REGISTRATION REPORT

# Part B

# Section 10

# Assessment of the relevance of metabolites in groundwater

Detailed summary of the risk assessment

Product code: ADM.06001.H.2.B

Product name(s): Edaptis

Chemical active substance(s):

Mesosulfuron-methyl, 12 g/L
Pinoxaden, 60 g/L

Safener: Mefenpyr-diethyl, 35 g/L

Central Zone

Zonal Rapporteur Member State: Poland

CORE ASSESSMENT

(authorization)

Sponsor: ADAMA Agan Ltd.
Applicant: Country organisation / representative of ADAMA, as given in Part A

Submission date: June 2021, updated September 2022

MS Finalisation date: July 2022, updated May 2023 (initial Core Assessment)

September 2023, December 2023 (final Core Assessment)

# Version history

| When | What |
|---|---|
| June 2021 | First version submitted by applicant |
| September 2022 | Updated PECgw values following comments of zRMS Poland |
| July 2022 | Initial assessment by the zRMS<br>The report in the dRR format has been prepared by the Applicant, therefore all comments, additional evaluations and conclusions of the zRMS are presented in grey commenting boxes. Minor changes are introduced directly in the text and highlighted in grey. Not agreed or not relevant information are ~~struck through and shaded for transparency~~.<br>Following the evaluation and before sending the document for commenting, all coloured highlighting was removed, from the parts updated by the Applicant, for better legibility. |
| May 2023 | Updated PECgw values based on zRMS assessment also Step 5 has been added. |
| September 2023 | Final report (Core Assessment updated following the commenting period)<br>Additional information/assessments included by the zRMS in the report in response to comments received from the cMS and the Applicant are highlighted in yellow. Information no longer relevant ~~is struck through and shaded~~. |
| December 2023 | Final report (Core Assessment updated following the second commenting period)<br>No additional information or assessments after the second commenting period. |

## DATA PROTECTION CLAIM

Under Article 59, Regulation 1107/2009/EC, on behalf of the Sponsor Company the applicant claims data protection for these studies. The data protection status and corresponding justification as valid for the respective country will be confirmed in the respective PART A

## STATEMENT FOR OWNERSHIP

The summaries and evaluations contained in this document may be based on unpublished proprietary data submitted for the purpose of the assessment undertaken by the regulatory authority that prepared it.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 document unless they have received the data on which the summaries and evaluation are based, either –

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**Reviewer comments:**

This part of dossier has been submitted to support registration of the plant protection product AG-E1-500 SC1 according art. 33 of 1107/2009. Document refers data related to the forming of metabolites in the environment (see dRR B8). dRR Part B10 has been reviewed for the purposes of ongoing registration and also checked its compliance with the current guidelines.

**NOTE:** ADAMA Polska Sp. z o.o. has been granted (LoA) to refer data of pinoxaden to support an application for registration for their OD formulation EDAPTIS 72 OD.

Discussion regarding pinoxaden metabolites:
In 2012 it has been finalized evaluation of the dossier on pinoxaden in the Draft Assessment Report. Conclusions has been laid down in the EFSA, 2013. "*Conclusion on the peer review of the pesticide risk assessment of the active substance pinoxaden*", EFSA Journal 2013;11(8):3269.

Regarding Mammalian toxicity among other things, it was found that: "(..)*The groundwater metabolites M2, M3, M11, M52, M54 M55 and M56 are considered relevant: M2 is a significant metabolite in the rat (94% in urine). It contributes to the toxicological profile of the active substance and it has comparable biological activity to pinoxaden. M3 should be considered relevant if EChA confirms R63 proposed for pinoxaden; the expert meeting set a specific ADI for M3 of 0.01 mg/kg bw per day. For the metabolites M11, M52, M54, M55 and M56 only genotoxicity data are available; they should all be considered relevant based on the toxicological properties of pinoxaden (provided the proposal for the classification of R63 is confirmed by EChA).*(..)"

In the updated ATP 13 (5th October 2018) entered into force from 1 December 2019 it has been confirmed hazard classification for pinoxaden as developmental toxicant in category Repro 2, H361d on the basis of an increased incidence of diaphragmatic hernia in the rabbit.

Taking into account the discussed above information, the main owner of the active substance decided to submit Confirmatory Data (evaluated by the RMS AT) in order to establish the developmental toxicity of metabolites requiring an assessment of relevance (i.e. metabolites M3, M11, M54, M55, and M56), and due to the impossibility to synthesise sufficient test material of M11, M54, M55 and M56 Notifier of a.s. have conducted a developmental toxicity study in the rabbit with metabolite M3 (Britton, 2017). This study demonstrates that M3 is not developmentally toxic.

Since the metabolites M11, M54, M55, and M56 are form from metabolite M3 in the environment, and therefore metabolite M3 should be considered to be the parent of these metabolites for the purposes of assessment of hazard classification carryover. therefore conducted a developmental toxicity study in the rabbit with metabolite M3 and propose to use this "grouping" approach to conclude on the developmental toxicity of metabolites M11, M54, M55, and M56.

The EFSA response (2016) to this proposed grouping approach was: "*According to applicant's claim above, M3 is the precursor of metabolites M11, M54, M55 and M56 in the environment, but not M52. On this basis, provided that adequate evidence is given that the M3 is their precursor and having into consideration the "general concept" of the guidance document on the relevance of groundwater metabolites for PPPs, we would agree that in terms of toxicity screening according to stage 3 of step 3, the relevance of metabolites formed from another metabolite would be covered by the toxicity profile of the precursor. This approach however does not seem to apply to M52.*"

Regarding last sentence, owner of the a.s stated that M52 is not included within this group as it does not form from M3 in the environment, however M52 has not been observed above 0.1 µg/L in the relevant spring applied lysimeter study.

In addition as part of the non-relevance position for metabolites M3, M11, M52, M54, M55, and M56 an *in vivo* micronucleus assay was conducted for each metabolite. These assays were all negative, demonstrating that these metabolites do not exhibit clastogenic or aneugenic activity *in vivo*.

RMS AT considered and agrees with the relevance assessment performed by the applicant. M3 is not considered relevant according to the criteria laid down in the EC guidance document SANCO/221/2000–rev.10 as M3 is not biologically active, not genotoxic and does not warrant the same development toxicity classification as pinoxaden (H361d).

M11, M54 and M56 are not biologically active and not genotoxic. The owner of a.s, performed a read across to M3

regarding developmental toxicity. According to this, M11, M54 and does not warrant the same development toxicity classification as pinoxaden (H361d).

Regarding M55 it was concluded that is not biologically active also owner of a.s, performed a read across to M3 regarding developmental toxicity. According to this, M55 does not warrant the same development toxicity classification as pinoxaden (H361d).

In case genotoxicity potential of M55 it was tested for genotoxic activity by the following data package of *in vitro* genotoxicity studies: Ames test, gene mutation test with mammalian cells, an *in vivo* micronucleus test, and an *in vivo* unscheduled DNA synthesis assay. M55 was negative the mammalian gene mutation assay and the *in vivo* micronucleus assay, but was one positive in a bacterial reverse mutation assay. This study was originally followed up with a rat liver un-scheduled DNA synthesis assay, this assay was clearly negative and was considered to be the appropriate follow-up study at the time. Since EFSA in 2017 states that in this situation an *in vivo* comet assay may be a more appropriate follow up assay. In order to further assess the genotoxicity of this metabolite a comet assay was conducted, examining both a site of contact and a site of metabolism tissue.

Outcome of this comet assay is supported by the previously conducted unscheduled DNA synthesis assay as no indication of genotoxicity was observed in the site of metabolism tissue, some indications of a genotoxic response were observed in the site of contact tissue. Notifier confirmed that, all sections of this tissue examined showed a significant increase of "hedgehog" cells, potentially indicating overdosing of this tissue. The presence of these "hedgehog" cells complicated the analysis of these tissues and made these sections uninterpretable. Based on this discussed assay is therefore considered to be clearly negative in the site of metabolism tissue, however a conclusion on the genotoxic potential observed in the site of contact tissue cannot be made.

Due to this study outcome the owner of a.s. presented recently to RMS AT a PBPK model to address the equivocal outcome of the COMET assay:
*Notifier took further steps to clarify the genotoxicity profile of M55 due to the equivocal findings in the in vivo Comet assay by conducting PBPK modelling to understand if the findings in the duodenum are the result of localized high concentrations of M55. The exposure to M55 in the duodenum was assessed to be 16125 – 43245 times higher than the exposure in the liver. This significantly increased (over)-exposure in the duodenum would account for the observations seen, and therefore the equivocal finding in the duodenum should be dismissed as biologically not relevant.*

Considering conclusions and results of Confirmatory Data reviewed by the RMS AT, zRMS PL agree that the metabolites of pinoxadene M11, M54 and M56 are not biologically active and not genotoxic. Read across to M3 regarding developmental toxicity confirm that M11, M54, M55 and M56 does not warrant the same development toxicity classification as pinoxaden (H361d). Thus they are not relevant and Step 4 and 5 can be performed.

In case genotoxicity potential of M55 considering whole pattern of observed effects (also discussed in the DRAR 2012) zRMS PL is in the opinion that mentioned metabolite M55 do not possess genotoxic potential thus it is not relevant however PL is cautious about the results of the equivocal outcome of the COMET test on the site of contact tissue (duodenum) and we agree with AT that this issue can be further discussed.

**Additional note of the Section B8 Reviewer:**
Initially, in the evaluation of the toxicological relevance of pinoxaden groundwater metabolites the Applicant referred to results of the EU agreed lysimeter studies, where all metabolites potentially migrating to groundwater were detected at concentrations <0.75 µg/L. However, no justification of the representativeness of the test sites in the lysimeter studies to conditions in particular countries in which authorization of ADM.06001.H.2.B has been presented by the Applicant and for this reason the zRMS efate expert concluded that results of the lysimeter studies may be used only as additional information but cannot be relied upon to derive final conclusion for the whole Central Zone. Therefore it was decided to rely on results of the Tier 2 groundwater modelling in the evaluation presented in area of Section 8. However, results of the lysimeter studies may be considered by particular cMS if considered reliable and sufficient for conditions of their countries.

