Statement on the impact of the harmonised classification on the conclusion on the peer review of the pesticide risk assessment of the active substance flutianil

European Food Safety Authority (EFSA)

Abstract

Following the publication of the EFSA conclusion on flutianil in 2014, the rapporteur Member State (RMS), the United Kingdom, launched a formal process for harmonising the classification of flutianil. The Committee for Risk Assessment (RAC) of the European Chemicals Agency (ECHA) finalised a RAC opinion on the proposed harmonised classification of flutianil in 2016. For some hazard classes, the harmonised classification proposed by the RAC was different than the provisional classification used in the EFSA conclusion. It should be noted that this difference was based on new information and does not constitute a scientific divergence as per Article 30 of Regulation (EC) No 178/2002. This statement updates the EFSA conclusion to consider the harmonised classification as proposed by the RAC. Concerns are clarified.

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Summary

Flutianil is a new active substance for which in accordance with Article 7 of the Regulation (EC) No 1107/2009 of the European Parliament and of the Council (hereinafter referred to as ‘the Regulation’), the rapporteur Member State (RMS) the United Kingdom received an application from Otsuka AgriTechno Co., Ltd. on 23 February 2011 for approval of the active substance flutianil.

Following the submission of the Draft Assessment Report (DAR) to the European Food Safety Authority (EFSA) by the RMS, the United Kingdom, which was received on 19 June 2013, EFSA initiated the peer review of the DAR in line with the provisions of the Regulation. After the completion of the peer review, including expert consultation in the areas of mammalian toxicology and environmental fate and behaviour, EFSA finalised its conclusion on whether flutianil can be expected to meet the approval criteria provided for in Article 4 of the Regulation on 28 July 2014 (EFSA, 2014a). In the absence of a process for harmonised classification, the EFSA conclusion included a comparison of the available information with the criteria established by the CLP Regulation (EC) No 1272/2008 in order to propose a provisional classification.

Following the publication of the EFSA conclusion, the RMS launched a formal process for harmonising the classification of flutianil. The Committee for Risk Assessment (RAC) of the European Chemicals Agency (ECHA) finalised a RAC opinion on the proposed harmonised classification of flutianil (ECHA RAC, 2016). For some hazard classes, the harmonised classification proposed by the RAC was different than the provisional classification used in the EFSA conclusion. It should be noted that this difference was based on new information and does not constitute a scientific divergence as per Article 30 of Regulation (EC) No 178/2002. This statement updates the EFSA conclusion to consider the harmonised classification as proposed by the RAC.

The critical areas of concern identified in the EFSA conclusion have been updated as a result of the RAC opinion on the harmonised classification of flutianil. No critical areas of concern are identified anymore. Some previously identified concerns regarding issues not finalised remain.
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1. Introduction

1.1. Introduction and background information

The European Food Safety Authority (EFSA) is responsible to deliver risk assessment or scientific and technical advice to the EU risk managers as outlined in Regulation (EC) No 178/20021 or in other relevant sectoral legal acts, such as Regulation (EC) No 1107/20097.

EFSA's Committee for Risk Assessment (RAC) is responsible for adopting opinions on proposals for harmonised classification and labelling according to the CLP Regulation (EC) No 1272/20083 (Article 37).

Flutianil is a new active substance for which in accordance with Article 7 of the Regulation (EC) No 1107/2009 of the European Parliament and of the Council (hereinafter referred to as 'the Regulation'), the RMS, the United Kingdom, received an application from Otsuka AgriTechno Co., Ltd. on 23 February 2011 for approval of this active substance.

Following the RMS's submission (the United Kingdom) of the Draft Assessment Report (DAR) to EFSA, which was received on 19 September 2014, EFSA initiated the peer review of the DAR in line with the provisions of Regulation (EC) No 1107/2009. After the completion of the peer review, including expert consultation in the areas of mammalian toxicology and environmental fate and behaviour, EFSA finalised its conclusion on whether flutianil can be expected to meet the approval criteria provided for in Article 4 of the Regulation on 28 July 2014 (EFSA, 2014a). Some approval criteria are linked to the classification of the active substance. In the absence of a process for harmonised classification, the EFSA conclusion included a comparison of the available information with the criteria established by the CLP Regulation (EC) No 1272/2008 in order to propose a provisional classification.

