

FINAL REGISTRATION REPORT

Part B

Section 10

Assessment of the relevance of metabolites in groundwater

Detailed summary of the risk assessment

Product code: TERBUT 500 SC

Product name(s): La Zina 500 SC; Tekno 500 SC

Chemical active substance(s):

Terbuthylazine, 500 g/L

Central Zone

Zonal Rapporteur Member State: Poland

CORE ASSESSMENT

(authorization)

Applicant: PUH Chemirol Sp. z o.o.

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When	What
December 2021	ZRMs evaluated dRR.
June 2022	Final Version after Commenting period

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10 Relevance of metabolites in groundwater

Comments of ZRMs:	<ul style="list-style-type: none"> - The results of consumer risk calculations indicate that the use of TERBUT 500 SC (La Zina 500 SC; Tekno 500 SC) can cause unacceptable risk for toddlers' and infants' health imposed by the exposure to the metabolite MT13 (assuming normal allocation of total daily intake for chemicals acc. to WHO recommendation). The exposure of infants and toddlers to metabolite MT13 contained in the food and drinking water will exceed the value of ADI in the presented scenario. - The critical area of concern includes the results of total exposure estimation to groundwater metabolites of terbuthylazine (MT1, MT13, MT14, LM5) which account to 46.68 % and 69.91 % for toddler and infants, respectively.
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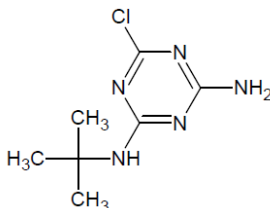
10.1 General information

Comments of ZRMs:	<p>According to EFSA Journal 2019;17(9):5817, <i>Updated peer review of the pesticide risk assessment for the active substance terbuthylazine in light of confirmatory submitted:</i></p> <ul style="list-style-type: none"> - for the metabolites LM5 and MT1, MT13, MT14 the reference values for terbuthylazine are applicable in consumer risk assessment, - in the case of metabolites LM3 and LM6 the toxicological data were insufficient to determine reference values, what does not allow to finalise the consumer risk assessment.
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The metabolites MT1, MT13, MT14, LM3, LM5, LM6 are predicted to occur in groundwater at concentrations above 0.1 µg/L (see PART B Section 8 of TERBUT 500 SCdRR). Assessment of the relevance of these metabolites according to the stepwise procedure of the EC guidance document SANCO/221/2000 – rev.10 is therefore required.

General information on the metabolites 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 KCP 9.2.4 of the dRR Part B, Section 8 (Environmental fate and behaviour).

Table 10.1-1: General information on the metabolite(s)

Name of active substance	Metabolite name and code	Structural/molecular formula	Trigger for relevance assessment	
Terbuthylazine	MT1 desethyl- terbuthylazine (GS 26379)		Max PEC _{gw} Based on:	0.253191 µg/L Focus PEARL 4.4.4 Okehampton

Name of active substance	Metabolite name and code	Structural/molecular formula	Trigger for relevance assessment	
	MT13 Hydroxy-terbuthylazine Or 2-hydroxy terbuthyl-lazine GS 23158		Max PEC _{gw} Based on:	14.62 µg/L Focus PEARL 4.4.4 Thivia
	MT14 desethyl-hydroxyterbuthylazine or desethyl-2-hydroxy terbuthylazine GS 28620		Max PEC _{gw} Based on:	2.098676 µg/L Focus PEARL 4.4.4 Hamburg
	LM1 MT24		Based on, lysimeter studies:	0.15µg/l
	LM 3 SM9 CSCD692760 SYN546009		Based on lysimeter:	3.569994 µg/L Focus PEARL 4.4.4., Thivia
	LM5 MT23 SM12 GS 16984		Max PEC _{gw} Based on:	1.691832 µg/L Focus PEARL 4.4.4., Hamburg
	LM6 SM6 CSCD648241 SYN545666		Max PEC _{gw} Based on:	2.937372 µg/L Focus 4.4.4., Thivia

10.2 Relevance assessment of MT1

Comments of ZRMs:	<ul style="list-style-type: none"> - According to the available data, the metabolite MT1 is considered relevant because of its pesticidal activity but it has no genotoxic potential. - The maximum PEC_{gw} of MT1 (acc. to the application rate presented in the GAP table) amounts to 0.253191 µg/L. The predicted max. PEC_{gw} value is below the upper limit for metabolites (<0.75 µg/L).
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<p>- Although the consumer risk calculation for this metabolite is not required, the results of risk calculations are presented below. This calculation was used in the total risk assessment concerning the exposure to terbuthylazine metabolites.</p>		
	Exposure (µg/kg b.w./d) (using default body weight values) ¹	% ADI (reference value of the parent substance: 0.004 mg/kg b.w./d)
Adults (70 ¹ /60 ² kg b.w.)	0.0072/0.0084	0.18/0.21
Toddlers (12 ¹ /10 ² kg b.w.)	0.0211/0.025	0.53/0.63
Infants (5 kg b.w.)	0.038	0.95

Conclusions:

Taking into account the results of available toxicological studies, the metabolite MT1 has no genotoxic potential. The results of consumer risk calculations indicate that the use of TERBUT 500 SC (La Zina 500 SC; Tekno 500 SC) according to the list of intended uses presented in GAP Table, causes no unacceptable risk for health resulting from exposure to metabolite MT1.