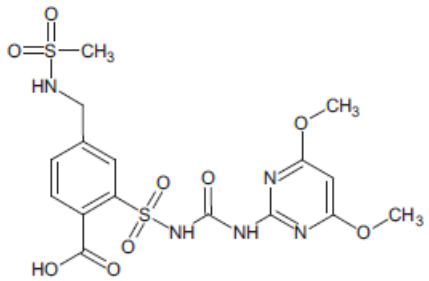
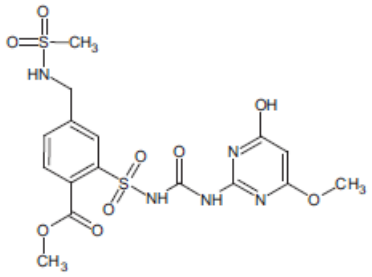
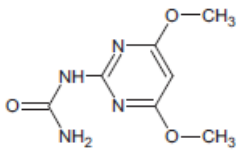
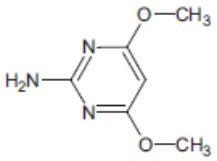
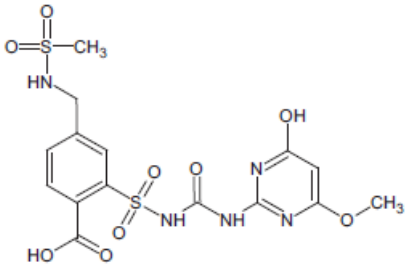
# 10 Relevance of metabolites in groundwater

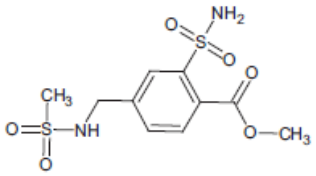
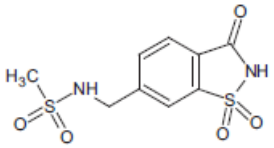
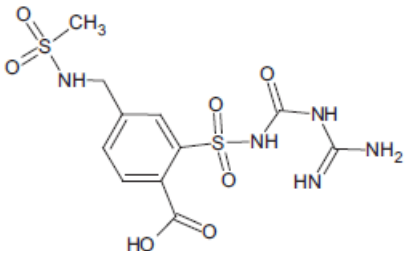
## 10.1 Mesosulfuron-methyl and metabolites

### 10.1.1 General information

General information on the metabolites of mesosulfuron-methyl 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 chapter 8.1 of the dRR Part B, Section 8 (Environmental fate and behaviour).

**Table 10.1-1: General information on the metabolites of mesosulfuron-methyl**

| Name of active sub-stance | Metabolite name and code | Structural/molecular formula | Trigger for relevance assessment | |
|---|---|---|---|---|
| Mesosulfuron-methyl | Mesosulfuron<br>AE F154851 |  | Max $PEC_{gw}$<br>Spring cereals<br>[µg/L]<br><br>Based on: | Annual: 0.046*<br><br>FOCUS PEARL 4.4.4<br>Scenario Hamburg<br>1 x 12 g/ha<br>Application post-emergence<br>BBCH 13-39 (0% interception) |
| Mesosulfuron-methyl | AE F160459 |  | Max $PEC_{gw}$<br>Spring cereals<br>[µg/L]<br><br>Based on: | Annual: 0.227*<br><br>FOCUS PEARL 4.4.4<br>Scenario Hamburg<br>1 x 12 g/ha<br>Application post-emergence<br>BBCH 13-39 (0% interception) |
| Mesosulfuron-methyl | AE F099095 |  | Max $PEC_{gw}$<br>Winter and Spring cereals<br>[µg/L]<br><br>Based on: | Annual: <0.001<br><br>All scenarios<br>1 x 12 g/ha<br>Application post-emergence<br>BBCH 13-20 (0% interception) |
| Mesosulfuron-methyl | AE F092944 |  | Max $PEC_{gw}$<br>Winter and Spring cereals<br>[µg/L]<br><br>Based on: | Annual: <0.001<br><br>All scenarios<br>1 x 12 g/ha<br>Application post-emergence<br>BBCH 13-20 (0% interception) |
| Mesosulfuron-methyl | AE F160460 |  | Max $PEC_{gw}$<br>Spring cereals<br>[µg/L]<br><br>Based on: | Annual:0.105*<br><br>FOCUS PEARL 4.4.4<br>Scenario Hamburg<br>1 x 12 g/ha<br>Application post-emergence<br>BBCH 13-39 (0% interception) |

| Name of active substance | Metabolite name and code | Structural/molecular formula | Trigger for relevance assessment | |
|---|---|---|---|---|
| Mesosulfuron-methyl | AE F140584 |  | Max $PEC_{gw}$ Spring cereals [µg/L]<br><br>Based on: | Annual: 0.019*<br><br>FOCUS PELMO 5.5.3 Scenario Jokioinen 1 x 12 g/ha Application post-emergence BBCH 13-39 (0% interception) |
| Mesosulfuron-methyl | AE F147447 |  | Max $PEC_{gw}$ Spring cereals [µg/L]<br><br>Based on: | Annual: 0.330*<br><br>FOCUS PEARL 4.4.4 Scenario Jokioinen 1 x 12 g/ha Application post-emergence BBCH 13-39 ~~13-20~~ (0% interception) |
| Mesosulfuron-methyl | BCS CV14885 |  | Max $PEC_{gw}$ Spring cereals [µg/L]<br><br>Based on: | Annual: 0.416*<br><br>FOCUS PEARL 4.4.4 Scenario Hamburg 1 x 12 g/ha Application post-emergence BBCH 13-39 (0% interception) |

The metabolites AE F154851, AE F099095, AE F092944 and AE F140584 are predicted to occur in groundwater at concentrations **below 0.1 µg/L** (see 8.8.2.1 of the dRR Part B, Section 8). Assessment of the relevance of these metabolites according to the stepwise procedure of the EC guidance document SANCO/221/2000 –rev.10 is therefore **not** required.

Assessment of the relevance of metabolites AE F160459, AE F160460, AE F147447 and BCS CV14885 is presented below.

## 10.1.2 Relevance assessment of AE F160459

**Summary:**

The groundwater metabolite AE F160459 is not considered as relevant according to the criteria laid down in the EC guidance document SANCO/221/2000 – rev.10. A summary of the relevance assessment for AE F160459 is given in Table 10.1-2. Studies supporting $PEC_{gw}$ data are evaluated in Section 8 (Environmental fate and behaviour) and the genotoxicity studies are evaluated in Section 6 (Mammalian Toxicology).

**Table 10.1-2: Summary of the relevance assessment for AE F160459**

| | Assessment step | | Result of assessment | |
|---|---|---|---|---|
| | STEP 1 | | Metabolite of no concern? | no |
| **Quantification of groundwater contamination** | STEP 2 | | Max $PEC_{gw}$ | 0.227 µg/L |
| | | | Based on | FOCUS PEARL 4.4.4<br>Scenario Hamburg<br>Spring cereals |
| **Hazard assessment** | STEP 3 | Stage 1 | Biological activity comparable to the parent? | Less toxic than parent |
| | | Stage 2 | Genotoxic properties of metabolite | Not genotoxic |
| | | Stage 3 | Toxic properties of metabolite; | |
| | | | Classification of parent | Not toxic or highly toxic |
| | | | Classification of metabolite | Not toxic or highly toxic |
| **Consumer health risk assessment** | STEP 4 | | Estimated consumer exposure via drinking water and other sources; threshold of concern approach | $PEC_{GW}$ <0.75 µg/L<br>~~Maximum concentration in lysimeter studies < 0.1 µg/L, which is less than 0.75 µg/L.~~ |
| | STEP 5 | | Refined risk assessment | N/A* |
| | | | Predicted exposure (% of ADI) | N/A* |
| | | | ADI based on | N/A* |

* N/A: not applicable

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

AE F160459 does not meet the criteria for products of no concern as defined in step 1 of the guidance and therefore needs further assessment.

It cannot be excluded as a product of no concern as it is not:

- $CO_2$ or an inorganic compound, not containing a heavy metal;
- an organic compound of aliphatic structure, with a chain length of 4 or less, which consists only of C, H, N or O atoms and which has no "alerting structures" such as epoxide, nitrosamine, nitrile or other functional groups of known toxicological concern;
- a substance which is known to be of no toxicological or ecotoxicological concern, and which is naturally occurring at much higher concentrations in the respective compartment

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

$PEC_{gw}$ calculations after leaching from soil for AE F160459 were performed (see Part B, Section 8, chapter 8.8). There were uses for which concentrations of AE F160459 were considered to exceed 0.1 µg/L therefore further assessment is required.

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

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

The biological activity of metabolite AE F160459 was compared to the biological activity of the active substance mesosulfuron-methyl. The table below summarizes endpoints for studies which have been carried out with both metabolite AE F160459 and mesosulfuron-methyl.

**Table 10.1-3 Comparison of metabolite and active substance endpoints**

| Study | Endpoint | units | Mesosulfuron-methyl | AE F160459 |
|---|---|---|---|---|

| | | | | |
|---|---|---|---|---|
| *Pseudokirchneriella subcapitata* 72h effects on growth | $E_rC_{50}$ | mg/L | 3.99 | >100 |
| *Lemna gibba* 7d effects on growth | $E_rC_{50}$ | mg/L | 0.001717 | 2.6 |

Screening data on herbicidal activity of metabolites of mesosulfuron-methyl indicated that AE F160459 has no herbicidal activity, please refer to the EFSA peer review of mesosulfuron-methyl, EFSA Journal 2016;14(10):4584.

Comparisons of available ecotoxicity endpoints indicate that AE F160459 is has lower biological activity than mesosulfuron-methyl.

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

AE F160459 is considered devoid of mutagenic potential based on structural similarities with mesosulfuron-methyl and AE F160460, please refer to the EFSA peer review of mesosulfuron-methyl, EFSA Journal 2016;14(10):4584.

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

Mesosulfuron-methyl is not classified as toxic, very toxic, reprotoxic or carcinogenic. Data presented in the EFSA peer review of mesosulfuron-methyl, EFSA Journal 2016;14(10):4584, indicates that metabolite AE F160459 should not be classified as toxic, very toxic, reprotoxic or carcinogenic, therefore AE F160459 can be considered as not relevant.

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

Metabolite AE F160459 is considered as not relevant. The exposure assessment at step 4 is still required in accordance with SANCO/221/2000 v.10.

The potential exposure to AE F160459 is < 0.75 µg/L according to the assessment summarised under Step 2. Therefore, a toxicological threshold of concern approach is considered.
The Scientific Committee on Plants proposed a toxicological threshold of concern of 1.5 µg/person/day or 0.02 µg/kg body weight/day, which is in line with the threshold developed by the US-FDA. Assuming a consumption of 2 litres of water per day, all of which comes from the upper soil layer, such an acceptable exposure level relates to an acceptable estimated upper limit for the concentration of a metabolite of 0.75 µg/L.

In addition, lysimeter studies were carried out to determine concentrations of mesosulfuron-methyl and its metabolites (refer to EFSA Journal 2016;14(10):4584). AE F154851 was not detected above 0.1 µg/L. Metabolite AE F160459 can be considered as not relevant.

### 10.1.2.5 STEP 5: Refined risk assessment

This step is not required, see step 4, point 10.1.2.4 of this document.

## 10.1.3 Relevance assessment of AE F160460

**Summary:**

The groundwater metabolite AE F160460 is not considered as relevant according to the criteria laid down in the EC guidance document SANCO/221/2000 –rev.10. A summary of the relevance assessment for AE F160460 is given in Table 10.1-4. Studies supporting $PEC_{gw}$ data are evaluated in Section 8 (Environmental fate and behaviour) and the genotoxicity studies are evaluated in Section 6 (Mammalian Toxicology).

**Table 10.1-4: Summary of the relevance assessment for AE F160460**

| | Assessment step | Result of assessment |
|---|---|---|

| | | | | |
|---|---|---|---|---|
| | STEP 1 | | Metabolite of no concern? | no |
| **Quantification of groundwater contamination** | STEP 2 | | Max $PEC_{gw}$ | 0.105 µg/L |
| | | | Based on | FOCUS PEARL 4.4.4<br>Scenario Hamburg<br>Spring cereals |
| **Hazard assessment** | STEP 3 | Stage 1 | Biological activity comparable to the parent? | Less toxic than parent |
| | | Stage 2 | Genotoxic properties of metabolite | Not genotoxic |
| | | Stage 3 | Toxic properties of metabolite; | |
| | | | Classification of parent | Not toxic or highly toxic |
| | | | Classification of metabolite | Not toxic or highly toxic |
| **Consumer health risk assessment** | STEP 4 | | Estimated consumer exposure via drinking water and other sources; threshold of concern approach | $PEC_{GW}$ <0.75 µg/L<br>~~Maximum concentration in lysimeter studies < 0.1 µg/L, which is less than 0.75 µg/L.~~ |
| | STEP 5 | | Refined risk assessment | N/A* |
| | | | Predicted exposure (% of ADI) | N/A* |
| | | | ADI based on | N/A* |

* N/A: not applicable

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

AE F160460 does not meet the criteria for products of no concern as defined in step 1 of the guidance and therefore needs further assessment.