Following the publication of the EFSA conclusion, the RMS launched a formal process for harmonising the classification of flutianil. The RAC of the European Chemicals Agency (ECHA), finalised a RAC opinion on the proposed harmonised classification of flutianil (ECHA RAC, 2016). The opinion as well as the background document to the opinion and responses to the comments received during the public consultation are available on ECHA's website4 . In accordance with Article 37(4) of the CLP Regulation, the opinion has been submitted to the Commission for the decision to include the substance in Annex VI of the CLP Regulation.

For some hazard classes, the harmonised classification proposed by the RAC was different than the provisional classification used in the EFSA conclusion. It should be noted that this difference was based on new information and does not constitute a scientific divergence as per Article 30 of Regulation (EC) No 178/2002. This statement updates the EFSA conclusion to consider the harmonised classification as proposed by the RAC.

The critical areas of concern identified in the EFSA conclusion have been updated as a result of the RAC opinion on the harmonised classification of flutianil. No critical areas of concern are identified, but there are some concerns regarding issues not finalised.

1.2. Re-assessment of carcinogenicity and reprotoxicity hazards

The carcinogenic potential, reproduction and developmental toxicity of flutianil were discussed at the pesticides peer review meeting 114 on mammalian toxicology (May 2014). Based on the information available at that time for the peer review, the experts proposed classification regarding carcinogenicity and developmental toxicity category 2 (EFSA, 2014a,b).

The RMS solely supported classification regarding developmental toxicity and in their CLH proposal submitted to ECHA proposed this classification (Repr. 2; H361d) (United Kingdom CLP CA, 2015). No classification for carcinogenicity was proposed in the CLH report.

New historical control data were incorporated in the CLH report to support a lack of carcinogenic potential of flutianil. During the public consultation under the RAC procedure, further historical control

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1 Regulation (EC) No 178/2002 of the European Parliament and of the Council of 28 January 2002 laying down the general principles and requirements of food law, establishing the European Food Safety Authority and laying down procedures in matters of food safety. OJ L 31, 1.2.2002, p. 1-24.
2 Regulation (EC) No 1107/2009 of the European Parliament and of the Council of 21 October 2009 concerning the placing of plant protection products on the market and repealing Council Directives 79/117/EEC and 91/414/EEC. OJ L 309, 24.11.2009, p. 1-50.
3 Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006. OJ L 353, 31.12.2008, p. 1-1355.
4 https://echa.europa.eu/
data were provided to the RAC that supported also a lack of developmental effects of flutianil. Taking into consideration this new information, in March 2016 RAC (ECHA RAC, 2016) concluded that classification, for carcinogenicity and regarding developmental toxicity was not required.

The different outcome is caused by the fact that a different dataset was available to RAC than the one which was used by EFSA for its conclusion in 2014. The RAC opinion took into account the additional data not available in the dossier and RMS assessment that was the subject of the EFSA peer review. The difference is not considered a scientific divergence in the meaning of Article 30 of Regulation (EC) No 178/2002, and EFSA considered that there is no need to re-discuss the toxicological profile of the active substance at an EFSA peer-review meeting. Nevertheless, as a RAC opinion is now available, EFSA has updated the assessment of flutianil regarding those elements impacted by the harmonised classification. The EFSA conclusion has not been amended as it reflects the view of the experts based on the information in the dossier that was available at the time of the adoption of the EFSA conclusion.

Those needing to consult the proposed harmonised classification and labelling of flutianil are advised to consult the RAC opinion (ECHA RAC, 2016) until the Commission decides to place the substance on Annex VI of the CLP Regulation.

1.3. Terms of Reference

EFSA was requested by the European Commission to clarify the impact of the harmonised classification on the EFSA conclusion of flutianil (EFSA, 2014a,b). For this purpose, it was considered appropriate not to republish the entire conclusion but to discuss the impact on the sections that were affected by the harmonised classification in a statement.

This document is not a stand-alone document and should be read alongside other supporting documents including the EFSA conclusion (EFSA, 2014a), the peer review report (EFSA, 2014b), the DAR (United Kingdom, 2013, 2014) and the ECHA RAC opinion (ECHA, 2016).

