

# **Renewal Assessment Report**

**under Regulation (EC) 1107/2009**



**Zoxamide**

**Volume 3**

**Active substance**

## **B.2 Physical and chemical properties of the active substance**

Rapporteur Member State: Latvia  
Co-Rapporteur Member State: France

**Version history**

<b>Date</b>	<b>Subject</b>
<b>2001</b>	Initial DAR Draft Assessment Report (DAR) – prepared in the context of the application for the first inclusion of the a.s. in Annex I to Council Directive 91/414/EEC. + 1st addendum Jun 2002 + 2nd addendum July 2002
<b>2016</b>	<b>Initial RAR</b>

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**B.2. PHYSICAL AND CHEMICAL PROPERTIES OF THE ACTIVE SUBSTANCE****Table B.2.1:** Physical and chemical properties of zoxamide

Section (Annex point)	Guideline and method	Test material purity and specification	Findings	RMS evaluation and conclusion	GLP Y/N	Reference
<b>B.2.1.1. Melting point (IIA 2.1)</b>	EEC method A1	98.8%	159.5-160.5°C	The study is acceptable.	Y	Arden 1998 (81756)
	EEC method A1	97.7%	159.5-161°C	The study is acceptable.	Y	Betteley 1998a (81757)
<b>B.2.1.2. Boiling point (IIA 2.1)</b>			Not determined, as decomposition begins at the melting point.	Active substance is solid and its melting point indicated in p. B 2.1.1.		
<b>B.2.1.3. Temperature of decomposition or sublimation (IIA 2.1)</b>	EEC method A1	97.7%	Irreversible chemical change (decomposition) occurs at the melting point.	The study is acceptable.	Y	Betteley 1998a (81757)
<b>B.2.2.1. Vapour pressure (IIA 2.3)</b>	EEC method A4	98.8%	$<1.3 \times 10^{-5}$ Pa at 25, 35 and 45°C	The study is acceptable.	Y	Kogovsek 1996 (81759)
<b>B.2.2.2. Volatility (IIA 2.3)</b>	Henry's law constant (Calculation)	98.8%	$<6.5906 \times 10^{-3}$ Pa m <sup>3</sup> mol <sup>-1</sup>	The study is acceptable.	N	Betteley 1998b (81760)
<b>B.2.3.1. Appearance: Physical state (IIA 2.4)</b>	Visual observation	98.8%	Lumpy white powder	The study is acceptable.	Y	Arden 1998 (81756)
	Visual observation	97.7%	Fine white powder	The study is acceptable.	Y	Betteley 1998c (81761)
<b>B.2.3.2. Appearance: Colour (IIA 2.4)</b>	Visual observation	98.8%	Munsell neutral scale N9.5 90%R	The study is acceptable.	Y	Arden 1998 (81756)
	Visual	97.7%	Munsell neutral scale N9.5 90%R	The study is	Y	Betteley 1998c

Section (Annex point)	Guideline and method	Test material purity and specification	Findings	RMS evaluation and conclusion	GLP Y/N	Reference
	observation			acceptable.		(81761)
B.2.4.1. Spectra (UV/VIS, IR, NMR, MS), molar extinction at relevant wavelengths, optical purity (IIA 2.5)	UV	98.8%	UV/VS Measured in methanol gave absorption maximum at 212 nm, ε = 46330 L/mol/cm. The molar absorption coefficient at wavelengths greater than 290 nm is ≤ 333 L/mol/cm. The spectra are consistent with the structure of zoxamide.	Acceptable	Y	Hafer, 1996 (81763)
	IR	98.8%	IR (KBr disc, FT measured between 4000 and 500 cm <sup>-1</sup> . The spectrum is consistent with the structure of zoxamide.	Acceptable	Y	Betteley, 1998d (81762)
	NMR	98.8%	<sup>1</sup> H NMR 250 MHz The spectrum is consistent with the structure of zoxamide.	Acceptable	Y	Betteley, 1998d (81762)
	MS	98.8%	MS CI 70 ev m/z – 336 (M+H) <sup>+</sup> The spectrum is consistent with the structure of zoxamide.	Acceptable	Y	Quinn, 1993 (81766)
B.2.4.2. Spectra (UV/VIS, IR, NMR, MS), molar extinction at relevant wavelengths, optical purity for the impurity RH-131,889	UV	98.0%	Conditions      λ max (nm)      ε (L/mol/cm) Neutral,            275                    35 Acidic,             275                    35 Basic,              290                    69 The spectra are consistent with the structure of RH-131,889.	RH-131,889 was analyzed because it is of toxicological significance as a skin sensitizer. Acceptable	Y	Betteley, 1998e (81770)
	IR	98.0%	Assignment                    cm <sup>-1</sup> N-H                            3156 &1589 CH <sub>2</sub> &CH <sub>3</sub> 2880, 1460, 1392 & 745 C=O                            1730 C-Cl                            784 The spectrum is consistent with the structure of RH-131,889.	Acceptable	Y	Betteley, 1998e (81770)