It cannot be excluded as a product of no concern as it is not:

- $CO_2$ or an inorganic compound, not containing a heavy metal;
- an organic compound of aliphatic structure, with a chain length of 4 or less, which consists only of C, H, N or O atoms and which has no "alerting structures" such as epoxide, nitrosamine, nitrile or other functional groups of known toxicological concern;
- a substance which is known to be of no toxicological or ecotoxicological concern, and which is naturally occurring at much higher concentrations in the respective compartment

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

$PEC_{gw}$ calculations after leaching from soil for AE F160460 were performed (see Part B, Section 8, chapter 8.8). There were uses for which concentrations of AE F160460 were considered to exceed 0.1 µg/L therefore further assessment is required.

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

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

The biological activity of metabolite AE F160460 was compared to the biological activity of the active substance mesosulfuron-methyl. The table below summarizes endpoints for studies which have been carried out with both metabolite AE F160460 and mesosulfuron-methyl.

**Table 10.1-5. Comparison of metabolite and active substance endpoints**

| Study | Endpoint | units | Mesosulfuron-methyl | AE F160460 |
|---|---|---|---|---|
| *Lemna gibba* 7d effects on growth | $E_rC_{50}$ | mg/L | 0.001717 | >100 |

Screening data on herbicidal activity of metabolites of mesosulfuron-methyl indicated that AE F160460 has no herbicidal activity, please refer to the EFSA peer review of mesosulfuron-methyl, EFSA Journal 2016;14(10):4584.

Comparisons of available ecotoxicity endpoints indicate that AE F160460 is lower biological activity than mesosulfuron-methyl.

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

Genotoxicity tests were performed with AE F160460. The AMES test, chromosome aberration test *in-vitro* and gene mutation test in mammalian cells *in-vitro* all gave negative results, please refer to the EFSA peer review of mesosulfuron-methyl, EFSA Journal 2016;14(10):4584.

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

Mesosulfuron-methyl is not classified as toxic, very toxic, reprotoxic or carcinogenic. Data presented in the EFSA assessment of mesosulfuron-methyl, EFSA Journal 2016(10):4584, indicates that metabolite AE F160460 should not be classified as toxic, very toxic, reprotoxic or carcinogenic, therefore AE F160460 can be considered as not relevant.

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

Metabolite AE F160460 is considered as not relevant. The exposure assessment at step 4 is still required in accordance with SANCO/221/2000 v.10.

The potential exposure to AE F160460 is < 0.75 µg/L according to the assessment summarised under Step 2. Therefore a toxicological threshold of concern approach is considered.

The Scientific Committee on Plants proposed a toxicological threshold of concern of 1.5 µg/person/day or 0.02 µg/kg body weight/day, which is in line with the threshold developed by the US-FDA. Assuming a consumption of 2 litres of water per day, all of which comes from the upper soil layer, such an acceptable exposure level relates to an acceptable estimated upper limit for the concentration of a metabolite of 0.75 µg/L.

Lysimeter studies were carried out to determine concentrations of mesosulfuron-methyl and its metabolites. AE F160460 was not detected above 0.1 µg/L. Metabolite AE F160460 can be considered as not relevant.

### 10.1.3.5 STEP 5: Refined risk assessment

This step is not required, see step 4, point 10.1.6.4 of this document.

## 10.1.4 Relevance assessment of AE F147447

**Summary:**

The groundwater metabolite AE F147447 is not considered as relevant according to the criteria laid down in the EC guidance document SANCO/221/2000 –rev.10. A summary of the relevance assessment for AE F147447 is given in Table 10.1-6. Studies supporting $PEC_{gw}$ data are evaluated in Section 8 (Environmental fate and behaviour) and the genotoxicity studies are evaluated in Section 6 (Mammalian Toxicology).

**Table 10.1-6: Summary of the relevance assessment for AE F147447**

| | Assessment step | | Result of assessment | |
|---|---|---|---|---|
| | STEP 1 | | Metabolite of no concern? | no |
| **Quantification of groundwater contamination** | STEP 2 | | Max $PEC_{gw}$ | 0.330 µg/L |
| | | | Based on | FOCUS PEARL 4.4.4<br>Scenario Hamburg<br>Spring cereals |
| **Hazard assessment** | STEP 3 | Stage 1 | Biological activity comparable to the parent? | Less toxic than parent |
| | | Stage 2 | Genotoxic properties of metabolite | Not genotoxic |
| | | Stage 3 | Toxic properties of metabolite; | |
| | | | Classification of parent | Not toxic or highly toxic |
| | | | Classification of metabolite | Not toxic or highly toxic |
| **Consumer health risk assessment** | STEP 4 | | Estimated consumer exposure via drinking water and other sources; threshold of concern approach | $PEC_{GW}$ <0.75 µg/L<br>~~Maximum concentration in lysimeter studies < 0.1 µg/L, which is less than 0.75 µg/L.~~ |
| | STEP 5 | | Refined risk assessment | N/A* |
| | | | Predicted exposure (% of ADI) | N/A* |
| | | | ADI based on | N/A* |

* N/A: not applicable

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

AE F147447 does not meet the criteria for products of no concern as defined in step 1 of the guidance and therefore needs further assessment.

It cannot be excluded as a product of no concern as it is not:

- $CO_2$ or an inorganic compound, not containing a heavy metal;
- an organic compound of aliphatic structure, with a chain length of 4 or less, which consists only of C, H, N or O atoms and which has no "alerting structures" such as epoxide, nitrosamine, nitrile or other functional groups of known toxicological concern;
- a substance which is known to be of no toxicological or ecotoxicological concern, and which is naturally occurring at much higher concentrations in the respective compartment.

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

$PEC_{gw}$ calculations after leaching from soil for AE F147447 were performed (see Part B, Section 8, chapter 8.8). There were uses for which concentrations of AE F147447 were considered to exceed 0.1 µg/L therefore further assessment is required.

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

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

The biological activity of metabolite AE F147447 was compared to the biological activity of the active substance mesosulfuron-methyl. The table below summarizes endpoints for studies which have been carried out with both metabolite AE F147447 and mesosulfuron-methyl.

**Table 10.1-7. Comparison of metabolite and active substance endpoints**

| Study | Endpoint | units | Mesosulfuron-methyl | AE F147447 |
|---|---|---|---|---|
| *Pseudokirchneriella subcapitata* 72h effects on growth | $E_rC_{50}$ | mg/L | 3.99 | >100 |
| *Lemna gibba* 7d effects on growth | $E_rC_{50}$ | mg/L | 0.001717 | >100 |

Screening data on herbicidal activity of metabolites of mesosulfuron-methyl indicated that AE F147447 has no herbicidal activity, please refer to the EFSA peer review of mesosulfuron-methyl, EFSA Journal 2016;14(10):4584.

Comparisons of available ecotoxicity endpoints indicate that AE F147447 has lower biological activity than mesosulfuron-methyl.

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

Genotoxicity tests were performed with AE F147447. The AMES test, chromosome aberration test *in-vitro* and gene mutation test in mammalian cells *in-vitro* all gave negative results, please refer to the EFSA peer review of mesosulfuron-methyl, EFSA Journal 2016;14(10):4584.

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

Mesosulfuron-methyl is not classified as toxic, very toxic, reprotoxic or carcinogenic. Data presented in the EFSA assessment of mesosulfuron-methyl, EFSA Journal 2016(10):4584, indicates that metabolite AE F147447 should not be classified as toxic, very toxic, reprotoxic or carcinogenic, therefore AE F147447 can be considered as not relevant.

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

Metabolite AE F147447 is considered as not relevant. The exposure assessment at step 4 is still required in accordance with SANCO/221/2000 v.10.

The potential exposure to AE F147447 is < 0.75 µg/L according to the assessment summarised under Step 2. Therefore a toxicological threshold of concern approach is considered.

The Scientific Committee on Plants proposed a toxicological threshold of concern of 1.5 µg/person/day or 0.02 µg/kg body weight/day, which is in line with the threshold developed by the US-FDA. Assuming a consumption of 2 litres of water per day, all of which comes from the upper soil layer, such an acceptable exposure level relates to an acceptable estimated upper limit for the concentration of a metabolite of 0.75 µg/L.

Lysimeter studies were carried out to determine concentrations of mesosulfuron-methyl and its metabolites. AE F147447 was not detected above 0.1 µg/L. Metabolite AE F147447 can be considered as not relevant.

### 10.1.4.5 STEP 5: Refined risk assessment

This step is not required, see step 4, point 10.1.8.4 of this document.

## 10.1.5 Relevance assessment of BCS CV14885

**Summary:**

The groundwater metabolite BCS CV14885 is not considered as relevant according to the criteria laid down in the EC guidance document SANCO/221/2000 –rev.10. A summary of the relevance assessment for BCS CV14885 is given in Table 10.1-8. Studies supporting $PEC_{gw}$ data are evaluated in Section 8 (Environmental fate and behaviour) and the genotoxicity studies are evaluated in Section 6 (Mammalian Toxicology).

**Table 10.1-8: Summary of the relevance assessment for BCS CV14885**

| | Assessment step | | Result of assessment | |
|---|---|---|---|---|
| | STEP 1 | | Metabolite of no concern? | no |
| **Quantification of groundwater contamination** | STEP 2 | | Max $PEC_{gw}$ | 0.416 µg/L |
| | | | Based on | FOCUS PEARL 4.4.4<br>Scenario Hamburg<br>Spring cereals |
| **Hazard assessment** | STEP 3 | Stage 1 | Biological activity comparable to the parent? | Less toxic than parent |
| | | Stage 2 | Genotoxic properties of metabolite | Not genotoxic |
| | | Stage 3 | Toxic properties of metabolite; | |
| | | | Classification of parent | Not toxic or highly toxic |
| | | | Classification of metabolite | Not toxic or highly toxic |
| **Consumer health risk assessment** | STEP 4 | | Estimated consumer exposure via drinking water and other sources; threshold of concern approach | $PEC_{GW}$ <0.75 µg/L<br>~~Maximum concentration in lysimeter studies = 0.481 µg/L, which is less than 0.75 µg/L.~~ |
| | STEP 5 | | Refined risk assessment | N/A* |
| | | | Predicted exposure (% of ADI) | N/A* |
| | | | ADI based on | N/A* |

* N/A: not applicable

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

BCS CV14885 does not meet the criteria for products of no concern as defined in step 1 of the guidance and therefore needs further assessment.

It cannot be excluded as a product of no concern as it is not:

- $CO_2$ or an inorganic compound, not containing a heavy metal;
- an organic compound of aliphatic structure, with a chain length of 4 or less, which consists only of C, H, N or O atoms and which has no "alerting structures" such as epoxide, nitrosamine, nitrile or other functional groups of known toxicological concern;
- a substance which is known to be of no toxicological or ecotoxicological concern, and which is naturally occurring at much higher concentrations in the respective compartment.