¹According to EFSA Journal 2012;10(3):2579, Guidance on selected default values to be used by the EFSA Scientific Committee, Scientific Panels and Units in the absence of actual measured data.

²WHO Guidelines for drinking-water quality: fourth edition incorporating the first addendum, 2017

Summary:

The relevance of the groundwater metabolite MT1 has already been assessed and the assessment agreed at EU level, and the relevance assessment is applicable as well for the GAP and groundwater scenarios considered in this dRR (i.e., the conclusions reached at Step 4 and 5 of the relevance assessment made at the EU-level are valid also with regard to the PEC_{gw} calculated for the GAP and groundwater scenarios considered in this dRR). MT1 is not considered relevant according to the criteria laid down in the EC guidance document SANCO/221/2000 –rev.10.

A summary of the relevance assessment is given in Table 10.2-1 and the corresponding studies are listed in the corresponding sections.

Table 10.2-1: Summary of the relevance assessment for MT1 according to the Addendum confirmatory data 2015.

	Assessment step		Result of assessment	
Hazard assessment of groundwater	STEP 1		Metabolite of no concern?	Yes
	STEP 2		Max PEC _{gw}	0.253191 µg/L
			Based on	FOCUS PEARL; Okehampton
Hazard assessment	STEP 3	Stage 1	Biological activity comparable to the parent?	Yes

		Stage 2	Genotoxic properties of metabolite	Non-genotoxic
		Stage 3	Toxic properties of metabolite;	Not toxic or very toxic (T or T+)
			Classification of parent	not currently classified as toxic or very toxic
			Classification of metabolite	not currently classified as toxic or very toxic
Consumer health risk assessment	STEP 4		Estimated consumer exposure via drinking water and other sources; threshold of concern approach	Acceptable <0.75 µg/L
	STEP 5		Refined risk assessment	Not required
			Predicted exposure (% of ADI)	Not required
				ADI based on

* N/A: not applicable

10.2.1 STEP 1: Exclusion of degradation products of no concern

Could not be excluded

10.2.2 STEP 2: Quantification of potential groundwater contamination

Max PEC _{gw}	0.253191 µg/L
Based on:	Focus PEARL 4.4.4 Okehmapton

In the field leaching study in Northern Italy annual average concentrations ranged from <0.01 up to 0.73µg/l in fields receiving basin irrigation. The maximum annual average concentration in fields receiving more conventional irrigation was 0.22µg/l. The conditions during the field leaching study in Northern Italy are likely to represent highly vulnerable conditions in terms of groundwater contamination in the EU due to the combination of soils, climate and extensive use of terbuthylazine on maize in the areas investigated. In addition this metabolite was not detected in an extensive and targeted German groundwater monitoring program. In further groundwater monitoring studies in Italy, Spain and Portugal the 90th percentile concentration was always <0.1µg/l. On the basis of the additional information from field leaching and groundwater monitoring programs it is clear that the first tier FOCUS groundwater exposure assessment represents a conservative assessment and such high concentrations are unlikely to be encountered under realistic use conditions.

10.2.3 STEP 3: Hazard assessment – identification of relevant metabolites

10.2.3.1 STEP 3, Stage 1: screening for biological activity

Data on MT1 (desethyl-terbuthylazine) which showed some signs of herbicidal activity. In addition, screening data (Corbin J, 2009) was provided as part of the resubmission and is presented in this Additional Report (see Section B.9.9.2. See also Attachment 1 DAR 2010). The conclusion was that the metabolite MT1 is herbicidally active. The biological activity of the metabolite is

broadly similar to that of terbuthylazine when applied at a dose at which the parent demonstrates good herbicidal activity on key species (common amaranth, fat hen, common chickweed, and wild oats) at the field rate of 750 g a.s./ha. On this basis this metabolite should be considered as being ‘relevant’ in terms of the guidance document.

10.2.3.2 STEP 3, Stage 2: screening for genotoxicity

Although weakly mutagenic in vitro (gene mutation) MT1 was negative in two in vivo assays and can be regarded as non-genotoxic.

10.2.3.3 STEP 3, Stage 3: screening for toxicity

MT1 was found to be of comparatively high acute oral toxicity in the rat (LD50 =236 mg/kg bw. Based on a comparison with the 90 day study with MT1 and the two 90 day studies with terbuthylazine in the original DAR it appears that MT1 produces some but not all the effects seen in the terbuthylazine studies at similar dose levels. It appears to have similar or slightly lower short term toxicity than parent. The 90 day study is not considered suitable for determining a reference value for MT1 (no NOAEL and lacking detail)

10.2.4 STEP 4: Exposure assessment – threshold of concern approach

PEC_{gw} value is below TTC 0.75 µg/L, therefore STEP 5 of refined risk assessment is not necessary.

