in their country.

# Table of Contents

# 10 Relevance of metabolites in groundwater

**Thiencarbazone-methyl (non renewed active ingredient)**
In agreement with the Guidance Document on the Renewal of Authorisations according to Article 43 of Regulation (EC) No 1107/2009 (SANCO/2010/13170), for products containing two or more active substances and when the 1st substance is renewed, there is no need to evaluate data related to the 2nd substance.
Thiencarbazone-methyl (TCM) is the active ingredient not being renewed and therefore data pertaining to TCM should not be evaluated in this application unless they are required for mixture toxicity risk assessment.

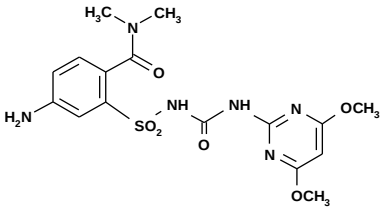
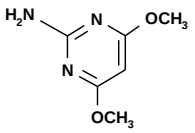
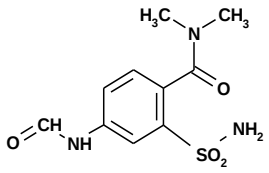
## 10.1 General information

### Foramsulfuron

None of the metabolites of foramsulfuron is predicted to occur in groundwater recharge at concentrations above 0.1 µg/L for the intended uses of the product (see dRR part B.8, Point 8.8). An assessment of the relevance of metabolites according to the stepwise procedure of the EC guidance document SANCO/221/2000 –rev.10 is therefore not required for this active substance.

General information on the metabolites is provided in Table 10.1-1. The impact of the relevance assessment on whether a particular GAP use leads to acceptable risk or not is presented in the summary of the cGAP evaluation in dRR Part B, Section 8 (Environmental fate and behaviour).

**Table 10.1-1: General information on the metabolites**

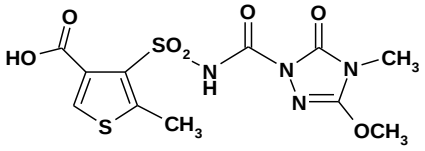
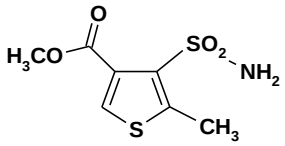
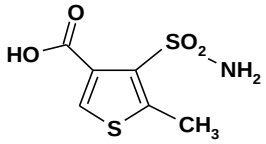
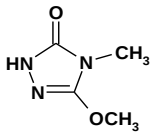
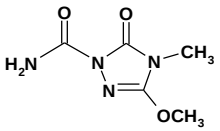
| Name of active substance | Metabolite name and code | Structural/molecular formula | Trigger for relevance assessment | |
|---|---|---|---|---|
| Foramsulfuron | AE F130619 |  | Max $PEC_{gw}$<br>Based on: | <0.001 µg/L<br>All uses, PEARL & PELMO |
| Foramsulfuron | AE F092944 |  | Max $PEC_{gw}$<br>Based on: | <0.001 µg/L<br>All uses, PEARL & PELMO |
| Foramsulfuron | AE F153745 |  | Max $PEC_{gw}$<br>Based on: | <0.001 µg/L<br>All uses, PEARL & PELMO |

### Thiencarbazone-methyl

The thiencarbazone-methyl metabolite BYH 18636-carboxylic acid is predicted to occur in groundwater recharge at concentrations above 0.1 µg/L (see dRR part B.8, Point 8.8). Assessment of the relevance of this metabolite according to the stepwise procedure of the EC guidance document SANCO/221/2000 – rev.10 is therefore required.

General information on the metabolite is provided in Table 10.1-2. The impact of the relevance assessment on whether a particular GAP use leads to acceptable risk or not is presented in the summary of the cGAP evaluation in chapter 8.8 of the dRR Part B, Section 8 (Environmental fate and behaviour).