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

$PEC_{gw}$ calculations after leaching from soil for BCS CV14885 were performed (see Part B, Section 8, chapter 8.8). There were uses for which concentrations of BCS CV14885 were considered to exceed 0.1 µg/L therefore further assessment is required.

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

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

No ecotoxicity studies on aquatic organisms or soil organisms are available for BCS CV14885.

Screening data on herbicidal activity of metabolites of mesosulfuron-methyl indicated that BCS CV14885 has no herbicidal activity, please refer to the EFSA peer review of mesosulfuron-methyl, EFSA Journal 2016;14(10):4584.

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

Genotoxicity tests were performed with BCS CV14885. The AMES test, chromosome aberration test *in-vitro* and gene mutation test in mammalian cells *in-vitro* all gave negative results, please refer to the EF-SA peer review of mesosulfuron-methyl, EFSA Journal 2016;14(10):4584.

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

Mesosulfuron-methyl is not classified as toxic, very toxic, reprotoxic or carcinogenic. Data presented in the EFSA assessment of mesosulfuron-methyl, EFSA Journal 2016(10):4584, indicates that metabolite BCS CV14885 should not be classified as toxic, very toxic, reprotoxic or carcinogenic, therefore BCS CV14885 can be considered as not relevant.

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

Metabolite BCS CV14885 is considered as not relevant. The exposure assessment at step 4 is still required in accordance with SANCO/221/2000 v.10.

The potential exposure to BCS CV14885 is < 0.75 µg/L according to the assessment summarised under Step 2. Therefore a toxicological threshold of concern approach is considered.

The Scientific Committee on Plants proposed a toxicological threshold of concern of 1.5 µg/person/day or 0.02 µg/kg body weight/day, which is in line with the threshold developed by the US-FDA. Assuming a consumption of 2 litres of water per day, all of which comes from the upper soil layer, such an acceptable exposure level relates to an acceptable estimated upper limit for the concentration of a metabolite of 0.75 µg/L.

Lysimeter studies were carried out to determine concentrations of mesosulfuron-methyl and its metabolites. BCS CV14885 was detected at a maximum concentration of 0.481 µg/L, which is considerably less than 0.75 µg/L. Metabolite BCS CV14885 can be considered as not relevant.

### 10.1.5.5 STEP 5: Refined risk assessment

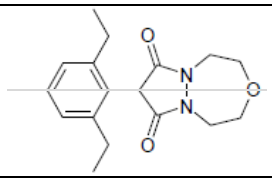
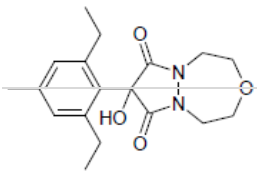
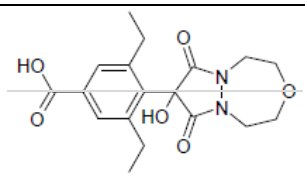
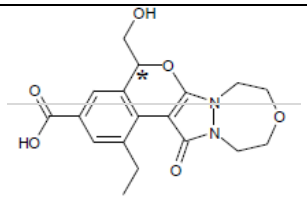
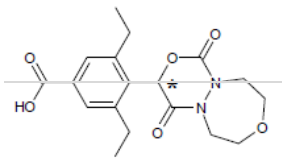
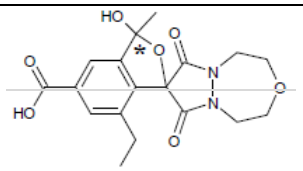
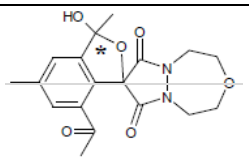
This step is not required, see step 4, point 10.1.9.4 of this document.

## 10.2 Pinoxaden and metabolites

### 10.2.1 General information

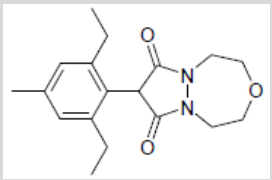
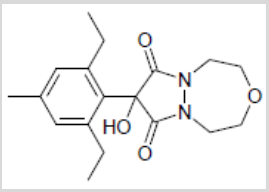
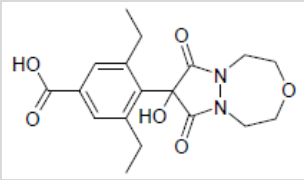
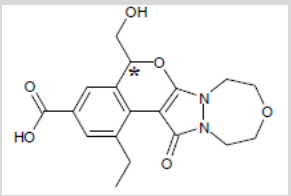
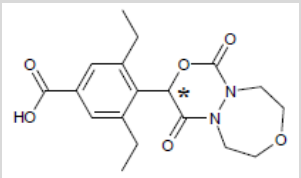
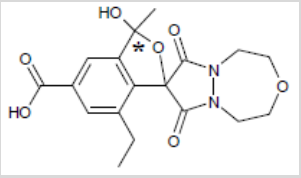
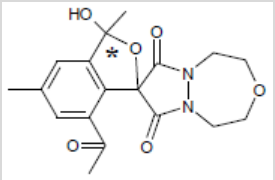
General information on the metabolites of pinoxaden is provided in Table 10.1-1. The impact of the relevance assessment on whether a particular GAP use leads to acceptable risk or not is presented in the summary of the cGAP evaluation in chapter 8.1 of the dRR Part B, Section 8 (Environmental fate and behaviour).

**Table 10.2-1: General information on the metabolite(s)**

| Name of active sub-stance | Metabolite name and code | Structural/molecular formula | Trigger for relevance assessment | |
|---|---|---|---|---|
| Pinoxaden | NOA 407854 (M2) |  | Max $PEC_{gw}$ Winter and Spring cereals [µg/L]<br><br>Based on: | Annual: <0.001<br><br>All scenarios<br>1 x 60 g/ha<br>Application post-emergence<br>BBCH 13-20 (0% interception) |
| Pinoxaden | NOA 447204 (M3) |  | Max $PEC_{gw}$ Spring cereals [µg/L]<br><br>Based on: | Annual: 5.515*<br><br>FOCUS_PEARL 4.4.4<br>Scenario Hamburg<br>Alkaline soils<br>1 x 60 g/ha<br>Application post-emergence<br>BBCH 13-39 (0% interception) |
| Pinoxaden | M11 |  | Max $PEC_{gw}$ Winter cereals [µg/L]<br><br>Based on: | Annual: 1.104*<br><br>FOCUS PEARL 4.4.4<br>Scenario Hamburg<br>1 x 60 g/ha<br>Application post-emergence<br>BBCH 20-39 (20% interception) |
| Pinoxaden | M52 |  | Max $PEC_{gw}$ Winter cereals [µg/L]<br><br>Based on: | Annual: 0.009*<br><br>FOCUS PEARL 4.4.4<br>Scenario Porto<br>1 x 60 g/ha<br>Application post-emergence<br>BBCH 20-39 (20% interception) |
| Pinoxaden | M54 |  | Max $PEC_{gw}$ Winter cereals [µg/L]<br><br>Based on: | Annual: 0.418*<br><br>FOCUS PEARL 4.4.4<br>Scenario Hamburg<br>1 x 60 g/ha<br>Application post-emergence<br>BBCH 20-39 (20% interception) |
| Pinoxaden | M55 |  | Max $PEC_{gw}$ Winter cereals [µg/L]<br><br>Based on: | Annual: 4.478*<br><br>FOCUS PEARL 4.4.4<br>Scenario Jokioinen<br>1 x 60 g/ha<br>Application post-emergence<br>BBCH 20-39 (20% interception) |
| Pinoxaden | M56 |  | Max $PEC_{gw}$ Winter cereals [µg/L]<br><br>Based on: | Annual: 7.944*<br><br>FOCUS PEARL 4.4.4<br>Scenario Jokioinen<br>1 x 60 g/ha<br>Application post-emergence<br>BBCH 20-39 (20% interception) |

**Reviewer comments:**

As already indicated in the zRMS comment in the introductory part of this document, the Applicants' approach to rely on results of the lysimeter studies was not agreed by the zRMS efate expert. For this reason Table 10.2-1 above has been struck through and new table, presenting all data relevant for the toxicological relevance assessment has been inserted by the zRMS below.

| Name of active substance | Metabolite name and code | Structural/molecular formula | Trigger for relevance assessment | |
|---|---|---|---|---|
| Pinoxaden | NOA 407854 (M2) |  | Max $PEC_{gw}$<br>Winter cereals<br>[µg/L]<br><br>Based on: | Annual: 0.152<br>Biennial: 0.080<br><br>FOCUS PELMO 5.5.3<br>Scenario Porto<br>1 x 60 g/ha<br>Application post-emergence BBCH 20-39 (20% interception) |
| Pinoxaden | NOA 447204 (M3) |  | Max $PEC_{gw}$<br>Spring cereals<br>[µg/L]<br><br>Based on: | Annual: 0.873<br><br>FOCUS PEARL 4.4.4<br>Scenario Hamburg<br>1 x 60 g/ha<br>Application post-emergence BBCH 13-39 (0% interception) |
| Pinoxaden | M11 |  | Max $PEC_{gw}$<br>Spring cereals<br>[µg/L]<br><br>Based on: | Annual: 1.072<br><br>FOCUS PEARL 4.4.4<br>Scenario Hamburg<br>1 x 60 g/ha<br>Application post-emergence BBCH 13-39 (0% interception) |
| Pinoxaden | M52 |  | Max $PEC_{gw}$<br>Spring cereals<br>[µg/L]<br><br>Based on: | Annual: 0.106<br>Biennial: 0.058<br><br>FOCUS PEARL 4.4.4<br>Scenario Hamburg<br>1 x 60 g/ha<br>Application post-emergence BBCH 13-39 (0% interception) |
| Pinoxaden | M54 |  | Max $PEC_{gw}$<br>Spring cereals<br>[µg/L]<br><br>Based on: | Annual: 0.445<br><br>FOCUS PEARL 4.4.4<br>Scenario Hamburg<br>1 x 60 g/ha<br>Application post-emergence BBCH 13-39 (0% interception) |
| Pinoxaden | M55 |  | Max $PEC_{gw}$<br>Spring cereals<br>[µg/L]<br><br>Based on: | Annual: 1.785<br><br>FOCUS PEARL 4.4.4<br>Scenario Hamburg<br>1 x 60 g/ha<br>Application post-emergence BBCH 13-39 (0% interception) |
| Pinoxaden | M56 |  | Max $PEC_{gw}$<br>winter cereals<br>[µg/L]<br><br>Based on: | Annual: 3.128<br><br>FOCUS PEARL 4.4.4<br>Scenario Châteaudun<br>1 x 60 g/ha<br>Application post-emergence BBCH 20-39 (20% interception) |

Note: The reference to the results of the lysimeter studies made by the Applicant in the evaluation below was not

struck through by the zRMS as these data are in line with EFSA Journal 2013;11(8):3269, however, they may be considered as additional and supportive information only. In order to be able to rely on results of these studies to derive the conclusion, the representativeness of the EU agreed lysimeter studies for conditions of each country included in the GAP should be evaluated, which was not done by the Applicant.