Section (Annex point)	Guideline and method	Test material purity and specification	Findings	RMS evaluation and conclusion	GLP Y/N	Reference														
	NMR	98.0%	The spectrum is consistent with the structure of RH-131,889.	Acceptable	Y	Betteley, 1998e (81770)														
	MS	98.0%	m/z = 150 (M+H)+ The spectrum is consistent with the structure of RH-131,889.	Acceptable	Y	Quinn, 1996 (81773)														
B.2.5. Solubility in water (IIA 2.6)	EEC method A6	98.7% Radiopurity SA = 90.2 mCi/g	0.681 ± 0.017 mg/l at 20 °C. Solubility in reagent grade water. Applicant states that RH-7281 does not protonate or ionise at pH values between 3 and 11 and therefore solubility will not be effected by pH.	Effect of pH not investigated, as zoxamide does not dissociate.	Y	Reynolds 1996a (81776)														
B.2.6. Solubility in organic solvents (IIA 2.7)	Method based on EEC A6	97.7%	Determined at 20°C: <table><tr><td>Solvent</td><td>Solubility (g/l)</td></tr><tr><td>Ethyl acetate</td><td>20.0</td></tr><tr><td>Acetone</td><td>55.7</td></tr><tr><td>Xylen</td><td>1.56</td></tr><tr><td>n-Octanol</td><td>6.49</td></tr><tr><td>n-Heptane</td><td>0.038</td></tr><tr><td>1,2-Dichloroethane</td><td>12.5</td></tr></table>	Solvent	Solubility (g/l)	Ethyl acetate	20.0	Acetone	55.7	Xylen	1.56	n-Octanol	6.49	n-Heptane	0.038	1,2-Dichloroethane	12.5	Acceptable	Y	Betteley, 1998f (81778)
Solvent	Solubility (g/l)																			
Ethyl acetate	20.0																			
Acetone	55.7																			
Xylen	1.56																			
n-Octanol	6.49																			
n-Heptane	0.038																			
1,2-Dichloroethane	12.5																			
B.2.7.1. Partition co-efficient n-octanol/water (IIA 2.8)	EEC method A8	98.7% Radiopurity SA = 90.2 mCi/g	Log Pow = 3.76 ± 0.04 RH-117281 contains no acid or base functionality – Kow is not dependent on pH.	The obtained data indicates that RH-117281 has the potential for bioaccumulation.	Y	Reynolds 1996b (81780)														
B.2.7.2. Partition co-efficient n-octanol/water of components of residue definition for risk	OECD no 117 HPLC)	RH 163353	Log Pow (pH 2.5) = 1.43		Y	Volkel, 1998														
	EEC method A8 (HPLC)	RH-127450	Log Pow = 3.5	Acceptable	Y	Tognucci, 1988														
	EEC method A8 (HPLC	RH-139432	Log Pow = 2.7	Acceptable	Y	Tognucci, 1988b														