**Table 10.1-2: General information on the metabolites of thiencarbazone-methyl**

| Name of active substance | Metabolite name and code | Structural/molecular formula | Trigger for relevance assessments | |
|---|---|---|---|---|
| Thiencarbazone-methyl | BYH 18636-carboxylic acid (AE 1394083) |  | Max $PEC_{gw}$<br>Based on: | **1.486 µg/L**<br>PEARL simulation for the use of 2 × 15 g a.s./ha in sugar beet, scenario Hamburg |
| Thiencarbazone-methyl | BYH 18636-sulfonamide (AE 1364547) |  | Max $PEC_{gw}$<br>Based on: | <0.001 µg/L<br>All uses, PEARL & PELMO |
| Thiencarbazone-methyl | BYH 18636-sulfonamide carboxylic acid (AE 1395853) |  | Max $PEC_{gw}$<br>Based on: | 0.058 µg/L<br>PEARL simulation for the use of 2 × 15 g a.s./ha in sugar beet, scenario Hamburg |
| Thiencarbazone-methyl | BYH 18636-MMT (AE 1277106) |  | Max $PEC_{gw}$<br>Based on: | 0.070 µg/L<br>PEARL simulation for the use of 2 × 15 g a.s./ha in sugar beet, scenario Jokioinen |
| Thiencarbazone-methyl | BYH 18636-triazolinone-carboxamide (AE 1430601) |  | Max $PEC_{gw}$<br>Based on: | 0.011 µg/L<br>PELMO simulation for the use of 2 × 15 g a.s./ha in sugar beet, scenario Sevilla |

## 10.2 Relevance assessment of BYH 18636-carboxylic acid, metabolite of thiencarbazone-methyl

**Summary:**

The relevance of the groundwater metabolite BYH 18636-carboxylic acid has been assessed and the assessment agreed at EU level (see EU DAR (2012) of thiencarbazone-methyl, and the corresponding EFSA conclusion (EFSA Journal 2013;11(7):3270). The relevance assessment agreed at EU level represents a worst case and covers in a risk envelope approach as well as the GAP and groundwater scenarios considered in this dRR (i.e., the conclusions reached at Step 4 and 5 of the relevance assessment made at the EU-level also cover the $PEC_{gw}$ calculated for the GAP and groundwater scenarios considered in this dRR). BYH 18636-carboxylic acid is not considered relevant according to the criteria laid down in the EC guidance document SANCO/221/2000 –rev.10. A summary of the relevance assessment is given in Table 10.2-1 and the related studies are listed in the corresponding sections.

**Table 10.2-1: Summary of the relevance assessment for BYH 18636-carboxylic acid**

| | Assessment step | | Result of assessment | |
|---|---|---|---|---|
| | STEP 1 | | Metabolite of no concern? | no |
| **Quantification of groundwater contamination** | STEP 2 | | Max $PEC_{gw}$ | 1.486 µg/L |
| | | | Based on | PEARL simulation for the use of 2 × 15 g a.s./ha in sugar beet, scenario Hamburg |
| **Hazard assessment** | STEP 3 | Stage 1 | Biological activity comparable to the parent? | no |
| | | Stage 2 | Genotoxic properties of metabolite | non-genotoxic |
| | | Stage 3 | Toxic properties of metabolite | |
| | | | Classification of parent | No classification and labelling proposed with respect to toxicological profile (ECHA 2018**) |
| | | | Classification of metabolite | none |
| **Consumer health risk assessment** | STEP 4 | | Estimated consumer exposure via drinking water and other sources; threshold of concern approach | not acceptable (>0.75 µg/L) |
| | STEP 5 | | Refined risk assessment | acceptable |
| | | | Predicted exposure (% of ADI) | 0.023% of ADI (infant)<br>0.015% of ADI (child)<br>0.005% of ADI (adult) |
| | | | ADI based on | NOAEL of 15000 ppm (equivalent to mean achieved dietary intake of 972 mg/kg bw/d in males) from 90-day rat study |

* N/A: not applicable

** Opinion of the committee for risk assessment on a dossier proposing harmonised classification and labelling at EU level (ECHA, 30th of November 2018. CLH-O-0000001412-86-244/F

### 10.2.1 STEP 1: Exclusion of degradation products of no concern

BYH 18636-carboxylic acid does not meet the criteria for products of no concern as defined in step 1 of the guidance and therefore needs further assessment.

### 10.2.2 STEP 2: Quantification of potential groundwater contamination

$PEC_{gw}$ calculations after leaching from soil for BYH 18636-carboxylic acid were performed (see Part B, Section 8, chapter 8.8). The use for which concentrations of BYH 18636-carboxylic acid were considered to exceed 0.1 µg/L is listed in Table 10.2-1. Details are given in Part B, Section 8, chapter 8.8.