Initially, in the evaluation of the toxicological relevance of pinoxaden groundwater metabolites the Applicant referred to results of the EU agreed lysimeter studies, where all metabolites potentially migrating to groundwater were detected at concentrations <0.75 µg/L. However, no justification of the representativeness of the test sites in the lysimeter studies to conditions in particular countries in which authorization of ADM.06001.H.2.B has been presented by the Applicant and for this reason the zRMS efate expert concluded that results of the lysimeter studies may be used only as additional information but cannot be relied upon to derive final conclusion for the whole Central Zone. Therefore it was decided to rely on results of the Tier 2 groundwater modelling in the evaluation presented in area of Section 8. However, results of the lysimeter studies may be considered by particular cMS if considered reliable and sufficient for conditions of their countries

The Step 5 assessment presented below was based on $PEC_{GW}$ values reported in table above and exceeding 0.75 µg/L.

The metabolites NOA 407854 (M2) and M52 are predicted to occur in groundwater at concentrations **below 0.1 µg/L** (see 8.8.2.1 of the dRR Part B, Section 8). Assessment of the relevance of these metabolites according to the stepwise procedure of the EC guidance document ~~SANCO/221/2000 – rev.10~~ **SANCO/221/2000 –rev.11 21October 2021** is therefore **not** required.

Assessment of the relevance of metabolites NOA 447204 (M3), M11, M54, M55 and M56 is presented below.

## 10.2.2 Relevance assessment of NOA 447204 (M3)

**Summary:**

The groundwater metabolite NOA 447204 (M3) is not considered as relevant according to the criteria laid down in the EC guidance document SANCO/221/2000–rev.10. A summary of the relevance assessment for NOA 447204 (M3) is given in 10.2-1. Studies supporting $PEC_{gw}$ data are evaluated in Section 8 (Environmental fate and behaviour) and the genotoxicity studies are evaluated in Section 6 (Mammalian Toxicology).

**Table 10.2-1: Summary of the relevance assessment for NOA 447204 (M3)**

| | Assessment step | | Result of assessment | |
|---|---|---|---|---|
| | STEP 1 | | Metabolite of no concern? | no |
| **Quantification of groundwater contamination** | STEP 2 | | Max $PEC_{gw}$ | ~~5.515~~<br>Annual: 0.8733 µg/L |
| | | | Based on | ~~PEARL 4.4.4~~<br>~~Scenario Hamburg~~<br>~~Spring cereals~~<br><br>Spring cereals<br>FOCUS PEARL 4.4.4<br>Scenario Hamburg<br>1 x 60 g/ha<br>Application post-emergence BBCH 13-39 (0% interception) |
| **Hazard assessment** | STEP 3 | Stage 1 | Biological activity comparable to the parent? | Less toxic than parent |

| | Assessment step | | Result of assessment | |
|---|---|---|---|---|
| | | Stage 2 | Genotoxic properties of metabolite | Not genotoxic |
| | | Stage 3 | Toxic properties of metabolite; | |
| | | | Classification of parent | Not toxic or highly toxic |
| | | | Classification of metabolite | Not toxic or highly toxic |
| **Consumer health risk assessment** | STEP 4 | | Estimated consumer exposure via drinking water and other sources; threshold of concern approach | ~~Maximum concentration in lysimeter studies = 0.206 µg/L, which is less than 0.75 µg/L.~~ Based on evaluation in area of Section 8, the conclusion for the Central Zone cannot be relied on results of the lysimeter studies ($PEC_{GW}$ > 0.75 µg/L) |
| | STEP 5 | | Refined risk assessment | ~~N/A.*~~ acceptable |
| | | | Predicted exposure (% of ADI) | ~~N/A.*~~ 1.3 % of ADI (infant), 0.9 % of ADI (child), 0.3 % of ADI (adult). |
| | | | ADI based on | ~~N/A.*~~ specific ADI has been set for M3, by reducing the parent ADI by 10, to obtain a value of 0.01 mg/kg bw/day EFSA Journal 2013;11(8):3269 |

* N/A: not applicable

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

NOA 447204 (M3) does not meet the criteria for products of no concern as defined in step 1 of the guidance and therefore needs further assessment.

It cannot be excluded as a product of no concern as it is not:

- $CO_2$ or an inorganic compound, not containing a heavy metal;
- an organic compound of aliphatic structure, with a chain length of 4 or less, which consists only of C, H, N or O atoms and which has no "alerting structures" such as epoxide, nitrosamine, nitrile or other functional groups of known toxicological concern;
- a substance which is known to be of no toxicological or ecotoxicological concern, and which is naturally occurring at much higher concentrations in the respective compartment

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

$PEC_{gw}$ calculations after leaching from soil for NOA 447204 (M3) were performed (see Part B, Section 8, chapter 8.8). There were uses for which concentrations of NOA 447204 (M3) were considered to exceed 0.1 µg/L therefore further assessment is required.

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

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

The biological activity of metabolite NOA 447204 (M3) was compared to the biological activity of the active substance pinoxaden. The table below summarizes endpoints for studies which have been carried out with both metabolite NOA 447204 (M3) and pinoxaden.

**Table 10.2-2: Comparison of metabolite and active substance endpoints**

| Study | Endpoint | units | Pinoxaden | NOA 447204 (M3) |
|---|---|---|---|---|
| *Pseudokirchneriella subcapitata* 96h ef- | $E_rC_{50}$ | mg/L | 41 | >120 |

| | | | | |
|---|---|---|---|---|
| fects on growth | | | | |
| *Lemna gibba* 7d effects on growth | $E_rC_{50}$ | mg/L | 9.73 | >100 |

A study was submitted as part of the active substance renewal of pinoxaden which investigates the herbicidal activity of metabolite NOA 447204 (M3) compared with pinoxaden. The substances applied post-emergence (with adjuvant) to wheat, barley *Avena sp*., *Lolium sp*. *Setaria sp*. and *Digitaria sp*. The results indicated that NOA 447204 (M3) had no inhibitory effects on any tested plant species.

A further study was submitted as part of the active substance renewal of pinoxaden which investigates the action of pinoxaden and its metabolites on the activity of the enzyme acetyl-CoA carboxylase from corn. The study demonstrated that pinoxaden inhibits con ACCase activity with an I50 of 1 µM/L, whereas metabolite NOA 447204 (M3) had no effect on the enzyme at the highest tested concentration of 200 ppm.

NOA 447204 (M3) has lower biological activity than pinoxaden, therefore metabolite NOA 447204 (M3) can be considered as not relevant.

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

Genotoxicity studies were submitted as part of the active substance renewal of pinoxaden. NOA 447204 (M3) was not mutagenic in bacterial cells or mammalian cells *in vitro.* It was weakly clastogenic in lymphocytes *in vitro*. *In vivo* test demonstrated no genotoxicity in the mouse bone marrow micronucleus study or the rat liver UDS assay, therefore it can be concluded that NOA 447204 (M3) is not genotoxic and can be considered as not relevant.

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

The toxicity of metabolite NOA447204 (M3) has been investigated in studies submitted as part of the active substance renewal of pinoxaden. A number of studies are summarised in the LoEP (see table 10.2.4 below) The data support that the metabolite should not be classified for toxicological properties..
The classification for pinoxaden with H361d has been confirmed after the approval of pinoxaden and published in Reg 2018/1480.Therefore according to SANCO/211/2000, rev 10, it must be documented that M3 does not share the toxic properties for reproduction of the parent compound. According to Implementing Regulation (EU) 2016/370 of 15 March 2016 the applicant shall submit confirmatory information as regards the relevance of the metabolite M3 and the corresponding groundwater risk assessment. We understand the confirmatory data has been submitted and ADAMA reference the information. Data is currently being evaluated by Austria (UK was the original RMS).

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

Metabolite NOA 447204 (M3) is considered as not relevant. The exposure assessment at step 4 is still required in accordance with SANCO/221/2000 v.10.

The Scientific Committee on Plants proposed a toxicological threshold of concern of 1.5 µg/person/day or 0.02 µg/kg body weight/day, which is in line with the threshold developed by the US-FDA. Assuming a consumption of 2 litres of water per day, all of which comes from the upper soil layer, such an acceptable exposure level relates to an acceptable estimated upper limit for the concentration of a metabolite of 0.75 µg/L.

**Reviewer comment:**
The PECgw for Metabolite M3 was >0.75 µg/L. There is potentially risk for consumer via drinking water. Metabolite M3 exceed the toxicological threshold of concern as defined in EC guidance document SANCO/221/2000 –rev.11. (21/10/2021) therefore STEP 5 is required.

The reference to the results of the lysimeter studies made by the Applicant in the evaluation below was not struck through by the zRMS as these data are in line with EFSA Journal 2013;11(8):3269, however,

they may be considered as additional and supportive information only. In order to be able to rely on results of these studies to derive the conclusion, the representativeness of the EU agreed lysimeter studies for conditions of each country included in the GAP should be evaluated, which was not done by the Applicant.

Lysimeter studies were carried out to determine concentrations of pinoxaden and its metabolites. NOA 447204 (M3) was detected at a maximum concentration of 0.206 µg/L, which is considerably lower than the acceptable estimated upper limit of 0.75 µg/L. Metabolite NOA 447204 (M3) can be considered as not relevant.

The studies reviewed at EU level are listed in the following table solely for the purpose of information.

**Table 10.2-3: Summary of evaluation of the toxicity studies for NOA 447204 (M3)**

| Study | Endpoint | units | NOA 447204 (M3) |
|---|---|---|---|
| Mammalian acute oral toxicity | $LD_{50}$ | mg/kg bw | 1089 |
| Mammalian 28d dietary toxicity | NOAEL | mg/kg bw/d | 67 |
| Mammalian 90d dietary toxicity | NOAEL | mg/kg bw/d | 99 |

### 10.2.2.5 STEP 5: Refined risk assessment

~~This step is not required, see step 4, point 10.2.2.4 of this document.~~

**Reviewer comment:**
Step 5 has been provided by the zRMS due to the newly estimated PECgw value for M3 metabolite

NOA 447204 (M3) has a $PEC_{gw}$ between 0.75 µg/L and 10 µg/L. 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 NOA 447204 (M3) are 1.3 % of ADI (infant), 0.9 % of ADI (child), 0.3 % of ADI (adult).

Justification for the selected ADI:

The ADI as defined in the LoEP EFSA Journal 2013;11(8):3269 has been set as specific ADI for M3, by reducing the parent ADI by 10, to obtain a value of 0.01 mg/kg bw/day.

ADI = 0.01 mg/kg bw/d
= 10 µg/kg bw/d

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:

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

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 = 0.13 µg/kg bw/d
Risk for 5-kg bottle fed infant (% ADI) = 1.3%

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

Worst case daily dietary exposure of 10 kg child = 0.09 µg/kg bw/d
Risk for 10 kg child (% ADI) = 0.9%

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

Worst case daily dietary exposure of 60-kg adult = 0.03 µg/kg bw/d
Risk for 60-kg adult (% ADI) = 0.3 %

### 10.2.3 Relevance assessment of M11

**Summary:**

The groundwater metabolite M11 is not considered as relevant according to the criteria laid down in the EC guidance document SANCO/221/2000–rev.10. A summary of the relevance assessment for M11 is given in 10.2-4. Studies supporting $PEC_{gw}$ data are evaluated in Section 8 (Environmental fate and behaviour) and the genotoxicity studies are evaluated in Section 6 (Mammalian Toxicology).

