Peer review of the pesticide risk assessment for the active substance isoxaflutole in light of negligible exposure data submitted

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Abstract

The conclusions of EFSA following the peer review of the initial risk assessment carried out by the competent authority of the rapporteur Member State, Italy, for the pesticide active substance isoxaflutole are reported. The context of the peer review was that requested by the European Commission following the submission and evaluation of negligible exposure data. EFSA prepared a conclusion where the assessment of the information is presented according to the draft technical guidance on assessment of negligible exposure of an active substance in a plant protection product under realistic conditions of use. The conclusions were reached on the basis of the evaluation of the representative uses of isoxaflutole as a herbicide on maize and sweet corn.

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Keywords: isoxaflutole, peer review, negligible exposure, risk assessment, pesticide, herbicide

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Summary

Isoxaflutole is listed in Commission Implementing Regulation (EU) No 686/2012. As part of the preceding peer review for renewal of approval of isoxaflutole according to Commission Implementing Regulation (EU) No 844/2012, the European Food Safety Authority (EFSA) proposed in its conclusion to classify isoxaflutole as carcinogen category 2 in addition to the harmonised classification as toxic for reproduction category 2. These two classifications trigger the lack of compliance with the approval criteria set out in Annex II of Regulation (EU) No 1107/2009 (in specific with point 3.6.5 of Annex II, as it meets the criteria established in the third paragraph concerning endocrine disrupting properties). By means of general mandate received on 13 January 2016 and a clarification to the general mandate received on 17 May 2016, EFSA was requested to carry out an assessment of the information submitted by the applicant to demonstrate whether the active substance isoxaflutole can be used such that exposure to humans may be considered negligible within 3 months from the receipt of the addenda to the renewal assessment report (RAR) namely by 18 February 2017.

The applicant, Bayer Crop Science, submitted an updated dossier in October 2016, which was evaluated by the rapporteur Member State (RMS), Italy, in the form of two addenda to Volume 3 of the RAR. The RMS provided its addenda to the RAR on 18 November 2016 to EFSA. EFSA distributed the addenda to Member States and applicant for comments on 23 November 2016, and provided comments as well. EFSA collated all comments and provided its scientific view on the comments received. A final consultation on the conclusions arising from the peer review took place with Member States via a written procedure in January and February 2017.

The residue situation for isoxaflutole and metabolite RPA 202248 in conventional maize commodities at harvest in the available field trials is consistently below the individual limit of quantifications (LOQs) of 0.01 mg/kg (sum LOQ 0.02 mg/kg) of the validated analytical method. The dietary risk assessments regarding residues of metabolite RPA 203328 in food and feed commodities (exceeding 0.01 mg/kg) and the consumption of drinking water abstracted from groundwater that potentially contains residues of metabolite RPA 203328 (a non-relevant groundwater metabolite), as presented in the conclusion of EFSA on the peer review (EFSA, 2016), remain unchanged.

Regarding the non-dietary exposure assessment, the estimates for operators were up to 5% of the acceptable operator exposure level (AOEL) with the use of personal protective equipment (at least workwear and gloves during mixing/loading), with a margin of exposure higher than 2,000 for the carcinogenic effect, and up to 10% of the acute acceptable operator exposure level (AAOEL) with workwear and gloves during mixing/loading and application. The estimates for workers were up to 3.5% of the AOEL with the use of workwear, and a margin of exposure higher than 2,000. The estimates for bystanders and residents were up to 5% of the AOEL or residential children, when taking into account a buffer zone of 10 m, drift reduction nozzles and a decreased air concentration due to very low vapour pressure.
Table of contents

| Section                                                                 | Page |
|------------------------------------------------------------------------|------|
| Abstract                                                               | 1    |
| Summary                                                                | 3    |
| Background                                                             | 5    |
| The active substance and the formulated product                       | 6    |
| Conclusions of the evaluation                                          | 6    |
| 1. Negligible exposure to humans                                       | 7    |
| 1.1. Dietary exposure                                                 | 7    |
| 1.2. Non-dietary exposure                                              | 7    |
| 2. Negligible exposure to non-target organisms                         | 10   |
| References                                                             | 10   |
| Abbreviations                                                          | 11   |
| Appendix A – Used compound codes                                       | 12   |
**Background**