2. Conclusions of the evaluation affected by the harmonised classification

Sections 2, 3, 4, 6, 7 and 9 of the previous EFSA conclusion (EFSA, 2014a) are clarified as follows:

Toxicological reference values were not derived for flutianil groundwater metabolites previously, as according to the guidance document on the assessment of the relevance of metabolites in groundwater (European Commission, 2003), the assessment was stopped at stage 3 of step 3 where the metabolites were deemed to be relevant. The change of the classification of the parent flutianil has led to the consideration that metabolites OC 53276 and OC 56635 are not toxicologically relevant groundwater metabolites up to stage 3 of step 3 of this guidance. Consequently, the assessment needed, now has to follow the last steps 4 and 5 of the guidance. Regarding metabolite OC 53276, it is unlikely to be genotoxic, but data were not available to address its toxicity in comparison with the parent flutianil and a data gap is identified to address its repeated-dose toxicological profile relevant to consumer exposure. The metabolite OC 56635 (free acid of OC 63421), it is also considered unlikely to be genotoxic based on the data available. With regard to a 28-day study performed with OC 63421, sodium salt of the metabolite OC 56635, an acceptable daily intake (ADI) of 1.38 rounded to 1.4 mg/kg body weight (bw) per day may be derived, based on the no observed adverse effect level (NOAEL) for reduced food efficiency and haematological effects (decreased erythrocytes, increased mean corpuscular volume, increased reticulocytes) observed at 4,700 mg/kg bw per day and applying an uncertainty factor of 1,000.

The consumer exposure with regard to residues of metabolites OC 56635 and OC 53276 in groundwater used as drinking water was assessed on the basis of the predicted maximum predicted environmental concentration (PEC) groundwater levels. The estimates are based on the default assumptions laid down in the WHO Guidelines (WHO, 2009) for drinking water quality for the consumer groups of adults (weighing 60 kg), toddlers (10 kg) and bottle-fed infants (5 kg) with a daily per capita consumption of 2 L, 1 L and 0.75 L, respectively. Based on metabolism data, both metabolites can occur as residues in primary crops. Residue levels in food commodities (grapes and vine leaves) were derived from the metabolism study. Food consumption data in the EFSA Pesticide Residues Intake Model (PRIMo) were used. Specifically for metabolite OC 56635, uptake of significant proportions from the soil also into succeeding crops cannot be excluded; however, data to address this concern were not available.
With regard to metabolite OC 53276, the total chronic exposure via food commodities and drinking water was calculated and compared to the acceptable overall threshold of 0.02 μg/kg bw per day (Step 4) (European Commission, 2003).

| Intakes via drinking water | Intakes via food (representative uses) | Total intakes |
|----------------------------|----------------------------------------|---------------|
| [μg/kg bw per day]         | [μg/kg bw per day]                     | [μg/kg bw per day] |
| Adult | Toddler | Infant | Adult | Toddler | Infant | Adult | Toddler | Infant |
| OC 53276 | 0.016 | 0.048 | 0.072 | 0.001 | 0.001 | < 0.001 | 0.017 | 0.049 | 0.072 |

bw: body weight.

Consumer exposure to OC 53276 is driven by the residue levels predicted for drinking water. For metabolite OC 53276, estimated intakes by adults are below 0.02 μg/kg bw per day but are above for toddlers and infants alone due to the consumption of drinking water. The consumer risk assessment (Step 5) (European Commission, 2003) cannot be finalised without toxicological reference values for OC 53276. This leads to the concern that the groundwater relevance assessment for OC 53276 cannot be finalised.

With regard to metabolite OC 56635, the total chronic exposure via food commodities and drinking water was calculated (Step 4) and compared to the ADI of 1.4 mg/kg bw per day for OC 56635 (Step 5). Due to a data gap, residues in succeeding crops could not be considered (mostly relevant to the use in ornamentals) and therefore the assessment is preliminary.

| Intakes via drinking water | Intakes via food (representative uses) | Consumer RA Total intakes |
|----------------------------|----------------------------------------|--------------------------|
| [μg/kg bw per day]         | [μg/kg bw per day]                     | % ADI                    |
| Adult | Toddler | Infant | Adult | Toddler | Infant | Adult | Toddler | Infant |
| OC 56635 | 0.455 | 1.36 | 2.05 | 0.014 | 0.008 | < 0.001 | 0.03 | 0.10 | 0.15 |

bw: body weight.