### 10.2.3 STEP 3: Hazard assessment – identification of relevant metabolites

#### 10.2.3.1 STEP 3, Stage 1: screening for biological activity

The biological activity of BYH 18636-carboxylic acid does not have comparable target activity as the parent active compound as shown in biological screening data. BYH 18636-carboxylic acid is considered not relevant and is further evaluated in Stage 2.

The biological screening on the metabolite has been considered within the EU peer review process (cf. DAR of thiencarbazone-methyl, 2012, Vol.3, Annex B.9: Ecotoxicology – Part A: Study evaluations, B.9.9.1 and EFSA conclusion on thiencarbazone-methyl (EFSA Journal 2013;11(7):3270)).

#### 10.2.3.2 STEP 3, Stage 2: screening for genotoxicity

BYH 18636-carboxylic acid was addressed for genotoxic activity by the following data package of *in vitro* genotoxicity studies: Ames Test on *Salmonella Typhimurium*, Chromosomal aberrations in Chinese Hamster V79 cells, Gene mutation (HPRT) in Chinese Hamster V79 cells and *in vitro* micronucleus test.

These genotoxicity studies, except the *in vitro* micronucleus, have been evaluated within the EU peer review process (cf. DAR of thiencarbazone-methyl, 2012, Vol.3, Annex B.6: Toxicology & Metabolism – Part A: Study evaluations, B.6.8.1).

The micronucleus test in human lymphocytes *in vitro* confirmed the absence of evidence for genotoxic potential of the BYH 18636-carboxylic acid (M-630020-01-1, 2018, Naumann, S.). The study summary is presented in dRR Section B6 Core Zone.

Negative results in all tests allow to conclude that the metabolite BYH 18636-carboxylic acid would be devoid of genotoxic potential (cf. EFSA conclusion on thiencarbazone-methyl, 2013, Section 2). BYH 18636-carboxylic acid is considered not relevant and is further evaluated in Stage 3.

#### 10.2.3.3 STEP 3, Stage 3: screening for toxicity

The parent compound thiencarbazone-methyl is not proposed for classification as toxic or very toxic, or for reproductive toxicity or carcinogenic properties. Consequently, according to Guidance Document Sanco/221/2000, rev.10-final, 25/02/2003, further toxicity testing with the metabolite is not required based on these criteria.

Nevertheless, acute and 90-day toxicity studies in the rat have been generated on metabolite BYH 18636-carboxylic acid to allow for the completion of a dietary risk assessment which may be triggered for some uses of thiencarbazone-methyl. These studies were evaluated at EU level (cf. DAR of thiencarbazone-methyl, 2012, Vol.3, Annex B.6: Toxicology & Metabolism – Part A: Study evaluations, B.6.8.1), and the following endpoints were agreed (cf. EFSA conclusion on thiencarbazone-methyl (EFSA Journal 2013;11(7):3270)):

- Acute oral $LD_{50}$ (rat) > 2000 mg/kg bw
- 90-day rat study: NOEL 972/1170 mg/kg bw per day (15000 ppm)
- An ADI can be set at 0.972 mg/kg bw per day based on a specific 90-day rat study NOAEL of 972 mg/kg bw per day (highest dose tested) where no evidence of crystal formation was observed."

Furthermore, according to the RAC Opinion (2018), thiencarbazone-methyl does not warrant any classification.

### 10.2.4 STEP 4: Exposure assessment – threshold of concern approach

The metabolite BYH 18636-carboxylic acid was considered not relevant in the hazard assessment of Step 3.
The potential exposure to BYH 18636-carboxylic acid is > 0.75 µg/L but < 10 µg/L. A further assessment in Step 5 is required.

### 10.2.5 STEP 5: Refined risk assessment

The metabolite BYH 18636-carboxylic acid has a $PEC_{gw}$ between 0.75 µg/L and 10 µg/L and thus the threshold of concern approach in Step 4 is not acceptable. A refined assessment of the potential toxicological significance including the selected ADI is presented here.

The consumer risk assessment demonstrates an acceptable risk. The estimated safety margin including potential exposure via other routes besides drinking water for BYH 18636-carboxylic acid are 0.023 % of ADI (infant), 0.015 % of ADI (child), 0.005 % of ADI (adult).

Exposure:
Taking the pore water concentration at 1 m depth under a treated field directly as drinking water, with no processing, the worst case concentration is given by the FOCUS model simulation for the Hamburg scenario to be 1.486 µg/L.