10.2.5 STEP 5: Refined risk assessment

Not applicable-please refer to point 10.2

10.3 Relevance assessment of MT 13

Comments of ZRMs:	<ul style="list-style-type: none"> - According to the available data, the metabolite MT13 has no pesticidal activity and it is not genotoxic. - The maximum PEC_{gw} of MT13 (acc. to the application rate presented in the GAP table) amounts to 14.62 µg/L. The predicted max. PEC_{gw} value exceeds the upper limit for metabolites and the consumer risk calculation for this metabolite is required. 		
		Exposure (µg/kg b.w./d) (using default body weight values) ¹	% ADI (reference value of the parent substance: 0.004 mg/kg b.w./d)
	Adults (70 ¹ /60 ² kg b.w.)	0.42/0.49	10.44/12.18
	Toddlers (12 ¹ /10 ² kg b.w.)	1.22/1.46	30.45/36.55
	Infants (5 kg b.w.)	2.19	54.75
According to WHO recommendation ³ , normal allocation of the total daily intake for			

	<p>chemicals with drinking water is 20% of ADI.</p> <p>Conclusions:</p> <p>Taking into account the results of all available toxicological studies, the metabolite MT13 has no genotoxic potential. The results of consumer risk calculations indicate that the use of TERBUT 500 SC (La Zina 500 SC; Tekno 500 SC) according to the list of intended uses presented in GAP Table, can cause unacceptable risk for toddlers' and infants' health resulting from the exposure to the metabolite MT13.</p> <p>¹According to EFSA Journal 2012;10(3):2579, Guidance on selected default values to be used by the EFSA Scientific Committee, Scientific Panels and Units in the absence of actual measured data.</p> <p>²WHO Guidelines for drinking-water quality: fourth edition incorporating the first addendum, 2017</p> <p>³Guidelines for drinking-water quality, fourth edition. WHO, Geneva (2011).</p>
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10.4 Summary:

The relevance of the groundwater metabolite MT13 has already been assessed and the assessment agreed at EU level (see DAR 2010) , and the relevance assessment is applicable as well for the GAP and groundwater scenarios considered in this dRR (i.e., the conclusions reached at Step 4 and 5 of the relevance assessment made at the EU-level are valid also with regard to the PEC_{gw} calculated for the GAP and groundwater scenarios considered in this dRR). MT13 is not considered relevant according to the criteria laid down in the EC guidance document SANCO/221/2000 –rev.10.

A summary of the relevance assessment is given in Table 10.2-1 and the corresponding studies are listed in the corresponding sections.

Table 10.4-1: Summary of the relevance assessment for MT13 according to the DAR Additional report 2010.

	Assessment step		Result of assessment	
tion of groun- dwa- ter	STEP 1		Metabolite of no concern?	Yes
	STEP 2		Max PEC _{gw}	14.62 µg/L
			Based on	FOCUS PEARL, Thivia
Hazard assessment	STEP 3	Stage 1	Biological activity comparable to the parent?	no
		Stage 2	Genotoxic properties of metabolite	Non-genotoxic
		Stage 3	Toxic properties of metabolite;	Not toxic or very toxic (T or T+)
			Classification of parent	not currently classified as toxic or very toxic
			Classification of metabolite	not currently classified as toxic or very toxic
Consumer health risk assessment	STEP 4		Estimated consumer exposure via drinking water and other sources; threshold of concern approach	Not Acceptable >0.75 µg/L
	STEP 5		Refined risk assessment	Required

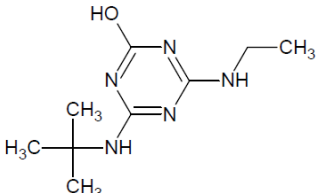
	Predicted exposure (% of ADI)	11.5%
	ADI based on	ADI for MT13 of 0.0034 mg/kg bw/d (3.4 µg/kg bw/d)

* N/A: not applicable

10.4.1 STEP 1: Exclusion of degradation products of no concern

Could not be excluded

10.4.2 STEP 2: Quantification of potential groundwater contamination

MT13 Hydroxy-terbuthylazine Or 2-hydroxy terbuthyl- lazine GS 23158		Max PEC _{gw} Based on:	14.62 µg/L Focus PEARL 4.4.4 Thivia
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Although the prediction of concentration in excess of 10µg/l may cause specific concerns in some MS, the RMS considers that these results represent conservative first tier exposure estimates only. The 2-hydroxy terbuthylazine metabolite was not detected above 0.1µg/l in the field leaching study performed in Northern Italy, even when other metabolites such as the desethyl-hydroxy terbuthylazine and the lysimeters leachate metabolites LM5 and LM6 were detected above 0.1µg/l as an annual average at some locations. In addition this metabolite was only detected in two wells (at < 0.05µg/l) in an extensive and targeted German groundwater monitoring program. In further recent groundwater monitoring studies in Italy in maize growing regions the 90th percentile concentration was only 0.03µg/l. On the basis of the additional information from field leaching and groundwater monitoring programs it is clear that the first tier FOCUS groundwater exposure assessments based on either the Notifier or conservative RMS approach represent a very conservative assessment and such high concentrations are unlikely to be encountered under realistic use conditions.

10.4.3 STEP 3: Hazard assessment – identification of relevant metabolites

10.4.3.1 STEP 3, Stage 1: screening for biological activity

It was concluded that this metabolite is not herbicidally active.