Consumer exposure to OC 56635 is driven by the residue levels predicted for drinking water. Total chronic intakes were preliminary estimated to be < 0.2% ADI for the consumer groups of adults, toddlers and infants. However, as the consumer risk assessment is only preliminary, the groundwater relevance assessment for OC 56635 remains open and not finalised.
### 2.1. Overview of the risk assessment of compounds listed in residue definitions triggering assessment of effects data for the environmental compartments (Table 1)

**Table 1: Ground water**

| Compound (name and/or code) | Mobility in soil | > 0.1 \(\mu g/L\) 1 m depth for the representative uses\(^{(a)}\) | Pesticidal activity | Toxicological relevance | Ecotoxicological activity |
|-----------------------------|------------------|-------------------------------------------------|---------------------|------------------------|-------------------------|
| Flutianil                   | Immobile         | No                                              | Yes                 | Yes                    | Yes                     |
|                             | \(K_{Foc}\) 20,631–79,448 mL/g |                                                  |                     |                        |                         |
| OC 53276                    | Medium to low mobility | Yes in 7/7 FOCUS groundwater scenarios 0.222–0.48 \(\mu g/L\) | No                  | Open: Information used up to stage 3 of step 3. Negative in bacterial and mammalian cell gene mutation (mouse lymphoma assay) tests *in vitro* and micronucleus assay *in vivo*. Unlikely to be genotoxic. Data gap to address repeated-dose toxicity relevant to consumer exposure. Step 4: Minor crop metabolite, potential exposure from other sources to be taken into account. Total chronic exposure is < 0.02 \(\mu g/kg\) bw for adults but exceeds 0.02 \(\mu g/kg\) bw for toddlers and infants. Step 5: not finalised. Consumer risk assessment not possible as toxicological reference values cannot be derived. Final conclusion on the groundwater relevance is open. | A low risk to aquatic organisms was indicated in the situation that groundwater becomes surface water |
| OC 56635                    | Very high mobility Adsorption was too low to measure | Yes in 7/7 FOCUS groundwater scenarios 2.53–13.64 \(\mu g/L\). 2/7 FOCUS groundwater scenarios > 10 \(\mu g/L\). At Sevilla 11.35 \(\mu g/L\). At Thiva 13.64 \(\mu g/L\) | No                  | Open: Information used up to stage 3 of step 3. Negative in bacterial and mammalian cell gene mutation (mouse lymphoma) tests *in vitro* and micronucleus assay *in vivo*. Unlikely to be genotoxic. Rat oral LD\(_{50}\) > 300 < 2,000 mg/kg bw. Sodium salt of OC 56635: Rat oral LD\(_{50}\) > 2,000 mg/kg bw. 28-day rat NOAEL 1,380 mg/kg bw per day based on food efficiency and haematological effects (of lower and different target toxicity than flutianil). An ADI may be derived at 1.38, rounded to 1.4 mg/kg bw per day based on the 28-day study, applying an uncertainty factor of 1,000. | A low risk to aquatic organisms was indicated in the situation that groundwater becomes surface water |
| Compound (name and/or code) | Mobiltiy in soil | > 0.1 µg/L 1 m depth for the representative uses\(^{(a)}\) | Pesticidal activity | Toxicological relevance | Ecotoxicological activity |
|-----------------------------|-----------------|-------------------------------------------------|---------------------|------------------------|-------------------------|
|                             |                 |                                                 |                     | Step 4: Potential exposure from other sources, i.e. crops should be taken into account. Sufficient residue data in crops is not available to address the use in ornamentals. With regard to the use in grapevine, total chronic intakes were estimated to be < 0.2% ADI. Final conclusion on the groundwater relevance is open. |

\(K_{Foc}\): Freundlich organic carbon adsorption coefficient; FOCUS: Forum for the Co-ordination of Pesticide Fate Models and their Use; bw: body weight; LD\(_{50}\): lethal dose, median; NOAEL: no observed adverse effect level; ADI: acceptable daily intake.

