FINAL REGISTRATION REPORT

Part B

Section 6

Mammalian Toxicology

Detailed summary of the risk assessment

Product code: CHR/H/TERIZ

Product name(s): Undito 650 WG, Jotamun 650 WG, Metodus 650 WG

Chemical active substances:

Terbuthylazine, 400 g/kg
Isoxaflutole, 100 g/kg
Mesotrione, 150 g/kg

Central Zone

Zonal Rapporteur Member State: POLAND

CORE ASSESSMENT- renewal of authorization

(Poland)

Applicant: Innvigo Sp. z o.o.

Submission date: October 2019

Update: November 2021

MS Finalisation date: November 2021; June 2023

Version history

When	What
May 2019	New data on dermal absorption and corresponding exposure assessment were provided (for Terbuthylazine)
October 2019	Renewal of authorisation based od new endpoints for isoxaflutole
November 2021	Risk assessment of bystander exposure was calculated based on AAOEL of isoxaflutole.
June 2023	Final Registration Report

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The document was prepared with the aim of adding risk assessment of bystander exposure towards isoxaflutole based on acute acceptable operator exposure level. Additionally, toxicological information of the metabolite RPA202248 was deleted. Based on new predicted environmental concentration in ground-water, the metabolite does not exceed 0.1 µg/L. New information was highlighted in green.

6 Mammalian Toxicology (KCP 7)

6.1 Summary

Table 6.1-1: Information on CHR/H/TERIZ

Product name and code	CHR/H/TERIZ
Formulation type	WG
Active substance(s) (incl. content)	Terbuthylazine 400 g/kg Isoxaflutol 100 or g/kg Mesotrione150 or g/kg
Function	herbicide
Product already evaluated as the 'representative formulation' during the approval of the active substance(s)	No
Product previously evaluated in another MS according to Uniform Principles	No

* Information on the detailed composition of CHR/H/TERIZ can be found in the confidential dRR Part C.

Justified proposals for classification and labelling

According to the criteria given in Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008, the following classification and labelling with regard to toxicological data is proposed for the preparation:

Table 6.1-2: Justified proposals for classification and labelling for CHR/H/TERIZ according to Regulation (EC) No 1272/2008

Hazard class(es), categories:	Acute Tox. 4 Skin Irrit. 2 Repr. 2, STOT RE 2
Hazard pictograms or Code(s) for hazard pictogram(s):	GHS07, GHS08
Signal word:	warning
Hazard statement(s):	H302 – Harmful if swallowed. (based on study) H315 – Causes skin irritation. (based on study) H361d– Suspected of damaging the unborn child (based on composition – isoxaflutole, mesotrione ≥3%) H373 (eyes, nervous system) – May cause damage to organs through prolonged or repeated exposure (based on composition – terbuthylazine, mesotrione ≥10%)
Precautionary statement(s):	<u>WARNING SECTION OF THE LABEL (first page):</u> P260: Do not breathe spray. P280: Wear protective gloves and protective clothing P301+312: IF SWALLOWED: Call a POISON CENTER or doctor/physician if you feel unwell. P302+352: IF ON SKIN: Wash with plenty of soap and water. P308+313: IF exposed or concerned: Get medical advice/attention. EUH401 – "To avoid risks to human health and the environment, comply with the instructions for use" <u>Other section of the label:</u> P201, P270, P260, P264, P405, P501 P280 as follows: OPERATOR: *Stosować rękawice ochronne oraz odzież ochronną zabezpieczającą przed oddziaływaniem środków ochrony roślin i odpowiednie obuwie w trakcie przygotowywania cieczy użytkowej oraz w trakcie wykonywania zabiegu.* *„*Wear protective gloves, protective clothing and sturdy footwear during mixing and loading and during application". WORKER: „*Stosować rękawice ochronne oraz odzież roboczą (długie spodnie, koszula z długim rękawem) oraz ograniczyć czas inspekcji terenu poddanego opryskowi do 2 godzin".* "Wear protective gloves and workwear (long trousers, long-sleeve shirt) and limit the time of inspection in the treated area to 2 hours". BYSTANDER/RESIDENT „*Podczas wykonywania zabiegu należy zachować 5 metrową strefę buforową oraz dysze ograniczające znos. Należy umieścić tablicę informacyjną: „Zakaz wejścia na teren poddany opryskowi do końca uprawy*". "Keep a 5 meter buffer zone and drift-reduction nozzles during application. Warning board: "Do not enter the treated area till the end of the plant growth" must be installed.