**Table 10.2-4: Summary of the relevance assessment for M11**

| | Assessment step | | Result of assessment | |
|---|---|---|---|---|
| | STEP 1 | | Metabolite of no concern? | no |
| **Quantification of groundwater contamination** | STEP 2 | | Max $PEC_{gw}$ | ~~1.104~~<br>Annual: 1.072 µg/L** |
| | | | Based on | ~~FOCUS PEARL 4.4.4~~<br>~~Scenario Hamburg~~<br>~~Winter cereals~~<br>Spring cereals<br>FOCUS PEARL 4.4.4<br>Scenario Hamburg<br>1 x 60 g/ha<br>Application post-emergence BBCH 13-39 (0% interception) |
| **Hazard assessment** | STEP 3 | Stage 1 | Biological activity comparable to the parent? | Less toxic than parent |
| | | Stage 2 | Genotoxic properties of metabolite | Not genotoxic |
| | | Stage 3 | Toxic properties of metabolite; | |
| | | | Classification of parent | Not toxic or highly toxic |
| | | | Classification of metabolite | Not toxic or highly toxic |
| **Consumer health risk assessment** | STEP 4 | | Estimated consumer exposure via drinking water and other sources; threshold of concern approach | ~~Maximum concentration in lysimeter studies = 0.206 µg/L, which is less than 0.75 µg/L.~~<br>Based on evaluation in area of Section 8, the conclusion for the Central Zone cannot be relied on results of the lysimeter studies ($PEC_{GW}$ > 0.75 µg/L) |
| | STEP 5 | | Refined risk assessment | ~~N/A*~~<br>acceptable |

| | Assessment step | Result of assessment | |
|---|---|---|---|
| | | Predicted exposure (% of ADI) | ~~N/A~~*<br>0.16 % of ADI (infant), 0.1 % of ADI (child), 0.04 % of ADI (adult). |
| | | ADI based on | ~~N/A~~*<br>0.1 mg/kg bw per day has been set as parent ADI in the dietary risk assessment for M11 which represents a conservative approach.<br>EFSA Journal 2013;11(8):3269 |

* N/A: not applicable, ** for details refer dRR Section B8

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

M11 does not meet the criteria for products of no concern as defined in step 1 of the guidance and therefore needs further assessment.

It cannot be excluded as a product of no concern as it is not:

- $CO_2$ or an inorganic compound, not containing a heavy metal;
- an organic compound of aliphatic structure, with a chain length of 4 or less, which consists only of C, H, N or O atoms and which has no "alerting structures" such as epoxide, nitrosamine, nitrile or other functional groups of known toxicological concern;
- a substance which is known to be of no toxicological or ecotoxicological concern, and which is naturally occurring at much higher concentrations in the respective compartment.

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

$PEC_{gw}$ calculations after leaching from soil for M11 were performed (see Part B, Section 8, chapter 8.8). There were uses for which concentrations of M11 were considered to exceed 0.1 µg/L therefore further assessment is required.

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

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

No studies on the toxicity of metabolite M11 to plants or ecotoxicological organisms are available.

A study was submitted as part of the active substance renewal of pinoxaden which investigates the action of pinoxaden and its metabolites on the activity of the enzyme acetyl-CoA carboxylase from corn. The study demonstrated that pinoxaden inhibits con ACCase activity with an I50 of 1 µM/L, whereas metabolite M11 had no effect on the enzyme at the highest tested concentration of 200 ppm.

M11 is considered to be structurally similar to metabolite NOA 447204 (M3), please see Table 10.2-1, therefore M11 is not expected to be more biologically active than pinoxaden. M11 can be considered as not relevant.

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

No studies on the genotoxicity of metabolite M11 are available. M11 is considered to be structurally similar to metabolite NOA 447204 (M3), please see Table 10.2-1, therefore M11 is not expected to be genotoxic. A QSAR (DEREK) analysis of M11 was carried out as part of the active substance renewal of pinoxaden, which indicated that M11 does not possess structural alerts for mutagenicity. M11 can be considered as not relevant.

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

No studies on the toxicity of metabolite M11 are available. M11 is considered to be structurally similar to metabolite NOA 447204 (M3), please see Table 10.2-1, therefore based on the screening for toxicity assessment of metabolite NOA 447204 (M3), M11 can be considered as not relevant.

The classification for pinoxaden with H361d has been confirmed after the approval of pinoxaden and published in Reg 2018/1480. Therefore according to SANCO/211/2000, rev 10, it must be documented that metabolites in groundwater do not share the toxic properties for reproduction of the parent compound. According to Implementing Regulation (EU) 2016/370 of 15 March 2016 the applicant shall submit confirmatory information as regards the relevance of the metabolites and the corresponding groundwater risk assessment. We understand the confirmatory data has been submitted and ADAMA reference the information. Data is currently being evaluated by Austria (UK was the original RMS).

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

Metabolite M11 is considered as not relevant. The exposure assessment at step 4 is still required in accordance with SANCO/221/2000 v.10.

The Scientific Committee on Plants proposed a toxicological threshold of concern of 1.5 µg/person/day or 0.02 µg/kg body weight/day, which is in line with the threshold developed by the US-FDA. Assuming a consumption of 2 litres of water per day, all of which comes from the upper soil layer, such an acceptable exposure level relates to an acceptable estimated upper limit for the concentration of a metabolite of 0.75 µg/L.

**Reviewer comment:**
The PECgw for Metabolite M11 was >0.75 µg/L. There is potentially risk for consumer via drinking water. Metabolite M11 exceed the toxicological threshold of concern as defined in EC guidance document SANCO/221/2000 –rev.11. (21/10/2021) therefore STEP 5 is required.
The reference to the results of the lysimeter studies made by the Applicant in the evaluation below was not struck through by the zRMS as these data are in line with EFSA Journal 2013;11(8):3269, however, they may be considered as additional and supportive information only. In order to be able to rely on results of these studies to derive the conclusion, the representativeness of the EU agreed lysimeter studies for conditions of each country included in the GAP should be evaluated, which was not done by the Applicant.

Lysimeter studies were carried out to determine concentrations of pinoxaden and its metabolites. M11 was detected at a maximum concentration of 0.229 µg/L (autumn application), which is considerably lower than the acceptable estimated upper limit of 0.75 µg/L. The metabolite M11 was only seen below 0.1 µg/ in the lysimeter studies for spring application. Metabolite M11 can be considered as not relevant for the intended application pattern.

### 10.2.3.5 STEP 5: Refined risk assessment

~~This step is not required, see step 4, point 10.2.4.4 of this document.~~

**Reviewer comment:**
Step 5 has been provided by the zRMS due to the newly estimated PECgw value for M11 metabolite

M11 has a $PEC_{gw}$ between 0.75 µg/L and 10 µg/L. 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 M11 are 0.16 % of ADI (infant), 0.1 % of ADI (child), 0.04 % of ADI (adult).

Justification for the selected ADI:

The ADI as defined in the LoEP EFSA Journal 2013;11(8):3269 has been set as parent ADI in the dietary risk assessment for M11 which represents a conservative approach.

ADI = 0.1 mg/kg bw/d
= 100 µg/kg bw/d

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:

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

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 = 0.16 µg/kg bw/d
Risk for 5-kg bottle fed infant (% ADI) = 0.16 %

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

Worst case daily dietary exposure of 10 kg child = 0.1 µg/kg bw/d
Risk for 10 kg child (% ADI) = 0.1 %

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

Worst case daily dietary exposure of 60-kg adult = 0.04 µg/kg bw/d
Risk for 60-kg adult (% ADI) = 0.04%

### 10.2.4 Relevance assessment of M54

**Summary:**

The groundwater metabolite M54 is not considered as relevant according to the criteria laid down in the EC guidance document SANCO/221/2000–rev.10. A summary of the relevance assessment for M54 is given in Table 10.2-5. Studies supporting $PEC_{gw}$ data are evaluated in Section 8 (Environmental fate and behaviour) and the genotoxicity studies are evaluated in Section 6 (Mammalian Toxicology).

**Table 10.2-5: Summary of the relevance assessment for M54**

| | Assessment step | | Result of assessment | |
|---|---|---|---|---|
| | STEP 1 | | Metabolite of no concern? | no |
| **Quantification of groundwater contamination** | STEP 2 | | Max $PEC_{gw}$ | ~~0.418~~<br>Annual: 0.445µg/L** |
| | | | Based on | ~~FOCUS PEARL 4.4.4~~<br>~~Scenario Hamburg~~<br>~~Winter cereals~~<br>Spring cereals<br>FOCUS PEARL 4.4.4<br>Scenario Hamburg<br>1 x 60 g/ha<br>Application post-emergence<br>BBCH 13-39 (0% interception) |
| **Hazard assessment** | STEP 3 | Stage 1 | Biological activity comparable to the parent? | Less toxic than parent |
| | | Stage 2 | Genotoxic properties of metabolite | Not genotoxic |
| | | Stage 3 | Toxic properties of metabolite; | |
| | | | Classification of parent | Not toxic or highly toxic |
| | | | Classification of metabolite | Not toxic or highly toxic |
| **Consumer health risk assessment** | STEP 4 | | Estimated consumer exposure via drinking water and other sources; threshold of concern approach | ~~Maximum concentration in lysimeter studies = 0.206 µg/L, which is less than 0.75 µg/L.~~<br>Acceptable (<0. 0.75 µg/L) |
| | STEP 5 | | Refined risk assessment | N/A* |
| | | | Predicted exposure (% of ADI) | N/A* |
| | | | ADI based on | N/A* |

* N/A: not applicable; ** for details refer dRR Section B8

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

M54 does not meet the criteria for products of no concern as defined in step 1 of the guidance and therefore needs further assessment.

It cannot be excluded as a product of no concern as it is not:

- $CO_2$ or an inorganic compound, not containing a heavy metal;
- an organic compound of aliphatic structure, with a chain length of 4 or less, which consists only of C, H, N or O atoms and which has no "alerting structures" such as epoxide, nitrosamine, nitrile or other functional groups of known toxicological concern;
- a substance which is known to be of no toxicological or ecotoxicological concern, and which is naturally occurring at much higher concentrations in the respective compartment.

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

$PEC_{gw}$ calculations after leaching from soil for M54 were performed (see Part B, Section 8, chapter 8.8). There were uses for which concentrations of M54 were considered to exceed 0.1 µg/L therefore further assessment is required.

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

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

No studies on the toxicity of metabolite M54 to plants or ecotoxicological organisms are available.

A study was submitted as part of the active substance renewal of pinoxaden which investigates the action of pinoxaden and its metabolites on the activity of the enzyme acetyl-CoA carboxylase from corn. Metabolite M54 was not included in this study, but is considered to be structurally similar to metabolite M57 (please see figure below) which was included in the test. The study demonstrated that pinoxaden inhibits con ACCase activity with an I50 of 1 µM/L, whereas metabolite M57 had no effect on the enzyme at the highest tested concentration of 200 ppm.