10.4.3.2 STEP 3, Stage 2: screening for genotoxicity

No evidence of genotoxicity was seen in a battery of studies in vitro.

10.4.3.3 STEP 3, Stage 3: screening for toxicity

MT13 was found to be of low acute oral toxicity in the rat. A NOAEL of 3.4 mg/kg bw/d was determined for a 90-day toxicity study in the rat. An ADI for MT13 of 0.0034 mg/kg bw/d (3.4 µg/kg bw/d) can therefore be derived for MT13, based on the NOAEL from the 90-day study and applying a safety factor of 1000.

10.4.4 STEP 4: Exposure assessment – threshold of concern approach

MT13 is also predicted to exceed the 10 µg/L thresholds defined in the guidance document. However the additional monitoring data does indicate that the first tier FOCUS groundwater exposure assessment represents a conservative assessment for this metabolite and such high concentrations are unlikely to be encountered under realistic use conditions. However, as the first tier exposure assessment shows metabolites above the threshold of concern then refined risk assessments are provided for these metabolites in the following section, based on the conservative first tier FOCUSgw estimates.

10.4.5 STEP 5: Refined risk assessment

The maximum level of MT13 is predicted to be 14.62 µg/l on the basis of the conservative FOCUSgw modelling independently performed by the RMS. Where actual or predicted concentrations of a non-relevant metabolite in groundwater exceed 10 µg/L, no general guidance is provided in the Relevance of Metabolites in Groundwater document (SANCO/221/2000/rev:10-final 25 Feb 2003). Therefore, it is necessary to evaluate case by case, whether the requirements of Article 5 (1) of the Directive are still fulfilled and the active substance can be included in Annex I to the Directive. Such an assessment must consider the overall profile and use pattern of the substance and it must be based on strict precaution. Again on the basis of the additional information from field leaching and groundwater monitoring programs it is clear that the first tier FOCUS groundwater exposure assessments based on either the Notifiers or more conservative RMS approach represent a very conservative assessment and such high concentrations are unlikely to be encountered under realistic use conditions.

No new studies have been provided for MT13. Data on biological activity for MT13 have previously been provided and it was concluded that it was not herbicidally active. MT13 was found to be of low acute oral toxicity in the rat; no evidence of genotoxicity was seen in a battery of studies *in vitro*. A NOAEL of 3.4 mg/kg bw/d was determined for a 90-day toxicity study in the rat. An ADI for MT13 of 0.0034 mg/kg bw/d (3.4 µg/kg bw/d) can therefore be derived for MT13, based on the NOAEL from the 90-day study and applying a safety factor of 1000.

MT13 was identified as a minor rat metabolite (<1%) in the Oxon metabolism study (DAR 2010 Table B.6.19; M13), but was not identified as a metabolite in the Syngenta study. As this metabolite is potentially an intermediate in the formation of MT14 (desethylhydroxy-terbuthylazine, GS 28620), systemic exposure may be higher but is not possible to quantify. MT13 is not considered to be a relevant metabolite according to current EC guidance.

Toxicological endpoints for MT13

metabolite	Endpoint	Value (mg/kg bw/day)	Study	Safety factor
MT13 Hydroxy- terbuthylazine Or 2-hydroxy terbuthyl-lazine	Acceptable Daily Intake (ADI)	0.0034	90-day toxicity study in the rat NOAEL	1000

Intake (µg/kg bw/d) = 0.0267 L/kg bw/d x upper limit concentration of terbuthylazine metabolite [µg/L]

The following amounts for flufenacet metabolites by means of intake from drinking water and the corresponding ADI usages are calculated:

Upper limit intake of MT13 through drinking water

Metabolite	Intake [µg/kg bw/d]	Usage of ADI [%]
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	expressed as parent equivalent	
MT13 Hydroxy-terbuthylazine Or 2-hydroxy terbuthylazine	0.3904	11.5

From the long-term and short-term exposure calculations above it can be concluded that possible intakes of Hydroxy-terbuthylazine by means of drinking water do not present a consumer health concern. The calculations are based on several worst case assumptions.

Conclusion:

In summary the metabolite MT 13 is considered to be biologically, toxicologically and ecotoxicologically non relevant.

10.5 Relevance assessment of MT 14

Comments of ZRMs:	<ul style="list-style-type: none"> - According to the available data, the metabolite MT14 has no pesticidal activity and it is not genotoxic. - The maximum PEC_{gw} of MT14 (acc. to the application rate presented in the GAP table) amounts to 2.098676 µg/L. The predicted max. PEC_{gw} value exceeds the upper limit for the metabolites. Thus, the consumer risk calculation for this metabolite is required. 		
		Exposure (µg/kg b.w./d) (using default body weight values) ¹	% ADI (reference value of the parent substance: 0.004 mg/kg b.w./d)
	Adults (70 ¹ /60 ² kg b.w.)	0.06/0.07	1.5/1.75
	Toddlers (12 ¹ /10 ² kg b.w.)	0.17/0.21	4.24/5.25
	Infants (5 kg b.w.)	0.31	7.87

Conclusions:

Taking into account the results of all available toxicological studies, the metabolite MT14 has no genotoxic potential. The results of consumer risk calculations indicate that the use of TERBUT 500 SC (La Zina 500 SC; Tekno 500 SC) according to the list of intended uses presented in GAP Table, **causes no unacceptable risk for health resulting from the exposure to the metabolite MT14.**

¹According to EFSA Journal 2012;10(3):2579, Guidance on selected default values to be used by the EFSA Scientific Committee, Scientific Panels and Units in the absence of actual measured data.