Justification for the selected ADI:
The oral toxicity of metabolite BYH 18636-carboxylic acid was characterised by means of a 90 days study on rat. No effects were observed up to the highest test dose of 15000 ppm, which translates into NOAEL value of 972 mg/kg bw/day. According to the EFSA LoEP, an ADI of 0.972 mg/kg bw/day can be used for risk assessment.

Because the groundwater concentrations are compared to a toxicological reference value of the metabolite, no conversion of the groundwater concentration of the metabolite to parent equivalents is needed.

According to EU/WHO the worst case dietary exposure via water is calculated to be:

$$(daily\ water\ consumption\ [L/day]\ \times PECgw\ [\mu g/L])/(body\ weight\ [kg]) = \text{worst case daily dietary exposure [µg/kg bw/day]}$$

The calculation of the risk (% ADI) is performed according to the following equation:

$$(worst\ case\ daily\ dietary\ exposure\ [\mu g/kg\ \text{bw/day}]\ /\text{ADI [µg/kg bw/day]}\ ) \times 100 = \text{ADI consumption[\%]}$$

Calculation of risk (% ADI) for 5-kg bottle-fed infant (consuming 0.75 L/day):

Worst case daily dietary exposure of 5-kg bottle fed infant = **0.223 µg/kg bw/d**
Risk for 5-kg bottle fed infant (% ADI) = **0.023 %**

Calculation of risk (% ADI) for 10-kg child (consuming 1.0 L/day):

Worst case daily dietary exposure of 10-kg child = **0.149 µg/kg bw/d**
Risk for 10-kg child (% ADI) = **0.015 %**

Calculation of risk (% ADI) for 60-kg adult (consuming 2.0 L/day):

Worst case daily dietary exposure of 60-kg adult = **0.050 µg/kg bw/d**
Risk for 60-kg adult (% ADI) = **0.005 %**

## Conclusions

## Thiencarbazone-methyl

## BYH18636-carboxylic acid (BCS-AT36039, AE 1394083): Micronucleus Test in Human Lymphocytes *In vitro;* M-630020; 29/05/2019

In conclusion, it can be stated that under the experimentl conditions reported, the test item did not induce micronuclei as determined by the *in vitro* micronucleus test in human lymphocytes.Therefore, BYH18636-carboxylic acid (BCS-AT36039, AE 1394083) is considered to be non-mutagenic in this *in vitro* micronucleus test, when tested up to the highest required concentration.

The results of the calculations for the chronic exposure show that possible intakes of the metabolite BYH 18636-carboxylic acid by the means of drinking water do not present a consumer health concern. The intended use of FSN+TCM OD 80 (50+30) would not lead to any unacceptable risk via groundwater exposure to metabolite BYH 18636-carboxylic acid of thiencarbazone-methyl.

**(Assessment of the relevance of metabolites in groundwater was in the dRR Part B8, Core Assessment 2015)**

## Foramsulfuron

**Ad. STEP 3, Stage 2: screening for genotoxicity**

**1/**

**MUTAGENICITY STUDY OF AE F092944 IN THE *SALMONELLA TYPHIMURIUM* REVERSE MUTATION ASSAY (*IN VITRO*) November 16, 2017. M-644749**

AE F092944 tested up to the concentration of 5000 µg/plate, caused no mutagenic effect in the *Salmonella typhimurium* strains TA98, TA100, TA102, TA1535 and TA1537 neither in the plate incorporation test nor in the preincubation test each carried out without and with metabolic activation.

**2 /**

**Regulatory Toxicology Position Paper Subject amidosulfuron, In silico assessment of the metabolite AE F092944; 26 March 2019; M-654051**

The in silico evaluation of AE F092944 showed no effect in long term studies in rats or mice with amidosulfuron in which this metabolite AE F092944 was an impurity at a concentration of 3 g / kg, no toxicological risk is to be expected. This is particularly important as consumer exposure is not to be expected as AE F092944 does not exceed the groundwater trigger value nor was it detected in plant metabolism studies.