Section (Annex point)	Guideline and method	Test material purity and specification	Findings	RMS evaluation and conclusion	GLP Y/N	Reference
assessment	EEC method A8 (HPLC)	RH-141452	Log Pow = 1.44	Acceptable	Y	O'Connor, 2014a
	EEC method A8 (HPLC)	RH-150721	Log Pow = 4.07	Acceptable	Y	O'Connor, 2014b
	EEC method A8 (HPLC)	RH-24549	Log Pow = 3.83	Acceptable	Y	O'Connor, 2014c
	Prediction (EPIWIN v.1.68)	RH-141455	Log Pow = 1.94 (prediction) The Log Pow for RH-141455 could not be determined experimentally in its non-ionised form due to an acidic pKa at approximately 2.0. However, RH-141455 is structurally similar to metabolite RH-141452 for which an experimental Log Pow value of 1.44 has been generated. The structural similarities and the roughly comparable Log Pow values suggest that the predicted value of 1.94 can be considered reliable.	Acceptable	N	Liney & Miles, 2014
<b>B.2.8. Dissociation in water</b> (IIA 2.9)	OECD Test Guideline 112	98.8	Not measurable by spectrophotometry (absorbance profile did not change in neutral, basic or acidic conditions), titration (solubility too low) or conductivity (No increase in reading observed with decrease in concentration).	Acceptable	Y	Betteley, 1998g (81790)
<b>B.2.9.1. Flammability</b> (IIA 2.11)	EEC method A 10	97.7%	Not highly flammable.	Acceptable	Y	Betteley, 1998i (81794)
<b>B.2.9.2. Auto-flammability (technical active substance)</b> (IIA 2.11)	EEC method A 16	97.7%	No relative self-ignition below 450 °C.	Acceptable	Y	Betteley, 1998j (81795)

Section (Annex point)	Guideline and method	Test material purity and specification	Findings	RMS evaluation and conclusion	GLP Y/N	Reference
<b>B.2.10. Flash point (technical active substance) (IIA 2.12)</b>			Not determined as melting point is above 40°C.	Acceptable		
<b>B.2.11. Explosive properties (IIA 2.13)</b>	EEC method A 14	97.7%	Not explosive.	Acceptable	Y	Betteley, 1998k (81796)
<b>B.2.12. Surface tension (IIA 2.14)</b>			Not determined, as solubility in water is < 1 mg/L.	Acceptable		
<b>B.2.13. Oxidising properties (IIA 2.15)</b>	EEC method A 17	97.7%	Not oxidising.	Acceptable	Y	Betteley, 1998k (81797)
<b>B.2.14. Other studies</b>			None			

#### Conclusion RMS:

Zoxamide is a white powder with a melting point of 159.5 – 160.5°C. It is neither flammable nor auto-flammable and is not classified as explosive or oxidising. It has a very low vapour pressure of  $< 1.3 \times 10^{-5}$  Pa at 25°C and a low solubility in water (0.681 mg/L at 20°C), but is more readily soluble in organic solvents (0.038 – >55.7 g/L). Zoxamide does not dissociate and the log Pow (octanol/ water partition coefficient) is 3.76, indicating a potential for bioaccumulation.



**B.2.15. References relied on****Physical and chemical properties of the active substance (Annex IIA 2)****Original dossier**

**Studies relied on for the first inclusion of zoxamide in Annex I to Directive 91/414/EEC and for renewal of approval under Regulation (EC) 1107/2009.**

Data point	Annex point (Old)	Author(s)	Year	Title, Source (where different from company), Company, Report No, GLP or GEP status (where relevant), Published or not	Vertebrate study Y/N	Data Protection Claimed Y/N	Justification if data protection claimed	Owner
CA, 2.1.1/01	IIA, 2.1/01	Ardern, D.	1998	RH-117281 Physicochemical Properties Huntingdon Life Sciences, Report No. RAS 056/982496, March 19, 1998, ER ref. no. 19.15 GLP, unpublished	N	N	NA	Gowan
CA, 2.1.1/02	IIA, 2.1/02	Betteley, J	1998a	RH-117,281 Melting Temperature Huntingdon Life Sciences, Report No.: RAS 092/98331, ER ref. no. 19.14 GLP, Unpublished	N	N	NA	Gowan
CA, 2.2.1/01	IIA, 2.3.1	Kogovsek, LM	1996	RH-117,281 Vapor Pressure, Ricerca, Inc., Rohm and Haas Technical Report No. 34-96-58, September 23, 1996, ER ref. no. 6.6 GLP, unpublished.	N	N	NA	Gowan
CA, 2.2.2/01	IIA, 2.3.2/01	Betteley, J.	1998b	RH-117,281 Henry's Law Constant, Huntingdon Life Sciences Report No. RAS 082/983272, June 26, 1998, ER ref. no. 19.16 GLP, unpublished	N	N	NA	Gowan
CA, 2.3.1/01	IIA, 2.4.1/01	Ardern, D.	1998	RH-117281 Physicochemical Properties Huntingdon Life Sciences, Report No. RAS 056/982496, March 19, 1998, ER ref. no. 19.15 GLP, unpublished	N	N	NA	Gowan