²WHO Guidelines for drinking-water quality: fourth edition incorporating the first addendum, 2017

Summary:

The relevance of the groundwater metabolite MT14 has already been assessed and the assessment agreed at EU level (DAR 2010 additional report) , and the relevance assessment is applicable as well for the GAP and groundwater scenarios considered in this dRR (i.e., the conclusions reached at Step 4 and 5 of

the relevance assessment made at the EU-level are valid also with regard to the PEC_{gw} calculated for the GAP and groundwater scenarios considered in this dRR). MT1 is not considered relevant according to the criteria laid down in the EC guidance document SANCO/221/2000 –rev.10.

A summary of the relevance assessment is given in Table 10.2-1 and the corresponding studies are listed in the corresponding sections.

Table 10.5-1: Summary of the relevance assessment for MT14 according to the Additional report 2010 DAR.

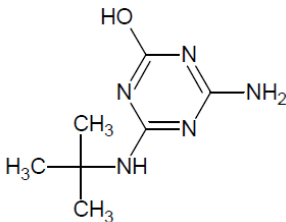
	Assessment step		Result of assessment	
tion of groun- dwa- ter	STEP 1		Metabolite of no concern?	Yes
	STEP 2		Max PEC _{gw}	2.098676 µg/L
			Based on	FOCUS PEARL, Hamburg
Hazard assessment	STEP 3	Stage 1	Biological activity comparable to the parent?	no
		Stage 2	Genotoxic properties of metabolite	Non-genotoxic
		Stage 3	Toxic properties of metabolite;	Not toxic or very toxic (T or T+)
			Classification of parent	not currently classified as toxic or very toxic
			Classification of metabolite	not currently classified as toxic or very toxic
Consumer health risk assessment	STEP 4		Estimated consumer exposure via drinking water and other sources; threshold of concern approach	Not Acceptable >0.75 µg/L
	STEP 5		Refined risk assessment	Required
			Predicted exposure (% of ADI)	0.5 %
			ADI based on	NOAEL from the 90-day study and applying a safety factor of 1000 ADI for MT14 of 0.0103 mg/kg bw/d (10.3 µg/kg bw/d)

* N/A: not applicable

10.5.1 STEP 1: Exclusion of degradation products of no concern

Could not be excluded.

10.5.2 STEP 2: Quantification of potential groundwater contamination

MT14 desethyl- hydroxyterbuthylazine or desethyl-2-hydroxy terbuthylazine GS 28620		Max PEC _{gw} Based on:	2.098676 µg/L Focus PEARL 4.4.4 Hamburg
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10.5.3 STEP 3: Hazard assessment – identification of relevant metabolites

10.5.3.1 STEP 3, Stage 1: screening for biological activity

It was concluded that this metabolite is not herbicidally active.

10.5.3.2 STEP 3, Stage 2: screening for genotoxicity

No evidence of genotoxicity was seen in a battery of studies in vitro.

10.5.3.3 STEP 3, Stage 3: screening for toxicity

MT14 was found to be of low acute oral toxicity in the rat. A NOAEL of 10.3 mg/kg bw/d was determined for a 90-day toxicity study in the rat. An ADI for MT14 of 0.0103 mg/kg bw/d (10.3 µg/kg bw/d) can therefore be derived for MT14, based on the NOAEL from the 90-day study and applying a safety factor of 1000.

10.5.4 STEP 4: Exposure assessment – threshold of concern approach

PEC_{gw} value is above TTC 0.75 µg/L, therefore STEP 5 of refined risk assessment is necessary.

10.5.5 STEP 5: Refined risk assessment

The maximum level of MT14 is predicted to be 2.098676 µg/l. A refined risk assessment therefore needs to be performed, according to current EC guidance. Data on biological activity for MT14 have previously been provided and it was concluded that it was not herbicidally active. MT14 was found to be of low acute oral toxicity in the rat; no evidence of genotoxicity was seen in a battery of studies in vitro. A NOAEL of 10.3 mg/kg bw/d was determined for a 90-day toxicity study in the rat. An ADI for MT14 of 0.0103 mg/kg bw/d (10.3 µg/kg bw/d) can therefore be derived for MT14, based on the NOAEL from the 90-day study and applying a safety factor of 1000.

MT14 was identified as a rat metabolite in studies submitted by both Notifiers. It was identified as a metabolite in urine and faeces, although not at very high levels in the studies by Syngenta (≤7.8%; DAR Table B.6.18) and Oxon (4.41-11.6%, DAR Table B.6.19). MT14 is not considered to be a relevant metabolite according to current EC guidance.