Commission Implementing Regulation (EU) No 844/2012 (hereinafter referred to as ‘the Regulation’) lays down the provisions for the procedure of the renewal of the approval of active substances, submitted under Article 14 of Regulation (EC) No 1107/2009. The list of those substances is established in Commission Implementing Regulation (EU) No 686/2012. Isoxaflutole is one of the active substances listed in Regulation (EU) No 686/2012. In accordance with Article 13 of the Regulation (EU) No 844/2012, the European Food Safety Authority (EFSA) finalised a conclusion on the peer review of the pesticide risk assessment of the active substance isoxaflutole on 16 February 2016 (EFSA, 2016) and provided its conclusion to the European Commission.

Annex II of Regulation (EU) No 1107/2009 provides in its points 3.6.3, 3.6.4 and 3.6.5 that active substances classified on the basis of Regulation (EC) No 1272/2008 as carcinogen category 1A or 1B or toxic for reproduction category 1A or 1B, or having endocrine disrupting properties which may cause adverse effects on humans cannot be approved unless the exposure of humans to that active substance in a plant protection product, under realistic proposed conditions of use, is negligible. These conditions under which negligible exposure is assumed is precondition for approval of substances in accordance with Article 4 of the Regulation (EU) No 1107/2009 read in combination with these points.

The European Commission shall propose a decision on renewal/non-renewal of approval for active substances considered under Regulation (EU) No 1107/2009 taking into account the approval criteria of Annex II, points 3.6.3, 3.6.4 and 3.6.5 of that Regulation. As part of the preceding peer review for renewal of approval of isoxaflutole, EFSA proposed in its conclusion on classification of isoxaflutole as carcinogen category 2 in addition to the harmonised classification of isoxaflutole as toxic for reproduction category 2. Considering the harmonised classification and the proposed classification by the EFSA peer review, a critical area of concern was identified with regard to Annex II, Point 3.6.5 of Regulation (EC) No 1107/2009 interim provisions for active substances that shall be considered to have endocrine disrupting properties. The lack of compliance with the approval criteria set out in Annex II of Regulation (EU) No 1107/2009 (in specific with point 3.6.5 of Annex II, as it meets the criteria established in the third paragraph concerning endocrine disrupting properties) was not known by the applicant at the time of the dossier submission. As a consequence, the applicant did not submit information in its dossier to demonstrate that exposure of humans to the substance, under realistic conditions of use, can be considered negligible. Therefore, in order to inform the decision-making process, the European Commission invited the applicant Bayer Crop Science to provide further information to demonstrate that the exposure of humans to isoxaflutole is negligible under realistic conditions of use. The European Commission then requested the rapporteur Member State (RMS), Italy, to carry out an evaluation of this information and to submit its assessment in the format of an addendum to EFSA.

By means of a general mandate received on 13 January 2016, the European Commission requested EFSA to conduct a peer review and provide its conclusions on particular active substances, to be communicated on an ad-hoc basis, on whether exposure of humans to an active substance, under realistic conditions of use, can be considered negligible, taking into account the draft 'Technical guidance on points 3.6.3 to 3.6.5 of Annex II to Regulation (EC) No 1107/2009, in particular regarding the demonstration of negligible exposure to an active substance in a plant protection product under realistic conditions of use'. With a clarification to the general mandate received on 17 May 2016, the European Commission clarified that taking into account the absence of a final guidance document and ongoing discussions in the Standing Committee on Plants, Animals, Food and Feed (PAFF Committee), the draft...
guidance document made available for stakeholder consultation and published on Commissions’ website on 25 June 2015 should be considered (draft dated May 2015; SANCO/2014/12096 (European Commission, 2015)). In the absence of agreed threshold values for assessing negligible exposure, a conclusion regarding such agreed threshold is not possible. However, in order to provide risk managers with the relevant information for decision-making, EFSA was requested to (a) calculate the actual expected exposure values in absolute values and percentage of the established toxicological reference values (e.g. acceptable operator exposure level (AOEL)); (b) consider potential technical mitigation measures to reduce exposure as those mentioned in the draft guidance, that have been proposed by the applicant and/or by the RMS, or by EFSA, if and when appropriate.