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CA, 2.3.1/02	IIA, 2.4.1/02	Betteley, J.	1998c	RH-117,281 Appearance Huntingdon Life Sciences, Report No.: RAS 085/983389, ER ref. no. 19.13 GLP, Unpublished	N	N	NA	Gowan
CA, 2.3.2/01	IIA, 2.4.2/01	Ardern, D.	1998	RH-117281 Physicochemical Properties Huntingdon Life Sciences, Report No. RAS 056/982496, March 19, 1998. ER ref. no. 19.15 GLP, unpublished	N	N	NA	Gowan
CA, 2.3.2/02	IIA, 2.4.2/02	Betteley, J.	1998c	RH-117,281 Appearance Huntingdon Life Sciences, Report No.: RAS 085/983389. ER ref. no. 19.13 GLP, Unpublished	N	N	NA	Gowan
CA, 2.4.1/01	IIA, 2.5.1/01	Betteley, J.	1998d	RH-117,281 Spectral Data (IR and NMR) Huntingdon Life Sciences, Report No.: RAS 100/983371. ER ref. no. 30.12 GLP, Unpublished	N	N	NA	Gowan
CA, 2.4.1/02	IIA, 2.5.1/02	Hafer, JH.	1996	UV-Visible Spectrum of RH-117281, Rohm and Haas Technical Report No. 13-96-013TR, February 26, 1996, ER ref. no. 30.15 GLP, unpublished	N	N	NA	Gowan
CA, 2.4.1/03	IIA, 2.5.1/03	Quinn, CJ	1993	Qualitative Analysis of RH-117281 Standard by Mass Spectrometry, Rohm and Haas Technical Report No. 13-93-130, November 3, 1993, ER ref. no. 30.11 GLP, unpublished	N	N	NA	Gowan
CA, 2.4.2/01	IIA, 2.5.2/01	Betteley, J.	1998e	RH-131,889 Spectral Data Huntingdon Life Sciences, Report No.: RAS 105/983943, ER ref. no. 19.6 GLP, Unpublished	N	N	NA	Gowan

Data point	Annex point (Old)	Author(s)	Year	Title, Source (where different from company), Company, Report No, GLP or GEP status (where relevant), Published or not	Vertebrate study Y/N	Data Protection Claimed Y/N	Justification if data protection claimed	Owner
CA, 2.4.2/02	IIA, 2.5.2/02	Quinn, CJ	1996	Qualitative Analysis of RH-016,971 and RH-131,889 by Desorption Chemical Ionization (DCI) Mass Spectrometry, Rohm and Haas Technical Report No. 13-96-085TR, August 20, 1996, ER ref. no. 30.13 GLP, unpublished	N	N	NA	Gowan
CA, 2.5/01	IIA, 2.6	Reynolds, JL	1996a	Water solubility of 14C-RH-117281, XenoBiotic Laboratories, Inc., Rohm and Haas Technical Report No. 34-95-163, March 22, 1996. ER ref. no. 1.8 GLP, unpublished.	N	N	NA	Gowan
CA, 2.6/01	IIA, 2.7/01	Betteley, J.	1998f	RH-117,281 Solubility in a Range of Organic Solvents Huntingdon Life Sciences, Report No.: RAS 084/983622. ER ref. no. 19.12 GLP, Unpublished	N	N	NA	Gowan
CA, 2.7.1/01	IIA, 2.8	Reynolds, JL	1996b	n-Octanol/water partition coefficient of [14C]RH-117281, XenoBiotic Laboratories, Inc., Rohm and Haas Technical Report No. 34-95-162, February 14, 1996, ER ref. no. 1.7 GLP, unpublished.	N	N	NA	Gowan
CA, 2.7.2/01	IIA, 7.1.2.2/03	Volkel, W.	1998c	Determination of the Adsorption Coefficient of 14C-RH-163353 on Soil and its Octanol/Water Partition Coefficient Using High Performance Liquid Chromatography (HPLC), RCC Ltd., Rohm and Haas Technical Report No. 34-98-55, November 9, 1998, GLP, unpublished. ER ref. no. 31.4	N	N	NA	Gowan
CA, 2.7.2/02	IIA, 8.2.3/03	Tognucci, A	1998a	Determination of the partition coefficient (n-octanol/water) of RH-127450, RCC Ltd, Rohm and Haas Technical Report No. 34-98-165, ER Ref. No. 18.3, October 12, 1998, GLP, unpublished.	Y	N	NA	Gowan