Toxicological endpoints for MT14

metabolite	Endpoint	Value (mg/kg bw/day)	Study	Safety factor
Metabolite MT14 (desethylhydroxy-	Acceptable Daily Intake	0.0103 mg/kg bw/d	90-day toxicity study in the rat	1000

terbuthylazine	(ADI)		NOAEL	
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Intake ($\mu\text{g/kg bw/d}$) = $0.0267 \text{ L/kg bw/d} \times \text{upper limit concentration of terbuthylazine metabolite } [\mu\text{g/L}]$

The following amounts for terbuthylazine metabolites by means of intake from drinking water and the corresponding ADI usages are calculated:

Upper limit intake of MT14 through drinking water

Metabolite	Intake [$\mu\text{g/kg bw/d}$] expressed as parent equivalent	Usage of ADI [%]
Metabolite MT14 (de- sethylhydroxy- terbuthylazine)	0.056	0.5%

From the long-term and short-term exposure calculations above it can be concluded that possible intakes of desethylhydroxy-terbuthylazine by means of drinking water do not present a consumer health concern. The calculations are based on several worst case assumptions.

Conclusion:

In summary the metabolite MT 14 is considered to be biologically, toxicologically and ecotoxicologically non relevant.

10.6 Relevance assessment of, LM3, LM5 and LM6

Comments of ZRMs:	<ul style="list-style-type: none"> - According to EFSA Journal 2019;17(9):5817, the metabolite LM1 has no pesticidal activity (the compound is the breakdown product of LM5) and is not toxicologically relevant. - Acc. to available data, the metabolite LM3 has no pesticidal activity and it is not genotoxic. The consumer risk for this metabolite cannot be concluded (no specific reference values could be derived on the basis of the available toxicological data). - Acc. to the available data, the metabolite LM6 has no pesticidal activity and is not genotoxic. The consumer risk for this metabolite cannot be concluded (no specific reference values could be derived on the basis of the available toxicological data). - Acc. to the available data, the metabolite LM5 has no pesticidal activity and is not genotoxic. The maximum PEC_{gw} of LM5 (acc. to the application rate presented in the GAP table) amounts to $1.691832 \mu\text{g/L}$. The predicted max. PEC_{gw} value exceeds the limit for metabolites ($>0.75 \mu\text{g/L}$) and the consumer risk calculation is required. The results of consumer risk calculations indicate that the use of TERBUT 500 SC (La Zina 500 SC; Tekno 500 SC) according to the list of intended uses presented in GAP Table, causes no unacceptable risk for health resulting from the exposure to the metabolite LM5. 		
		Exposure ($\mu\text{g/kg b.w./d}$) (using default body weight values) ¹	% ADI (reference value of the parent substance: $0.004 \text{ mg/kg b.w./d}$)
	Adults ($70^{1/60^2} \text{ kg b.w.}$)	0.048/0.056	1.21/1.4
	Toddlers	0.14/0.17	3.5/4.25

	(12 ¹ /10 ² kg b.w.)		
	Infants (5 kg b.w.)	0.25	6.34
¹ According to EFSA Journal 2012;10(3):2579, Guidance on selected default values to be used by the EFSA Scientific Committee, Scientific Panels and Units in the absence of actual measured data.			

Summary:

In total seven novel leachate metabolites were characterised from the terbuthylazine lysimeters studies. Four of these metabolites (LM3, LM4, LM5 and LM6) represented the major identified fractions of the leachate and were subject to further analysis of their potential to contaminate groundwater using the FOCUSgw models. Two other metabolites were tentatively identified and considered to occur at or around the 0.1µg/l limit on an annual average basis. These two metabolites were coded LM1 and LM2 but have not been subject to further analysis via the FOCUSgw models. Since they represented more minor fractions of the lysimeters leachates compared with the other fractions (i.e. LM1 maximum annual average of 0.15µg/l and LM2 maximum annual average of 0.10µg/l) the RMS accepted the approach of the Notifiers to concentrate the additional quantification work using the FOCUS models on the major lysimeters fractions. In the opinion of the RMS the identity of the LM1 metabolite could only be tentatively assigned on the basis of the new mass spectral elucidation work evaluated in the fate section of the Additional Report (see Section B.8.2.3). In addition the LM2 metabolite occurred at a maximum annual average of 0.10µg/l. Nonetheless the non-relevance of LM1 and LM2 is discussed briefly below. The seventh novel leachate metabolite (LM7) was detected at a maximum annual average concentration of only 0.03µg/l has been excluded from further consideration of its relevance.

For metabolite LM3 simulations gave PECgw highest values 3.569994 µg/l for Focus PEARL Thivia scenario. For LM5 the simulations gave PECgw highest values in 1.691832 µg/l for Focus PEARL Hamburg scenario. For LM6 the simulations gave PECgw highest values in 2.937372 µg/l for Focus PEARL Thivia scenario.