The applicant, Bayer Crop Science, submitted an updated dossier in October 2016, which was evaluated by the RMS, Italy, in the form of two addenda to Volume 3 of the renewal assessment report (RAR) (Italy, 2016). The RMS provided its addenda to the RAR on 18 November 2016 to EFSA. EFSA distributed the addenda to Member States and applicant for comments on 23 November 2016, and provided comments as well. EFSA collated all comments and provided its scientific view on the comments received.

A final consultation on the conclusions arising from the peer review took place with Member States via a written procedure in January and February 2017.

The conclusions laid down in this report were reached on the basis of the peer review of the RMS’s evaluation of the negligible exposure data submitted. A key supporting document to this conclusion is the peer review report, which is a compilation of the documentation developed to evaluate and address all issues raised in the peer review, from the compilation of comments to the conclusion. The peer review report (EFSA, 2017) comprises the following documents, in which all views expressed during the course of the peer review, including minority views, can be found:

- the comments received on the addendum to the RAR;
- the comments received on the draft EFSA conclusion.

Given the importance of the addenda to the RAR (Italy, 2016) and the peer review report, these documents are considered as background documents to this conclusion.

It is recommended that this conclusion report and its background documents would not be accepted to support any registration outside the European Union (EU) for which the applicant has not demonstrated to have regulatory access to the information on which this conclusion report is based.

The active substance and the formulated product

Isoxaflutole is the ISO common name for (5-cyclopropyl-1,2-oxazol-4-yl)(α,α,α-trifluoro-2-mesyl-p-tolyl)methanone (IUPAC).

The representative formulated product for the evaluation was ‘Isoxaflutole + Cyprosulfamide SC 480 (Merlin Flexx)’, a suspension concentrate (SC) containing 240 g/L isoxaflutole and 240 g/L cyprosulfamide as a safener.

The representative uses evaluated in the peer review for renewal of approval of isoxaflutole were application by spraying against annual broadleaved weeds and grasses in maize and sweet corn. The applicant proposed the same uses as for renewal to be considered for negligible exposure. Full details of the Good Agricultural Practice (GAP) can be found in the list of end points in Appendix A of the previous EFSA conclusion (EFSA, 2016).

Conclusions of the evaluation

The applicant has submitted to the Commission information to demonstrate that the exposure of humans to isoxaflutole can be considered negligible under the proposed condition of use.

The assessment of the information was presented in two addenda to Volume 3 of the RAR (Italy, 2016) prepared according to the draft Technical Guidance Document on assessment of negligible exposure of an active substance in a plant protection product under realistic conditions of use (points 3.6.3 to 3.6.5, and 3.8.2 of Annex II of Regulation (EC) No 1107/2009) SANCO/2014/12096 (European Commission, 2015) and the EFSA guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products (EFSA, 2014).
1. **Negligible exposure to humans**

1.1. **Dietary exposure**

The residue situation for isoxaflutole and metabolite RPA 202248 in conventional maize commodities at harvest in the available field trials is consistently below the individual limit of quantifications (LOQs) of 0.01 mg/kg (sum LOQ 0.02 mg/kg) of the validated analytical method. The dietary risk assessments regarding residues of metabolite RPA 203328 in food and feed commodities (exceeding 0.01 mg/kg) and the consumption of drinking water abstracted from groundwater that potentially contains residues of metabolite RPA 203328 (a non-relevant groundwater metabolite), as presented in the conclusion of EFSA on the peer review (EFSA, 2016), remain unchanged.

Exposure to RPA 202248 via the consumption of drinking water has not been considered by EFSA in this conclusion. The reason for this is, that although the conclusion of EFSA (EFSA, 2016) was that ‘the available groundwater exposure assessment for these representative uses indicated that the herbicidally active and groundwater toxicologically relevant metabolite RPA 202248 would be expected to exceed the parametric drinking water limit of 0.1 µg/L in geoclimatic situations represented by more than half (5 out of 8) FOCUS groundwater scenarios’ which lead to a critical area of concern, as Member States should only ever authorise the use of products in geoclimatic conditions where groundwater exposure of RPA 202248 can be precluded, groundwater abstracted for drinking water purposes should not contain relevant metabolite RPA 202248.