Data point	Annex point (Old)	Author(s)	Year	Title, Source (where different from company), Company, Report No, GLP or GEP status (where relevant), Published or not	Vertebrate study Y/N	Data Protection Claimed Y/N	Justification if data protection claimed	Owner
CA, 2.7.2/03	IIA, 8.2.3/04	Tognucci, A	1998b	Determination of the partition coefficient (n-octanol/water) of RH-139432, RCC Ltd, Rohm and Haas Technical Report No. 34-98-53, ER Ref. No. 31.3, October 22, 1998, GLP, unpublished.	Y	N	NA	Gowan
CA, 2.8/01	IIA, 2.9.4	Betteley, J.	1998g	RH-117,281 Determination of Dissociation Constant, Huntingdon Life Sciences, Report No.: RAS 090/983783, August 13, 1998, ER ref. no. 19.11 GLP, unpublished	N	N	NA	Gowan
CA, 2.9.1/01	IIA, 2.11.1/01	Betteley, J.	1998i	RH-117281 Flammability (Solids) Huntingdon Life Sciences Report No.: RAS 086/983225, ER ref. no. 19.9 GLP, Unpublished	N	N	NA	Gowan
CA, 2.9.2/01	IIA, 2.11.2/01	Betteley, J.	1998j	RH-117,281 Relative Self Ignition Temperature for Solids Huntingdon Life Sciences, Report No.: RAS 088/983290, ER ref. no. 19.8 GLP, Unpublished	N	N	NA	Gowan
CA, 2.11/01	IIA, 2.13/01	Betteley, J.	1998k	RH-117,281 Explosive Properties Huntingdon Life Sciences, Report No.: RAS 087/983530, ER ref. no. 19.7 GLP, Unpublished	N	N	NA	Gowan
IIA, 2.13/01	IIA, 2.15/01	Betteley, J.	1998l	RH-117,281 Oxidising Properties Huntingdon Life Sciences, Report No.: RAS 089/983438, ER ref. no. 19.5 GLP, Unpublished	N	N	NA	Gowan

## New studies

Data point	Author(s)	Year	Title Source (where different from company) Company, Report No GLP or GEP status (where relevant), Published or not	Vertebrate study Y/N	Data protection claimed (Y/N)	Justification if data protection claimed	Owner
KCA, 2.7.2 /04	O'Connor, B.J.	2014	Zoxamide metabolite, RH-24549: Determination of partition coefficient Harlan Laboratories Ltd Shardlow Business Park Derbyshire, DE72 2GD, UK Study No. 41400466 GLP, not published	N	Y	New data requirement.	Gowan
KCA, 2.7.2 /05	O'Connor, B.J.	2014	Zoxamide metabolite, RH-141452: Determination of partition coefficient Harlan Laboratories Ltd Shardlow Business Park Derbyshire, DE72 2GD, UK Study No. 41400467 GLP, not published	N	Y	New data requirement.	Gowan
KCA, 2.7.2 /06	O'Connor, B.J.	2014	Zoxamide metabolite, RH-150721: Determination of partition coefficient Harlan Laboratories Ltd Shardlow Business Park Derbyshire, DE72 2GD, UK Study No. 41400468 GLP, not published	N	Y	New data requirement.	Gowan

<b>Data point</b>	<b>Author(s)</b>	<b>Year</b>	<b>Title Source (where different from company) Company, Report No GLP or GEP status (where relevant), Published or not</b>	<b>Vertebrate study Y/N</b>	<b>Data protection claimed (Y/N)</b>	<b>Justification if data protection claimed</b>	<b>Owner</b>
KCA, 2.7.2 /07	Liney, P. and Miles, D	2014	Metabolite of Zoxamide (RH-141455) Octanol-Water Partition Coefficient Exponent International Ltd. Hornbeam Business Park Harrogate, Yorkshire, HG2 8RE, UK Project Number: 0907598.UK0 Report Number: 0907598 – 5495 Not GLP, not published	N	Y	New data requirement.	Gowan