**3/**

## DEREK NEXUS REPORT 02/10/2015

A QSAR analysis by DEREK analysis (2015, M-685932-01-1) confirmed that the toxicity profile of AE F092944 was similar to that of the parent. The DEREK analysis gave alerts for foramsulfuron of bladder urothelial hyperplasia, hepatotoxicity, phototoxicity and skin sensitization, which, however, were not confirmed by the experimental data. These alerts are hence not relevant and similar alerts which were given for some of the metabolites are also not regarded as relevant. Therefore, the DEREK analysis did not give results for AE F092944 which would raise concerns. Also another QSAR analysis of AE F092944 as metabolite of another parent compound, amidosulfuron, with Derek Nexus, Leadscope and Toxtree models (Shipp, 2019, M-654051-01-1) did not indicate a higher toxicity than that of this parent.

As none of the metabolites of foramsulfuron are expected to occur in the groundwater feed at concentrations above 0.1 µg / l for the intended uses of the product no further research is warranted. The conducted study and evaluation of insilico did not show any genotoxic activity of the metabolite AE F092944

It can be concluded that AE F092944 has no higher toxic potential than foramsulfuron and thus does not present a hazard.

# Appendix 1 Lists of data considered in support of the evaluation

Tables considered not relevant can be deleted as appropriate.

MS to blacken authors of vertebrate studies in the version made available to third parties/public.

All presented information required for assessment of the relevance of metabolites in groundwater is found included in the EU review documentation (DAR, RAR, or EFSA journals) to the active substances of this formulation, or the previous dRR sections; no additional data was necessary to complete the assessments.
Please note that all data mentioned as part of DAR, RAR, or EFSA journals are considered as relied on.

| **Data point** | **Author(s)** | **Year** | **Title**<br>**Company Report No.**<br>**Source (where different from company)**<br>**GLP or GEP status**<br>**Published or not** | **Vertebrate study**<br>**Y/N** | **Owner** |
|---|---|---|---|---|---|
| - | - | - | - | -- | |

**List of data submitted or referred to by the applicant and relied on, but already evaluated at EU peer review**

Please note that all data mentioned as part of DAR, RAR, or EFSA journals are considered as relied upon.
Bayer is the owner of the data package peer-reviewed for the EU re-approval of the active substance **foramsulfuron** and the EU approval of **thiencarbazone-methyl.**
Data protection will be requested when relevant at MS level in the Part A.

**Metabolite BYH 18636-carboxylic acid**
The following studies are considered as already evaluated at EU peer review as they are referenced in the document entitled ("Council Directive 91/414/EEC. Thiencarbazone-methyl (BYH 18636) - Volume 2 - Annex A to the Draft Report and Proposed Decision - List of tests and studies submitted and information available (by Annex point). 2012)

| Data point | Author(s) | Year | **Title**<br>**Company Report No.**<br>**Source (where different from company)**<br>**GLP or GEP status**<br>**Published or not** | **Vertebrate study Y/N** | Owner |
|---|---|---|---|---|---|
| KIIA 8.12 /05 | Hess, M. | 2006 | Evaluation of the pre-emergence biological activity of AE 1394083, the carboxylic acid of thiencarbazone.methyl<br>Bayer CropScience GmbH, Frankfurt am Main, Germany<br>Bayer CropScience AG,<br>Report No.: PP03067, Edition Number: M-274414-02-1<br>Date: 22.06.2006<br>Non GLP, unpublished | No | Bayer |
| KIIA 8.12 /06 | Hess, M. | 2006 | Evaluation of the post-emergence biological activity of AE 1394083, the carboxylic acid of thiencarbazone-methyl<br>Bayer CropScience GmbH, Frankfurt am Main, Germany<br>Bayer CropScience AG,<br>Report No.: PP04013, Edition Number: M-274413-02-1<br>Date: 22.06.2006<br>Non GLP, unpublished | No | Bayer |

The following tables are to be completed by MS

**List of data submitted by the applicant and not relied on**

| Data point | Author(s) | Year | Title<br>Company Report No.<br>Source (where different from company)<br>GLP or GEP status<br>Published or not | Vertebrate study<br>Y/N | Owner |
|---|---|---|---|---|---|
| | | | | | |

**List of data relied on not submitted by the applicant but necessary for evaluation**

| Data point | Author(s) | Year | Title<br>Company Report No.<br>Source (where different from company)<br>GLP or GEP status<br>Published or not | Vertebrate study<br>Y/N | Owner |
|---|---|---|---|---|---|
| | | | | | |

# Appendix 2 Additional information

Not needed.