The recommendation in the draft technical guidance on assessment of negligible exposure (European Commission, 2015) to ensure that validated analytical methods are available for at least the four main plant matrix groups is addressed for isoxaflutole and for metabolite RPA 202248 but is not fully addressed for metabolite RPA 203328 according to the findings of the peer review (EFSA, 2016). Further, there is no validated analytical method available for any of the matrix groups, which is covering all three compounds at the same time.

1.2. **Non-dietary exposure**

The reference values for isoxaflutole are presented in Table 1. The acute acceptable operator exposure level (AAOEL) was not discussed during the peer review and can be set at 0.03 mg/kg body weight (bw) on the basis of the rabbit developmental toxicity study (uncertainty factor (UF) 100 + correction for oral absorption). The dermal absorption values for the formulation ‘Merlin Flexx’ are 0.7% for the concentrate, 1% for the intermediate spray dilution (44 g/L) and 3% for the highest spray dilution (0.3 g/L).

The calculations reported below in the Tables 2–5 have been partially taken from the RMS’s assessment and partially calculated by EFSA (for completeness of the presented results) with the EFSA calculator (EFSA, 2014).

**First tier assessment:**

The exposure estimates have been provided for operators, workers, bystanders and residents, for the representative uses on maize and sweet corn. The resident exposure assessment also covers longer term exposure for the bystander, and the acute exposure assessment for the bystander also covers acute exposure scenarios for the resident. The results are presented in Tables 2, 3, 4 and 5, including possible risk mitigation measures.
A refinement has been provided for the residential exposure of children, taking into account a revised air concentration based on the low vapour pressure of isoxaflutole (according to Henry’s Law). This resulted in an exposure estimate of 5% of the AOEL.

Second tier assessment:

Considerations were also given to the margin of exposure (MoE) between non-dietary exposure and the no observed adverse effect levels (NOAELs) for the critical effects. For the tumorigenic effect (relevant for short- to long-term exposure), the lowest systemic NOAEL is 1.2 mg/kg bw per day. For the developmental effect (relevant for acute exposure), the lowest systemic NOAEL is 3 mg/kg bw per day. The results are also included in the Tables 2, 3, 4 and 5.

Table 2: Non-dietary exposure scenarios and margin of exposure (MoE) – Operators

| EFSA Model | Risk mitigation measures                                                                 | Systemic dose (mg/kg bw per day) | % AOEL or AAOEL (a) | MoE(c) Repr | MoE(c) Carc |
|------------|-------------------------------------------------------------------------------------------|----------------------------------|---------------------|-------------|-------------|
| Short- to long-term exposure | Workwear (arms, body and legs covered) | 0.0025225 | 21 | – | 476 |
| | Workwear + gloves during mixing/loading (M/L) | 0.0005778 | 5 | – | 2,077 |
| | Workwear + gloves during M/L and application (A) | 0.0002578 | 2 | – | 4,655 |
| | Workwear + gloves during M/L and A + RPE (FP1, P1 and similar) during M/L(b) | 0.0001770 | 1.5 | – | 6,780 |
| | Workwear + gloves and RPE (FP1, P1 and similar) during M/L and A(b) | 0.0001461 | 1.2 | – | 8,214 |
| | Workwear + gloves during M/L and A + RPE (FP2, P2 and similar) during M/L(b) | 0.0001621 | 1.3 | – | 7,403 |
| | Workwear + gloves and RPE (FP2, P2 and similar) during M/L and A | 0.0001253 | 1 | – | 9,577 |
| | Workwear + gloves during M/L and A + drift reducing nozzles | 0.0001973 | 1.6 | – | 6,082 |
| | Workwear + gloves during M/L and A + RPE (FP1, P1 and similar) during M/L + drift reducing nozzles | 0.0001166 | 2 | – | 10,292 |
| | Workwear + gloves during M/L and A + RPE (FP2, P2 and similar) during M/L + drift reducing nozzles | 0.0001016 | 0.8 | – | 11,811 |
| Acute exposure | Workwear (arms, body and legs covered) | 0.0119088 | 40 | 252 | – |
| | Workwear + gloves during mixing/loading (M/L) | 0.0047544 | 16 | 631 | – |
| | Workwear + gloves during M/L and application (A) | 0.0030405 | 10 | 987 | – |
| | Workwear + gloves during M/L and A + RPE (FP1, P1 and similar) during M/L(b) | 0.0026344 | 9 | 1,139 | – |
| | Workwear + gloves and RPE (FP1, P1 and similar) during M/L and A | 0.0025367 | 8.5 | 1,183 | – |
| | Workwear + gloves during M/L and A + RPE (FP2, P2 and similar) during M/L(b) | 0.0025598 | 8.5 | 1,172 | – |
| | Workwear + gloves and RPE (FP2, P2 and similar) during M/L and A | 0.0024437 | 8.1 | 1,228 | – |
| | Workwear + gloves during M/L and A + drift reducing nozzles | 0.0009575 | 3 | 3,133 | – |
| | Workwear + gloves during M/L and A + RPE (FP1, P1 and similar) during M/L + drift reducing nozzles | 0.0005514 | 1.8 | 5,441 | – |
### Table 3: Non-dietary exposure scenarios and margin of exposure (MoE) – Workers