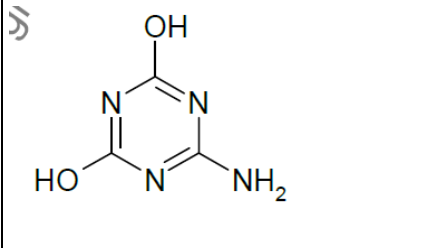
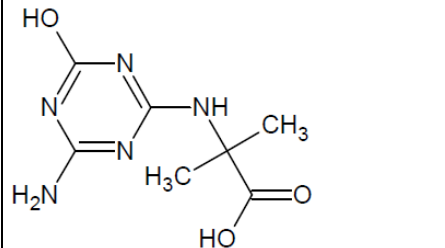
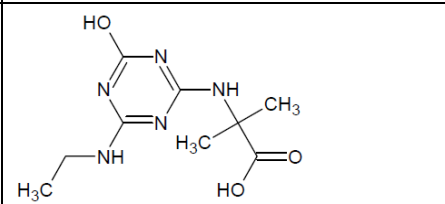
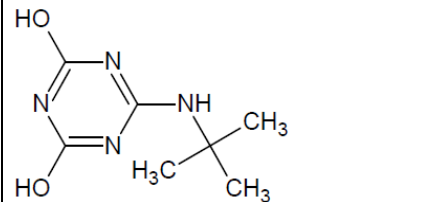
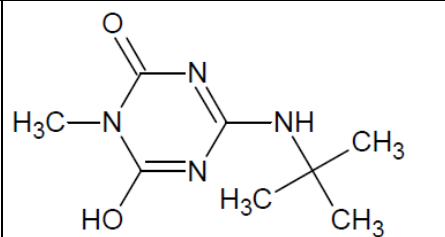
The predicted values for CSCD648241 (LM6) were noted to be in the same order of magnitude but higher than the residues measured in Germany in shallow groundwater wells (maximum 0.66 µg/l) and in Italy in piezometers under the treated field (annual average 1.3 µg/l). A similar result was found for GS16984 (LM5) where the maximum residue in German wells was 0.98 µg/l and the annual average in the Italian piezometers was 0.48 µg/l. CSCD692760 (LM3) residue data is only available for the German wells but again there was noted to be a close relationship between the predicted and measured (maximum 0.69 µg/L) values. Therefore, although some assumptions had to be made about the appropriate input values, the modelling does appear to be able to predict the field residues with reasonable accuracy.

Overall, despite the numerous uncertainties, the RMS chose to accept the groundwater simulations provided for the lysimeters metabolites in this case. The results of these simulations were broadly supported by results of the Italian field leaching study and the German groundwater monitoring program.

10.6.1 STEP 1: Exclusion of degradation products of no concern

Could not be excluded

10.6.2 STEP 2: Quantification of potential groundwater contamination

LM1 MT24		Based on, lysimeter studies:	0.15µg/l
LM 2 MT28		Based on lysimeter:	0.10 µg/l
LM 3 SM9 CSCD692760 SYN546009		Based on lysimeter:	3.569994 µg/L Focus PEARL 4.4.4., Thivia
LM5 MT23 SM12 GS 16984		Max PEC _{gw} Based on:	1.691832 µg/L Focus PEARL 4.4.4., Hamburg
LM6 SM6 CSCD648241 SYN545666		Max PEC _{gw} Based on:	2.937372 µg/L Focus PEARL 4.4.4., Thivia

10.6.3 STEP 3: Hazard assessment – identification of relevant metabolites

10.6.3.1 STEP 3, Stage 1: screening for biological activity

Biological activity testing studies for five of the six lysimeter metabolites found at > 0.1 µg/L have also been submitted as part of this resubmission (i.e. LM2 to LM6). The only exception was G035713 (LM1) but the Notifiers stated that this is a degradate of GS16984 (LM5, MT23) which has been shown to have no biological activity.

The biological activity of the metabolites CSCD648241 (LM6), CSCD692760 (LM3), GS16984 (LM5, MT23), CSAA036479 (LM2) and CSAA404949 (LM4) is less than 50% of the parent molecule when applied at a dose at which the parent demonstrates good herbicidal activity on key species. On this basis these metabolites should not be considered as being ‘relevant’ in terms of biological activity.

10.6.3.2 STEP 3, Stage 2: screening for genotoxicity

Metabolite LM3

The Notifiers have provided an Ames assay with this metabolite and it is negative. The metabolite does not possess any structural alerts for genotoxicity according to DEREK and does not contain any additional functional groups that are not present in terbuthylazine or its metabolites (including metabolites MT1, MT13, MT14 and M20 which have been tested for genotoxicity). A mammalian gene mutation test is also available but was concluded too late to be included in the resubmission so has not been considered.

Metabolite LM5 (GS 16984)

The Notifiers have provided an Ames assay with this compound and it is negative. The metabolite does not possess any structural alerts for genotoxicity according to DEREK and does not contain any additional functional groups that are not present in terbuthylazine or its metabolites (including metabolites MT1, MT13, MT14 and M20 which have been tested for genotoxicity). An in-vitro chromosome aberration test and a mammalian gene mutation test are also available but were concluded too late to be included in the resubmission so have not been considered.

Metabolite LM6

In the resubmission package the Notifiers have provided a reverse mutation assay, a mouse lymphoma assay, in vitro chromosome aberration study in Human Lymphocytes, and an in vivo rat bone marrow micronucleus test. Although positive at cytotoxic levels in the gene mutation assay overall it is considered non-genotoxic. The metabolite does not possess any structural alerts for genotoxicity according to DEREK and is structurally similar to MT13 and MT14.