	Section :First Aid" P301+312: IF SWALLOWED: Call a POISON CENTER or doctor/physician if you feel unwell. P330: Rinse mouth. P302+352: IF ON SKIN: Wash with plenty of soap and water. P308+313: IF exposed or concerned: Get medical advice/attention.
Additional labelling phrases:	To avoid risks to man and the environment, comply with the instructions for use. [EUH401]

Table 6.1-3: Summary of risk assessment for operators, workers, bystanders and residents for CHR/H/TERIZ

	Substances	Result	PPE / Risk mitigation measures
Operators	terbuthylazine	**Acceptable** acc. to AOEM	Gloves, work wear during mixing/loading and application.
	mesotrione	**Acceptable** acc. to AOEM	Exposure and toxicological data: Gloves, protective clothing during mixing/loading and during application.
	isoxaflutol	**Acceptable** acc. to AOEM	Exposure and toxicological data: Gloves, protective clothing during mixing/loading and during application.
Workers	terbuthylazine	**Acceptable** acc. to EUROPOEM II	Gloves and workwear (long trousers, long-sleeve shirt) and limit the time of inspection of the treated area to 2 hours.
	mesotrione	**Acceptable** acc. to EUROPOEM II	Gloves and workwear (long trousers, long-sleeve shirt)
	isoxaflutol	**Acceptable** acc. to EUROPOEM II	None Workwear (arms, body and legs covered)
Bystanders	terbuthylazine	Not accepted acc. to AOEM. **Acceptable** with additional risk mitigation measures	Drift reduction, no entry to the treated area, min 5 m buffer zone
	mesotrione	Not accepted acc. to AOEM, **Acceptable** with additional risk mitigation measures	Drift reduction, no entry to the treated area, min 5 m buffer zone
	isoxaflutol	**Acceptable** acc. to AOEM	Accepted: buffer zone: 5m
Residents	terbuthylazine	Not accepted acc. to AOEM,	Drift reduction, no entry to the treated area, min 5 m buffer

	Substances	Result	PPE / Risk mitigation measures
		Acceptable with additional risk mitigation measures	zone
	mesotrione	Not accepted acc. to AOEM, **Acceptable** with additional risk mitigation measures	Drift reduction, no entry to the treated area, min 5 m buffer zone
	isoxaflutol	**Acceptable** acc. to AOEM	None

No unacceptable risk for operators (for terbuthylazine the risk is acceptable according to Additional Report to the DAR, public version, Volume 3, Annex B, part 2, B.6, February 2010, point B.6.14.1.2), workers, bystanders and residents was identified when the product is used as intended and provided that the PPE/ risk mitigation measures stated in Table 6.1-3 are applied.

A summary of the critical uses and the overall conclusion regarding exposure for operators, workers and bystanders/residents is presented in the following table.

Table 6.1-4 Critical uses and overall conclusion of exposure assessment

1	2	3	4	5	6	7	8	9	10			
Use-No.*	**Crops and situation (e.g. growth stage of crop)**	**F, Fn, Fpn G, Gn, Gpn or I ****	**Application**		**Application rate**		**PHI (d)**	**Remarks:** **(e.g. safener/synergist (L/ha))** **critical gap for operator, worker, bystander or resident exposure based on [Exposure model]**	**Acceptability of exposure assessment**			
			Method / Kind **(incl. application technique *****	**Max. number (min. interval between applications)** **a) per use** **b) per crop/ season**	**Max. application rate kg as/ha** **a) terbuthylazine** **b) isoxaflutole** **c) mesotrione**	**Water L/ha** **min / max**			**Operator**	**Worker**	**Bystander**	**Residents**
1.	Maize (ZEAMX) Spring BBCH 00, max. 3 days after sowing	F	LC TM	a)1 b)1	0.52 kg a.s./ha a) 0.32 b) 0.08 c) 0.12) 0.65 kg a.s./ha a) 0.4 b) 0.1 c) 0.15	200-400	n/a	Operators (AOEM) Worker (EUROPOEM II) Bystander, Resident (AOEM)				

* Use number(s) in accordance with the list of all intended GAPs in Part B, Section 0 should be given in column 1

** F: professional field use, Fn: non-professional field use, Fpn: professional and non-professional field use, G: professional greenhouse use, Gn: non-professional greenhouse use, Gpn: professional and non-professional greenhouse use, I: indoor application

*** e.g. LC: low crops, HC: high crop, TM: tractor-mounted, HH: hand-held

Explanation for column 10 "Acceptability of exposure assessment"

A	Exposure acceptable without PPE / risk mitigation measures
R	Further refinement and/or risk mitigation measures required
N	Exposure not acceptable/ Evaluation not possible

6.2 Toxicological Information on Active Substance(s)

Information regarding classification of the active substances and on EU endpoints and critical areas of concern identified during the EU review are given in Table 6.2-1.