| EFSA Model | Risk mitigation measures | Systemic dose (mg/kg bw per day) | % AOEL(a) | MoE(c) | Carc |
|------------|--------------------------|----------------------------------|-----------|--------|------|
| Short- to long-term exposure | Workwear | 0.0004768 | 1.6 | 6,292 | – |

a.s.: active substance; bw: body weight.
(a): AOEL: acceptable operator exposure level (short- to long-term exposure).
(b): MoE: margin of exposure for carcinogenicity (for short- to long-term exposure) or reproductive toxicity (for acute exposure), being the ratio between critical systemic NOAEL and estimated exposure.

### Table 4: Non-dietary exposure scenarios and margin of exposure (MoE) – Residents

| EFSA Model | Risk mitigation measures | Systemic dose (mg/kg bw per day) | % AOEL(a) | MoE(b) | Carc |
|------------|--------------------------|----------------------------------|-----------|--------|------|
| All pathways – child | Buffer zone 2-3 m | 0.0018478 | 15 | 649 |
| All pathways – adult | Buffer zone 2-3 m | 0.0005312 | 4 | 2,259 |
| All pathways – child | Buffer zone 10 m | 0.0016615 | 14 | 722 |
| All pathways – adult | Buffer zone 10 m | 0.0004887 | 4 | 2,455 |
| All pathways – child | Buffer zone 10 m + drift reduction nozzles 50% | 0.0015676 | 13 | 765 |
| All pathways – adult | Buffer zone 10 m + drift reduction nozzles 50% + refinement for low VP | 0.0005486 | 5 | 2,187 |
| All pathways – child | Buffer zone 10 m + drift reduction nozzles 50% + refinement for low VP | 0.002524 | 2 | 4,754 |

a.s.: active substance; bw: body weight.
(a): AOEL: acceptable operator exposure level (short- to long-term exposure); AAOEL: acute AOEL (acute exposure), reference value used with the EFSA calculator for acute exposure.
(b): MoE: margin of exposure for carcinogenicity (for short- to long-term exposure), being the ratio between critical systemic NOAEL and estimated exposure.

### Table 5: Non-dietary exposure scenarios and margin of exposure (MoE) – Bystanders

| EFSA Model | Risk mitigation measures | Systemic dose (mg/kg bw per day) | % AAOEL(a) | MoE(b) | Repr |
|------------|--------------------------|----------------------------------|-----------|--------|------|
| Child | Spray drift | Buffer zone 2-3 m | 0.0013 | 4 | 2,308 |
| | Vapour | Buffer zone 2-3 m | 0.0011 | 4 | 2,727 |
| | Surface deposits | Buffer zone 2-3 m | 0.0003 | 1 | 10,000 |
| | Entry in crops | Buffer zone 2-3 m | 0.0005 | 2 | 6,000 |

a.s.: active substance; bw: body weight.
(a): AAOEL: acute AOEL (acute exposure).
(b): MoE: margin of exposure for carcinogenicity (for short- to long-term exposure), being the ratio between critical systemic NOAEL and estimated exposure.
2. Negligible exposure to non-target organisms

The draft Technical Guidance on assessment of negligible exposure of an active substance in a plant protection product under realistic conditions of use (SANCO/2014/12096 (European Commission, 2015)) does not give any guidance for consideration of negligible exposure for non-target organisms other than humans. That is the reason that the assessment of potential negligible exposure to non-target organisms is not assessed in this conclusion. For most environmental exposure (excluding plants used for human food or feed and groundwater that may be consumed as drinking water discussed in this conclusion) and non-target organism risk assessment, the EFSA conclusion (EFSA, 2016) remains applicable.