\(^{(a)}\): FOCUS scenarios or a relevant lysimeter.
2.2. Data gaps

The list of data gaps identified during the peer review process (EFSA, 2014a) remains unchanged and includes the gap regarding the assessment of the uptake of OC 56635 from soil by following crops noted in Section 2 of the statement. In addition, the following data gap has been identified following the assessment in this statement.

- Repeated-dose toxicity of metabolite OC 53276 relevant to consumer exposure (relevant for all representative uses evaluated; submission data proposed by the applicant: unknown, see section 2 of the statement).

2.3. Concerns

2.3.1. Issues that could not be finalised

An issue is listed as an issue that could not be finalised where there is not enough information available to perform an assessment, even at the lowest tier level, for the representative uses in line with the Uniform Principles in accordance with Article 29(6) of the Regulation and as set out in Commission Regulation (EU) No 546/2011\(^5\) and where the issue is of such importance that it could, when finalised, become a concern (which would also be listed as a critical area of concern if it is of relevance to all representative uses).

An issue is also listed as an issue that could not be finalised where the available information is considered insufficient to conclude on whether the active substance can be expected to meet the approval criteria provided for in Article 4 of the Regulation.

All issues not finalised including those from the previous conclusion (EFSA, 2014a) have been listed here.

1) The consumer risk assessment is not finalised with regard to residues of the highly persistent soil metabolite OC 56635. Preliminary data suggest a preferential uptake of significant proportions of OC 56635 from the soil into the crops (relevant for residues).

2) The consumer risk assessment is not finalised with regard to residues of metabolite OC 56635 for use on grapevines and OC 53276 for use on grapevines and ornamentals, in situations where groundwater is used as drinking water. Therefore, the relevance assessment of these metabolites for groundwater in accordance with European Commission (2003) guidance was not finalised (relevant for environmental fate and behaviour).

3) The consumer risk assessment is not finalised with regard to the unknown nature of residues that might be present in drinking water, consequent to water treatment following abstraction of surface and groundwater water that might contain metabolites OC 56635, APSA and OC 53276 (relevant for environmental fate and behaviour).

4) Flutianil produced adverse effects on endocrine organs across different species and timelines and an endocrine-mediated mode of action could not be ruled out. This issue could not be finalised since mechanistic information is not available (relevant for toxicology and ecotoxicology).

2.3.2. Critical areas of concern

An issue is listed as a critical area of concern where there is enough information available to perform an assessment for the representative uses in line with the Uniform Principles in accordance with Article 29 (6) of the Regulation and as set out in Commission Regulation (EU) No 546/2011, and where this assessment does not permit to conclude that for at least one of the representative uses it may be expected that a plant protection product containing the active substance will not have any harmful effect on human or animal health or on groundwater or any unacceptable influence on the environment.

An issue is also listed as a critical area of concern where the assessment at a higher tier level could not be finalised due to a lack of information, and where the assessment performed at the lower tier level does not permit to conclude that for at least one of the representative uses it may be expected that a plant protection product containing the active substance will not have any harmful effect on human or animal health or on groundwater or any unacceptable influence on the environment.

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\(^5\) Commission Regulation (EU) No 546/2011 of 10 June 2011 implementing Regulation (EC) No 1107/2009 of the European Parliament and of the Council as regards uniform principles for evaluation and authorisation of plant protection products. OJ L 155, 11.6.2011, p. 127–175.
An issue is also listed as a critical area of concern where in the light of current scientific and technical knowledge using guidance documents available at the time of application the active substance is not expected to meet the approval criteria provided for in Article 4 of the Regulation.

The critical areas of concern have been clarified as follows:

- None.