Table 6.2-1: Information on active substance(s)

	Terbuthylazine	**Mesotrione**	**Isoxaflutole**
Common Name	Terbuthylazine	Mesotrione	Isoxaflutole
CAS-No.	5915-41-3	104206-8	141112-29-0
Classification and proposed labelling			
With regard to toxicological endpoints (according to the criteria in Reg. 1272/2008, as amended)	**Hazard classes (s), categories:** Acute Tox. 4 STOR RE 2 Aquatic Acute 1 Aquatic Chronic 1 **Code(s) for hazard pictogram(s):** GHS07, GHS08, GHS09 **Signal word:** Warning **Hazard statement(s):** H302 - Harmful if swallowed. H373 – May cause damage to organs through prolonged or repeated exposure. H400 - Very toxic to aquatic life. H410 - Very toxic to aquatic life with long lasting effects. **Precautionary statement(s):** P301 + P312 – IF SWALLOWED: Call a POISON CENTER or doctor/physician if you feel unwell. P260- Do not breathe spray. P391 – Collect spillage. P501 - Dispose of contents of as hazardous waste.	**Hazard classes (s), categories:** Repr 2, H361d /RAC Opinion/ STOT RE 2, H373 (eyes, nervous system) /RAC Opinion/ Aquatic Acute 1 Aquatic Chronic 1 **Code(s) for hazard pictogram(s):** GHS09, GHS08 **Signal word:** Warning **Hazard statement(s):** H400 - Very toxic to aquatic life. H410 - Very toxic to aquatic life with long lasting effects. **Precautionary statement(s):** P202 - Do not handle until all safety precautions have been read and understood. P280 – Wear protective gloves/protective clothing/eye protection/face protection. P308 + P313 – IF exposed or concerned: Get medical advice/attention. P273 – Avoid release to the environment. P391 – Collect spillage. P501 - Dispose of contents of as hazardous waste.	**Hazard classes (s), categories:** Repr. 2 Aquatic Acute 1 Aquatic Chronic 1 **Code(s) for hazard pictogram(s):** GHS09, GHS08 **Signal word**: Warning **Hazard statement(s):** H361 d– Suspected of damaging ~~fertility or the~~ unborn child . H400 - Very toxic to aquatic life. H410 - Very toxic to aquatic life with long lasting effects. **Precautionary statement(s):** P202 - Do not handle until all safety precautions have been read and understood**.** P280 – Wear protective gloves/protective clothing/eye protection/face protection. P308 + P313 – IF exposed or concerned: Get medical advice/attention. P273 – Avoid release to the environment. P391 – Collect spillage. P501 - Dispose of contents of as hazardous waste.
Additional C&L proposal		Please insert proposal for additional C&L if no	Please insert proposal for additional C&L if no

	Terbuthylazine	Mesotrione	Isoxaflutole
		(sufficient) harmonized classification is available.	(sufficient) harmonized classification is available
Agreed EU endpoints			
AOEL systemic	0.0032 mg/kg bw/d (corrected for 79% oral absorption)	0.005 mg/kg bw/d	0.012 mg/kg bw/d (corrected for 60 % oral absorption
AAOEL	Not allocated	Not allocated	0.03 mg/kg bw/d
Reference	EFSA Journal 2011; 9(1):1969/ DAR Addendum confirmatory data, update November 2015	EFSA Journal 2016;14(3):4419	~~Sanco/3136/99 Final 7 April 2003~~ SANTE/11653/2017 Rev 2 22 March 2019
Conditions to take into account/critical areas of concern with regard to toxicology			
EFSA Conclusion for active substance	**Operator exposure** without PPE and with PPE at mixing/loading in German Model are much above 100% of the AOEL, with PPE during m/l and application are below AOEL. In UK POEM are above 100% of AOEL in each case. **Worker exposure** in EUROPOEM II re-entry model: without PPE are above 100% AOEL, with PPE– below 100% AOEL. **Bystaders exposure** are below 100% AOEL.	None	None

6.3 Toxicological Evaluation of Plant Protection Product

A summary of the toxicological evaluation for CHR/H/TERIZ is given in the following tables. Full summaries of studies on the product that have not been previously considered within an EU peer review process are described in detail in Appendix 2.