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### Table: Bystander – Use in maize/corn and sweet corn (100 g a.s./ha, 150 L/ha)

| EFSA Model | Risk mitigation measures | Systemic dose (mg/kg bw per day) | % AAOEL(a) | MoE(b) | Repr |
|------------|-------------------------|----------------------------------|------------|--------|------|
| **Adult**  |                         |                                   |            |        |      |
| Spray drift| Buffer zone 2–3 m       | 0.0003                           | 1          | 10,000 |      |
| Vapour     |                         | 0.0002                           | 1          | 15,000 |      |
| Surface deposits |                  | 0.0001                           | 0.2        | 30,000 |      |
| Entry in crops |                       | 0.0003                           | 1          | 10,000 |      |
| **Child**  |                         |                                   |            |        |      |
| Spray drift| Buffer zone 10 m        | 0.0007                           | 2          | 4,286  |      |
| Vapour     |                         | 0.0011                           | 4          | 2,727  |      |
| Surface deposits |                 | 0.0001                           | 0.2        | 30,000 |      |
| Entry in crops |                       | 0.0005                           | 2          | 6,000  |      |
| **Adult**  | Spray drift Buffer zone 10 m + drift reduction nozzles 50% | 0.0003 | 1 | 10,000 |
| Vapour     |                         | 0.0011                           | 4          | 2,727  |      |
| Surface deposits |                 | 0.0000                           | 0.1        | > 30,000 | |
| Entry in crops |                       | 0.0005                           | 2          | 6,000  |      |
| **Child**  | Spray drift Buffer zone 10 m + drift reduction nozzles 50% | 0.0003 | 1 | 10,000 |
| Vapour     |                         | 0.0011                           | 4          | 2,727  |      |
| Surface deposits |                 | 0.0000                           | 0.1        | > 30,000 | |
| Entry in crops |                       | 0.0005                           | 2          | 6,000  |      |

a.s.: active substance; bw: body weight.
(a): AAOEL: acute AOEL (acute exposure), reference value used with the EFSA calculator for acute exposure.
(b): MoE: margin of exposure reproductive toxicity (for acute exposure), being the ratio between critical systemic NOAEL and estimated exposure.
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Abbreviations

a.s. active substance
AAOEL acute acceptable operator exposure level
ADI acceptable daily intake
AOEL acceptable operator exposure level
ARFD acute reference dose
bw body weight
FOCUS Forum for the Co-ordination of Pesticide Fate Models and their Use
GAP Good Agricultural Practice
ISO International Organization for Standardization
IUPAC International Union of Pure and Applied Chemistry
LOQ limit of quantification (determination)
M/L mixing and loading
MOE margin of exposure
NOAEL no observed adverse effect level
NOEL no observed effect level
PAFF Standing Committee on Plants, Animals, Food and Feed
PPE personal protective equipment
RAR renewal assessment report
RMS rapporteur Member State
RPE respiratory protective equipment
SC suspension concentrate
SMILES simplified molecular-input line-entry system
UF uncertainty factor
## Appendix A – Used compound codes

| Code/trivial name\(^{(a)}\) | Chemical name/SMILES notation | Structural formula |
|----------------------------|--------------------------------|-------------------|
| RPA 202248                 | (2RS)-3-Cyclopropyl-2-[2-(methylsulfonyl)-4-(trifluoromethyl)benzoyl]-3-oxopropanenitrile  O=C(C(C#N)C(=O)C1CC1)c2ccc(cc2S(C)(=O)=O) C(F)(F)F | ![Structural formula](image) |
| RPA 203328                 | 2-Mesyl-4-trifluoromethylbenzoic acid  FC(F)(F)c1ccc(c(c1)S(C)(=O)=O)C(O)=O | ![Structural formula](image) |

SMILES: simplified molecular-input line-entry system.
\(^{(a)}\): The metabolite name in bold is the name used in the conclusion.