**2.3.3. Overview of the concerns identified for each representative use considered**

(If a particular condition proposed to be taken into account to manage an identified risk, as listed in section 8, has been evaluated as being effective, then 'risk identified' is not indicated in this table.)

| Representative use                                      | Grapevine | Ornamental crops in glasshouses |
|---------------------------------------------------------|-----------|---------------------------------|
| Operator risk                                           | Risk identified | Assessment not finalised        |
| Worker risk                                             | Risk identified | Assessment not finalised        |
| Bystander risk                                          | Risk identified | Assessment not finalised        |
| Consumer risk                                           | Risk identified | Assessment not finalised        |
| Risk to wild non target terrestrial vertebrates         | Risk identified | Assessment not finalised        |
| Risk to wild non target terrestrial organisms other than vertebrates | Risk identified | Assessment not finalised        |
| Risk to aquatic organisms                               | Risk identified | Assessment not finalised        |
| Groundwater exposure active substance                   | Legal parametric value breached | Assessment not finalised        |
| Groundwater exposure metabolites                        | Legal parametric value breached | Assessment not finalised        |
|                                                          | Parametric value of 10 $\mu$g/L$^{(a)}$ breached | 2/7 FOCUS scenarios |
|                                                          | Assessment not finalised | 2/7 FOCUS scenarios |
|                                                          | $X^2$ | $X^2$ |

Columns are grey if no safe use can be identified. The superscript numbers in this table relate to the numbered points indicated in Section 2.3.1.

(a): Value for non-relevant metabolites prescribed in SANCO/221/2000-rev 10-final, European Commission, 2003.

**References**

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Abbreviations

ADI acceptable daily intake
bw body weight
DAR draft assessment report
ECHA European Chemicals Agency
EEC European Economic Community
FOCUS Forum for the Co-ordination of Pesticide Fate Models and their Use
$K_{\text{Foc}}$ Freundlich organic carbon adsorption coefficient
LD$_{50}$ lethal dose, median; dosis letalis media
NOAEL no observed adverse effect level
PEC predicted environmental concentration
RAC Committee for Risk Assessment
SMILES simplified molecular-input line-entry system
WHO World Health Organization
### Appendix A – Used compound codes

| Code/trivial name<sup>(a)</sup> | IUPAC name/SMILES notation/InChiKey<sup>(b)</sup> | Structural formula<sup>(c)</sup> |
|---------------------------------|-------------------------------------------------|-------------------------------|
| OC 56635                        | 2-fluoro-5-(trifluoromethyl)benzenesulfonic acid | ![Structural formula](image1) |
|                                 | Fc1ccc(cclS(O)(=-O)=O)C(F)(F)F                  | ![Structural formula](image2) |
|                                 | JESPXRDHXJOQOK-UHFFFAOYSA-N                    | ![Structural formula](image3) |
| OC 63421                        | sodium 2-fluoro-5-(trifluoromethyl)benzenesulfonate | ![Structural formula](image4) |
|                                 | [Na+].Fc1ccc(cc1S(O)(=-O)=O)C(F)(F)F           | ![Structural formula](image5) |
|                                 | OKBZMTXTMPTXIT-UHFFFAOYSA-M                    | ![Structural formula](image6) |
| OC 53276                        | (2Z)-[2-fluoro-5-(trifluoromethyl)phenyl]sulfanyl| ![Structural formula](image7) |
|                                 | [3-(2-methoxyphenyl)-1,3-thiazolidin-2-ylidene]ethanenitrile | ![Structural formula](image8) |
|                                 | FC(F)(F)c1cc(c(F)cc1)S(-)O=C(C#N)-C3/SCCN3c2ccc2OC | ![Structural formula](image9) |
|                                 | BGBAPIYCURMGNW-ZCXUNETKSA-N                    | ![Structural formula](image10) |
| APSA                            | (2E)-[3-(2-methoxyphenyl)-1,3-thiazolidin-2-ylidene]acetonitrile | ![Structural formula](image11) |
|                                 | COc1ccc1N2CCS\C2–C\C#N                       | ![Structural formula](image12) |
|                                 | KEAFTPHSTHVGCX-WUXMJOGZSA-N                    | ![Structural formula](image13) |

IUPAC: International Union of Pure and Applied Chemistry; SMILES: simplified molecular-input line-entry system.

<sup>(a)</sup> The metabolite name in bold is the name used in the conclusion.

<sup>(b)</sup> ACD/Name 2015 ACD/Labs 2015 Release (File version N20E41, Build 75170, 19 December 2014).

<sup>(c)</sup> ACD/ChemSketch 2015 ACD/Labs 2015 Release (File version C10H41, Build 75059, 17 December 2014).