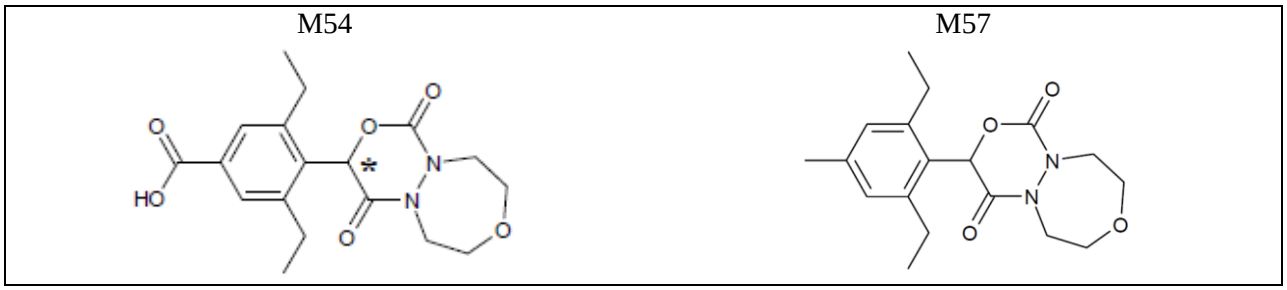



**Figure 10.2-1. Comparison of molecular structures of metabolites M54 and M57**

M54 is also considered to be structurally similar to metabolite NOA 447204 (M3), please see Table 10.2-1, therefore M54 is not expected to be more biologically active than pinoxaden. M54 can be considered as not relevant.

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

No studies on the genotoxicity of metabolite M54 are available. M54 is considered to be structurally similar to metabolite NOA 447204 (M3), please see Table 10.2-1, therefore M54 is not expected to be genotoxic. A QSAR (DEREK) analysis of M54 was carried out as part of the active substance renewal of pinoxaden,, which indicated that M54 does not possess structural alerts for mutagenicity. M54 can be considered as not relevant.

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

No studies on the toxicity of metabolite M54 are available. M54 is considered to be structurally similar to metabolite NOA 447204 (M3), please see Table 10.2-1, therefore based on the screening for toxicity assessment of metabolite NOA 447204 (M3), M54 can be considered as not relevant.
The classification for pinoxaden with H361d has been confirmed after the approval of pinoxaden and published in Reg 2018/1480. Therefore according to SANCO/211/2000, rev 10, it must be documented that metabolites in groundwater do not share the toxic properties for reproduction of the parent compound. According to Implementing Regulation (EU) 2016/370 of 15 March 2016 the applicant shall submit confirmatory information as regards the relevance of the metabolites and the corresponding groundwater risk assessment. We understand the confirmatory data has been submitted and ADAMA reference the information. Data is currently being evaluated by Austria (UK was the original RMS).

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

Metabolite M54 is considered as not relevant. The exposure assessment at step 4 is still required in accordance with SANCO/221/2000 v.10.

The Scientific Committee on Plants proposed a toxicological threshold of concern of 1.5 µg/person/day or 0.02 µg/kg body weight/day, which is in line with the threshold developed by the US-FDA. Assuming a

consumption of 2 litres of water per day, all of which comes from the upper soil layer, such an acceptable exposure level relates to an acceptable estimated upper limit for the concentration of a metabolite of 0.75 µg/L.

**Reviewer comment:**
The PECgw for Metabolite M54 was < 0.75 µg/L. There is no consumer exposure via other routes. Metabolite M54 is not considered to exceed the toxicological threshold of concern as defined in EC guidance document SANCO/221/2000 –rev.11. (21/10/2021)

The reference to the results of the lysimeter studies made by the Applicant in the evaluation below was not struck through by the zRMS as these data are in line with EFSA Journal 2013;11(8):3269, however, they may be considered as additional and supportive information only. In order to be able to rely on results of these studies to derive the conclusion, the representativeness of the EU agreed lysimeter studies for conditions of each country included in the GAP should be evaluated, which was not done by the Applicant.

Lysimeter studies were carried out to determine concentrations of pinoxaden and its metabolites. M54 was detected at a maximum concentration of 0.15 µg/L (autumn application), which is considerably lower than the acceptable estimated upper limit of 0.75 µg/L. The metabolite M54 was not seen in the lysimeter studies for spring application. Metabolite M54 can be considered as not relevant for the intended application pattern.

### 10.2.4.5 STEP 5: Refined risk assessment

~~This step is not required, see step 4, point 10.2.6.4 of this document.~~

**Reviewer comment:**
Metabolite M54 has a $PEC_{gw}$ of <0.75 µg/L and the threshold of concern approach in Step 4 is acceptable. A refined assessment of the potential toxicological significance including the selected ADI is not required.

## 10.2.5 Relevance assessment of M55

**Summary:**

The groundwater metabolite M55 is not considered as relevant according to the criteria laid down in the EC guidance document SANCO/221/2000–rev.10. A summary of the relevance assessment for M55 is given in Table 10.2-6. Studies supporting $PEC_{gw}$ data are evaluated in Section 8 (Environmental fate and behaviour) and the genotoxicity studies are evaluated in Section 6 (Mammalian Toxicology).

**Table 10.2-6: Summary of the relevance assessment for M55**

| | Assessment step | | Result of assessment | |
|---|---|---|---|---|
| | STEP 1 | | Metabolite of no concern? | no |
| **Quantification of groundwater contamination** | STEP 2 | | Max $PEC_{gw}$ | ~~4.478~~<br>Annual: 1.785 µg/L** |
| | | | Based on | ~~FOCUS PEARL 4.4.4~~<br>~~Scenario Jokioinen~~<br>~~Winter cereals~~<br>Spring cereals<br>FOCUS PEARL 4.4.4<br>Scenario Hamburg<br>1 x 60 g/ha<br>Application post-emergence<br>BBCH 13-39 (20% interception) |
| **Hazard assessment** | STEP 3 | Stage 1 | Biological activity comparable to the parent? | Less toxic than parent |
| | | Stage 2 | Genotoxic properties of metabolite | Not genotoxic |
| | | Stage 3 | Toxic properties of metabolite; | |
| | | | Classification of parent | Not toxic or highly toxic |
| | | | Classification of metabolite | Not toxic or highly toxic |
| **Consumer health risk assessment** | STEP 4 | | Estimated consumer exposure via drinking water and other sources; threshold of concern approach | ~~Maximum concentration in lysimeter studies = 0.206 µg/L, which is less than 0.75 µg/L.~~<br>Based on evaluation in area of Section 8, the conclusion for the Central Zone cannot be relied on results of the lysimeter studies ($PEC_{GW}$ > 0.75 µg/L) |
| | STEP 5 | | Refined risk assessment | ~~N/A*~~<br>acceptable |
| | | | Predicted exposure (% of ADI) | ~~N/A*~~<br>0.27 % of ADI (infant), 0.17 % of ADI (child), 0.06 % of ADI (adult). |
| | | | ADI based on | ~~N/A*~~<br>0.1 mg/kg bw per day has been set as parent ADI in the dietary risk assessment for M55 which represents a conservative approach.<br>EFSA Journal 2013;11(8):3269 |

* N/A: not applicable; ** for details refer dRR Section B8

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

M55 does not meet the criteria for products of no concern as defined in step 1 of the guidance and therefore needs further assessment.

It cannot be excluded as a product of no concern as it is not:

- $CO_2$ or an inorganic compound, not containing a heavy metal;
- an organic compound of aliphatic structure, with a chain length of 4 or less, which consists only of C, H, N or O atoms and which has no "alerting structures" such as epoxide, nitrosamine, nitrile or other functional groups of known toxicological concern;
- a substance which is known to be of no toxicological or ecotoxicological concern, and which is naturally occurring at much higher concentrations in the respective compartment

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

$PEC_{gw}$ calculations after leaching from soil for M55 were performed (see Part B, Section 8, chapter 8.8). There were uses for which concentrations of M55 were considered to exceed 0.1 µg/L therefore further assessment is required.

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

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

No studies on the toxicity of metabolite M55 to plants or ecotoxicological organisms are available.

A study was submitted as part of the active substance renewal of pinoxaden which investigates the action of pinoxaden and its metabolites on the activity of the enzyme acetyl-CoA carboxylase from corn. Metabolite M55 was not included in this test, but is considered to be structurally similar to metabolite NOA 447204 (M3). The study demonstrated that pinoxaden inhibits con ACCase activity with an I50 of 1 µM/L, whereas metabolite NOA 447204 (M3) had no effect on the enzyme at the highest tested concentration of 200 ppm.
M55 is considered to be structurally similar to metabolite NOA 447204 (M3), please see Table 10.2-1, therefore M55 is not expected to be more biologically active than pinoxaden. M55 can be considered as not relevant.

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

No studies on the genotoxicity of metabolite M55 are available. M55 is considered to be structurally similar to metabolite NOA 447204 (M3), please see Table 10.2-1, therefore M55 is not expected to be genotoxic. A QSAR (DEREK) analysis of M55 was carried out as part of the active substance renewal of pinoxaden,, which indicated that M55 does not possess structural alerts for mutagenicity. M55 can be considered as not relevant.

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

No studies on the toxicity of metabolite M55 are available. M55 is considered to be structurally similar to metabolite NOA 447204 (M3), please see Table 10.2-1, therefore based on the screening for toxicity assessment of metabolite NOA 447204 (M3), M55 can be considered as not relevant.

The classification for pinoxaden with H361d has been confirmed after the approval of pinoxaden and published in Reg 2018/1480. Therefore according to SANCO/211/2000, rev 10, it must be documented that metabolites in groundwater do not share the toxic properties for reproduction of the parent compound. According to Implementing Regulation (EU) 2016/370 of 15 March 2016 the applicant shall submit confirmatory information as regards the relevance of the metabolites and the corresponding groundwater risk assessment. We understand the confirmatory data has been submitted and ADAMA reference the information. Data is currently being evaluated by Austria (UK was the original RMS).

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

Metabolite M55 is considered as not relevant. The exposure assessment at step 4 is still required in accordance with SANCO/221/2000 v.10.

The Scientific Committee on Plants proposed a toxicological threshold of concern of 1.5 µg/person/day or 0.02 µg/kg body weight/day, which is in line with the threshold developed by the US-FDA. Assuming a consumption of 2 litres of water per day, all of which comes from the upper soil layer, such an acceptable exposure level relates to an acceptable estimated upper limit for the concentration of a metabolite of 0.75 µg/L.

**Reviewer comment:**
The PECgw for Metabolite M55 was >0.75 µg/L. There is potentially risk for consumer via drinking water. Metabolite M55 exceed the toxicological threshold of concern as defined in EC guidance document SANCO/221/2000 –rev.11. (21/10/2021) therefore STEP 5 is required.

The reference to the results of the lysimeter studies made by the Applicant in the evaluation below was not struck through by the zRMS as these data are in line with EFSA Journal 2013;11(8):3269, however, they may be considered as additional and supportive information only. In order to be able to rely on results of these studies to derive the conclusion, the representativeness of the EU agreed lysimeter studies for conditions of each country included in the GAP should be evaluated, which was not done by the Applicant.

Lysimeter studies were carried out to determine concentrations of pinoxaden and its metabolites. M55 was detected at a maximum concentration of 0.134 µg/L (autumn application), which is considerably lower than the acceptable estimated upper limit of 0.75 µg/L. The metabolite M55 was not seen in the lysimeter studies for spring application. Metabolite M55 can be considered as not relevant for the intended application pattern.