10.6.3.3 STEP 3, Stage 3: screening for toxicity

Metabolite LM3

Metabolite LM3 contains an additional carboxylic acid functional group (when compared to terbuthylazine and the tested metabolites), but in this respect is structurally similar to the carboxylic acid metabolites MT5, MT8 (GS 33022) and MT10 (GS 31398). It can be reasonably predicted that the toxicity of metabolite LM3 is less than that of terbuthylazine and the tested metabolites.

Metabolite LM5 (GS 16984)

The metabolite does not contain any additional functional groups that are not present in terbuthylazine or its metabolites (including metabolites MT1, MT13, MT14 and M20 which have been tested for genotoxicity). It can be reasonably predicted that the toxicity of metabolite LM5 is less than that of terbuthylazine.

Metabolite LM6

The metabolite is structurally similar to MT13 and MT14. It can be reasonably predicted that the toxicity of metabolite LM6 is less than that of terbuthylazine.

10.6.4 STEP 4: Exposure assessment – threshold of concern approach

The concentration of the metabolites LM3, LM5 and LM6 are predicted to exceed the 0.75 µg/L.. However, as the first tier exposure assessment shows metabolites above the threshold of concern then refined risk assessments are provided for these metabolites in the following section, based on the conservative first tier FOCUSgw estimates.

10.6.5 STEP 5: Refined risk assessment

Metabolite LM3

The maximum level of LM3 is predicted to be 3.57 µg/l. A refined risk assessment therefore needs to be performed, according to current EC guidance. Data on biological activity for this metabolite have been provided and demonstrated it is less than 50% of the parent molecule when applied at a dose at which the parent demonstrates good herbicidal activity on key species. The Notifiers have provided an Ames assay with this metabolite and it is negative. The metabolite does not possess any structural alerts for genotoxicity according to DEREK and does not contain any additional functional groups that are not present in terbuthylazine or its metabolites (including metabolites

MT1, MT13, MT14 and M20 which have been tested for genotoxicity). Metabolite LM3 contains an additional carboxylic acid functional groupRegistration(when compared to terbuthylazine and the tested metabolites), but in this respect structurally similar to the carboxylic acid metabolites MT5, MT8 (GS 33022) and MT10 (GS 31398). It can be reasonably predicted that the toxicity of metabolite LM3 is less than that of terbuthylazine and the tested metabolites.

Using the highest predicted groundwater concentration of 3.57 µg/l. The maximum predicted consumer intake is equivalent to 2.9% of the proposed ADI for terbuthylazine of 0.004 mg/kg bw/d (4 µg/kg bw/d) and is therefore considered to be acceptable.

Metabolite LM5 (GS 16984)

The maximum level of LM5 is predicted to be 1.69 µg/l. A refined risk assessment therefore needs to be performed, according to current EC guidance. Data on biological activity for this metabolite have been provided and demonstrated it is less than 50% of the parent molecule when applied at a dose at which the parent demonstrates good herbicidal activity on key species. The Notifiers have provided an Ames assay with this compound and it is negative. The metabolite does not possess any structural alerts for genotoxicity according to DEREK and does not contain any additional functional groups that are not present in terbuthylazine or its metabolites (including metabolites MT1, MT13, MT14 and M20 which have been tested for genotoxicity). It can be reasonably predicted that the toxicity of metabolite LM5 is less than that of terbuthylazine.

Using the highest predicted groundwater concentration of 1.69 µg/l. The maximum predicted consumer intake is equivalent to 1.38% of the proposed ADI for terbuthylazine of 0.004 mg/kg bw/d (4 µg/kg bw/d) and is therefore considered to be acceptable.

Metabolite LM6

The maximum level of LM6 is predicted by modelling to be Registration 2.94 µg/l. A refined risk assessment therefore needs to be performed, according to current EC guidance. Data on biological activity for this metabolite have been provided and demonstrated it is less than 50% of the parent molecule when applied at a dose which the parent demonstrates good herbicidal activity on key species. On this basis these metabolites should not be considered as being ‘relevant’ in terms of biological activity. In the resubmission package the Notifiers have provided a reverse mutation assay, a

mouse lymphoma assay, in vitro chromosome aberration study in Human Lymphocytes, and an in vivo rat bone marrow micronucleus test. Although positive at cytotoxic levels in the gene mutation assay overall it is considered non-genotoxic. The metabolite does not possess any structural alerts for genotoxicity according to DEREK and is structurally similar to MT13 and MT14. It can be reasonably predicted that the toxicity of metabolite LM6 is less than that of terbuthylazine.

Using the highest predicted groundwater concentration of 2.94 µg/l. The maximum predicted consumer intake is equivalent to 2.4% of the proposed ADI for terbuthylazine of 0.004 mg/kg bw/d (4 µg/kg bw/d) and is therefore considered to be acceptable.

Appendix 1 Lists of data considered in support of the evaluation

Not relevant

Tables considered not relevant can be deleted as appropriate.

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

Appendix 2 Additional information