### 10.2.5.5 STEP 5: Refined risk assessment

~~This step is not required, see step 4, point 10.2.7.4 of this document.~~

**Reviewer comment:**
Step 5 has been provided by the zRMS due to the newly estimated PECgw value for M55 metabolite

M55 has a $PEC_{gw}$ between 0.75 µg/L and 10 µg/L. 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 M55 are 0.27 % of ADI (infant), 0.17 % of ADI (child), 0.06 % of ADI (adult).

Justification for the selected ADI:

The ADI as defined in the LoEP EFSA Journal 2013;11(8):3269 has been set as parent ADI in the dietary risk assessment for M55 which represents a conservative approach.

ADI = 0.1 mg/kg bw/d
= 100 µg/kg bw/d

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:

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

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 = 0.27 µg/kg bw/d
Risk for 5-kg bottle fed infant (% ADI) = 0.27 %

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

Worst case daily dietary exposure of 10 kg child = 0.17 µg/kg bw/d
Risk for 10 kg child (% ADI) = 0.17%

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

Worst case daily dietary exposure of 60-kg adult = 0.06 µg/kg bw/d
Risk for 60-kg adult (% ADI) = 0.06%

### 10.2.6 Relevance assessment of M56

**Summary:**

The groundwater metabolite M56 is not considered as relevant according to the criteria laid down in the EC guidance document SANCO/221/2000–rev.10. A summary of the relevance assessment for M56 is given in Table 10.2-7. Studies supporting $PEC_{gw}$ data are evaluated in Section 8 (Environmental fate and behaviour) and the genotoxicity studies are evaluated in Section 6 (Mammalian Toxicology).

**Table 10.2-7: Summary of the relevance assessment for M56**

| | Assessment step | | Result of assessment | |
|---|---|---|---|---|
| | STEP 1 | | Metabolite of no concern? | no |
| **Quantification of groundwater contamination** | STEP 2 | | Max $PEC_{gw}$ | ~~7.944~~<br>Annual: 3.128 µg/L** |
| | | | Based on | ~~FOCUS PEARL 4.4.4~~<br>~~Scenario Jokioinen~~<br>~~Winter cereals~~<br>winter cereals<br>FOCUS PEARL 4.4.4<br>Scenario Châteaudun<br>1 x 60 g/ha<br>Application post-emergence<br>BBCH 20-39 (0% interception) |
| **Hazard assessment** | STEP 3 | Stage 1 | Biological activity comparable to the parent? | Less toxic than parent |

| | Assessment step | | Result of assessment | |
|---|---|---|---|---|
| | | Stage 2 | Genotoxic properties of metabolite | Not genotoxic |
| | | Stage 3 | Toxic properties of metabolite; | |
| | | | Classification of parent | Not toxic or highly toxic |
| | | | Classification of metabolite | Not toxic or highly toxic |
| **Consumer health risk assessment** | STEP 4 | | Estimated consumer exposure via drinking water and other sources; threshold of concern approach | ~~Maximum concentration in lysimeter studies = 0.206 µg/L, which is less than 0.75 µg/L.~~<br>Based on evaluation in area of Section 8, the conclusion for the Central Zone cannot be relied on results of the lysimeter studies ($PEC_{GW}$ > 0.75 µg/L) |
| | STEP 5 | | Refined risk assessment | ~~N/A.*~~<br>acceptable |
| | | | Predicted exposure (% of ADI) | ~~N/A.*~~<br>0.47 % of ADI (infant), 0.31 % of ADI (child), 0.1 % of ADI (adult). |
| | | | ADI based on | ~~N/A.*~~<br>0.1 mg/kg bw per day has been set as parent ADI in the dietary risk assessment for M11 which represents a conservative approach.<br>EFSA Journal 2013;11(8):3269 |

*N/A: not applicable; ** for details refer dRR Section B8

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

M56 does not meet the criteria for products of no concern as defined in step 1 of the guidance and therefore needs further assessment.
It cannot be excluded as a product of no concern as it is not:

- $CO_2$ or an inorganic compound, not containing a heavy metal;
- an organic compound of aliphatic structure, with a chain length of 4 or less, which consists only of C, H, N or O atoms and which has no "alerting structures" such as epoxide, nitrosamine, nitrile or other functional groups of known toxicological concern;
- a substance which is known to be of no toxicological or ecotoxicological concern, and which is naturally occurring at much higher concentrations in the respective compartment.

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

$PEC_{gw}$ calculations after leaching from soil for M56 were performed (see Part B, Section 8, chapter 8.8). There were uses for which concentrations of M56 were considered to exceed 0.1 µg/L therefore further assessment is required.

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

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

No studies on the toxicity of metabolite M56 to plants or ecotoxicological organisms are available.

A study was submitted as part of the active substance renewal of pinoxaden which investigates the action of pinoxaden and its metabolites on the activity of the enzyme acetyl-CoA carboxylase from corn. Metabolite M56 was not included in this test, but is considered to be structurally similar to metabolite NOA 447204 (M3). The study demonstrated that pinoxaden inhibits con ACCase activity with an I50 of

1 µM/L, whereas metabolite NOA 447204 (M3) had no effect on the enzyme at the highest tested concentration of 200 ppm.

M56 is considered to be structurally similar to metabolite NOA 447204 (M3), please see Table 10.2-1, therefore M56 is not expected to be more biologically active than pinoxaden. M56 can be considered as not relevant.

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

No studies on the genotoxicity of metabolite M56 are available. M56 is considered to be structurally similar to metabolite NOA 447204 (M3), please see Table 10.2-1, therefore M56 is not expected to be genotoxic. A QSAR (DEREK) analysis of M56 was carried out as part of the active substance renewal of pinoxaden, which indicated that M56 does not possess structural alerts for mutagenicity. M56 can be considered as not relevant.

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

No studies on the toxicity of metabolite M56 are available. M56 is considered to be structurally similar to metabolite NOA 447204 (M3), please see Table 10.2-1, therefore based on the screening for toxicity assessment of NOA 447204 (M3), M56 can be considered as not relevant.

The classification for pinoxaden with H361d has been confirmed after the approval of pinoxaden and published in Reg 2018/1480. Therefore according to SANCO/211/2000, rev 10, it must be documented that metabolites in groundwater do not share the toxic properties for reproduction of the parent compound. According to Implementing Regulation (EU) 2016/370 of 15 March 2016 the applicant shall submit confirmatory information as regards the relevance of the metabolites and the corresponding groundwater risk assessment. We understand the confirmatory data has been submitted and ADAMA reference the information. Data is currently being evaluated by Austria (UK was the original RMS).

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

Metabolite M56 is considered as not relevant. The exposure assessment at step 4 is still required in accordance with SANCO/221/2000 v.10.

The Scientific Committee on Plants proposed a toxicological threshold of concern of 1.5 µg/person/day or 0.02 µg/kg body weight/day, which is in line with the threshold developed by the US-FDA. Assuming a consumption of 2 litres of water per day, all of which comes from the upper soil layer, such an acceptable exposure level relates to an acceptable estimated upper limit for the concentration of a metabolite of 0.75 µg/L.

**Reviewer comment:**
The PECgw for Metabolite M56 was >0.75 µg/L. There is potentially risk for consumer via drinking water. Metabolite M56 exceed the toxicological threshold of concern as defined in EC guidance document SANCO/221/2000 –rev.11. (21/10/2021) therefore STEP 5 is required.

The reference to the results of the lysimeter studies made by the Applicant in the evaluation below was not struck through by the zRMS as these data are in line with EFSA Journal 2013;11(8):3269, however, they may be considered as additional and supportive information only. In order to be able to rely on results of these studies to derive the conclusion, the representativeness of the EU agreed lysimeter studies for conditions of each country included in the GAP should be evaluated, which was not done by the Applicant.

Lysimeter studies were carried out to determine concentrations of pinoxaden and its metabolites. M56 was detected at a maximum concentration of 0.266 µg/L (autumn application), which is considerably lower than the acceptable estimated upper limit of 0.75 µg/L. The metabolite M56 was not seen in the

lysimeter studies for spring application. Metabolite M56 can be considered as not relevant for the intended application pattern.

### 10.2.6.5 STEP 5: Refined risk assessment

~~This step is not required, see step 4, point 10.2.8.4 of this document.~~

**Reviewer comment:**
Step 5 has been provided by the zRMS due to the newly estimated PECgw value for M56 metabolite

M56 has a $PEC_{gw}$ between 0.75 µg/L and 10 µg/L. 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 M56 are 0.47 % of ADI (infant), 0.31 % of ADI (child), 0.1 % of ADI (adult).

Justification for the selected ADI:

The ADI as defined in the LoEP EFSA Journal 2013;11(8):3269 has been set as parent ADI in the dietary risk assessment for M11 which represents a conservative approach.

ADI = 0.1 mg/kg bw/d
= 100 µg/kg bw/d

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:

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

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 = 0.47 µg/kg bw/d
Risk for 5-kg bottle fed infant (% ADI) = 0.47 %

Calculation of risk (% ADI) for 10 kg child (consuming 1.0 l/day):
Worst case daily dietary exposure of 10 kg child = 0.31 µg/kg bw/d
Risk for 10 kg child (% ADI) = 0.31%

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

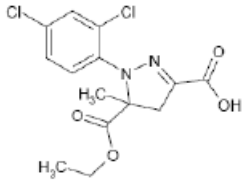
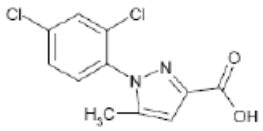
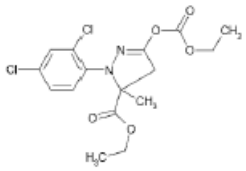
Worst case daily dietary exposure of 60-kg adult = 0.10 µg/kg bw/d
Risk for 60-kg adult (% ADI) = 0.1 %

## 10.3 Mefenpyr-diethyl and metabolites

### 10.3.1 General information

General information on the metabolites of mefenpyr-diethyl 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 chapter 8.1 of the dRR Part B, Section 8 (Environmental fate and behaviour).

**Table 10.3-1: General information on the metabolite(s)**

| Name of active substance | Metabolite name and code | Structural/molecular formula | Trigger for relevance assessment | |
|---|---|---|---|---|
| Mefenpyr-diethyl | AE F113225 |  | Max $PEC_{gw}$ Winter and spring cereals [µg/L]<br><br>Based on: | Annual: <0.001<br><br>All scenarios<br>1 x 35 g/ha<br>Application post-emergence<br>BBCH 13-20 (0% interception) |
| Mefenpyr-diethyl | AE F094270 |  | Max $PEC_{gw}$ Winter and spring cereals [µg/L]<br><br>Based on: | Annual: <0.001<br><br>All scenarios<br>1 x 35 g/ha<br>Application post-emergence<br>BBCH 13-20 (0% interception) |
| Mefenpyr-diethyl | AE F2211046 |  | Max $PEC_{gw}$ Winter ceeals [µg/L]<br><br>Based on: | Annual: 0.085<br><br>FOCUS PEARL 4.4.4<br>Scenario Okehampton<br>1 x 35 g/ha<br>Application post-emergence<br>BBCH 20-39 (20% interception) |

The metabolites AE F133225, AE F094270 and AE F2211046 are predicted to occur in groundwater at concentrations **below 0.1 µg/L** (see 8.8.2.1 of the dRR Part B, Section 8). Assessment of the relevance of these metabolites according to the stepwise procedure of the EC guidance document SANCO/221/2000 – rev.10 is therefore **not** required.

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

## List of data submitted by the applicant and 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

| 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 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

None.