Table 6.3-1: Summary of evaluation of the studies on acute toxicity including irritancy and skin sensitisation for CHR/H/TERIZ

Type of test, species, model system (Guideline)	Result	Acceptability	Classification (acc. to the criteria in Reg. 1272/2008)	Reference
LD_{50} oral, rat (OECD 420, EU method B.1BIS)	>300 mg/kg bw	The study was evaluated and accepted during the evaluation completed in 2017. No re-evaluation is required.	Acute Tox. 4, H302	xxx 2016
LD_{50} dermal, rat (OECD 402 / EU Method B.3.)	>2000 mg/kg bw	The study was evaluated and accepted during	None	xxx., 2016

		the evaluation completed in 2017. No re-evaluation is required.		
LC_{50} inhalation, rat	Not submitted, not necessary. Justification presented in Appendix 2			
In Vitro Skin Corrosion (TER) (OECD 430 / EU Method B.40.)	Not corrosive	The study was evaluated and accepted during the evaluation completed in 2017. No re-evaluation is required.	None	xxx, 2016
In vitro skin irritation potential, reconstructed human epidermis (RHE) (OECD 439/ EU method B.46)	Irritant to skin	The study was evaluated and accepted during the evaluation completed in 2017. No re-evaluation is required.	Skin Irrit. 2, H315	xxx 2016
Isolated chicken eye test (OECD 438 / EU Method B.48.)	CHR/H/TERIZ did not cause serious eye damage	The study was evaluated and accepted during the evaluation completed in 2017. No re-evaluation is required.	None	xxx, 2016
Eye irritation, albino rabbits (OECD 405 / EU Method B.5.)	Non-irritant	The study was evaluated and accepted during the evaluation completed in 2017. No re-evaluation is required.	None	xxx, 2016
Skin sensitisation (OECD 406 / EU Method B.6.), guinea pig maximization test of Magnusson and Kligman	Non-sensitising	The study was evaluated and accepted during the evaluation completed in 2017. No re-evaluation is required.	None	xxx, 2016
Supplementary studies for combinations of plant protection products	No data – not required	-	-	-

Table 6.3-2: Additional toxicological information relevant for classification/labelling of CHR/H/TERIZ

	Substance (Concentration in product, % w/w)	**Classification of the substance (acc. to the criteria in Reg. 1272/2008)**	**Reference**	**Classification of product (acc. to the criteria in Reg. 1272/2008)**
Toxicological properties of active	Terbuthylazine (40 % (w/w))	STOT RE. 2 H373 (≥ 10 %)	DAR Addendum	STOT RE. 2, H373

	Substance (Concentration in product, % w/w)	**Classification of the substance (acc. to the criteria in Reg. 1272/2008)**	**Reference**	**Classification of product (acc. to the criteria in Reg. 1272/2008)**
substance(s) (relevant for classification of product)			confirmatory data, update November 2015	
Toxicological properties of active substance(s) (relevant for classification of product)	Isoxaflutole (10 % (w/w))	Repr. 2, H361d (≥ 3 %)	Reg. 1272/2008	Repr. 2, H361d
Toxicological properties of active substance(s) (relevant for classification of product)	Mesotrione (15 % (w/w))	Repr. 2, H361d (≥ 3 %) STOT RE. 2 H373 (≥ 10 %)	RAC Opinion	Repr. 2, H361d STOT RE. 2, H373
Toxicological properties of non-active substance(s) (relevant for classification of product)*	-	-	-	-
Further toxicological information**	-	-	-	-

* Please use concentration range or concentration limit (e.g. 1-10 % or > 1 %) as provided in MSDS.
** Material safety data sheet by the applicant

6.4 Toxicological Evaluation of Groundwater Metabolites

Comments of zRMS:	The detailed metabolite assessment of terbuthylazine and mesotrione are presented in the previous dRR provided in 2017 and finalized in 2019. RPA 202248: 1. The metabolite RPA 202248 **has pesticidal activity.** It is the major rat metabolite of low acute oral toxicity and negative results of Ames test. 2. Since isoxaflutole is classified as Repr. 2, H361d, convincing evidence must be provided to demonstrate that the metabolite RPA 203328 does not qualify for the same classification. **The available toxicological data were not sufficient to exclude reproduction toxicity of metabolite RPA 202248**. 3. As the pesticidal active and mammalian toxicologically relevant, the metabolite RPA 202248 should not exceed drinking water limit of 0.1 µg/L. 4. Taking into account that the max. PEC_{gw} amounts to 1.154 µg/L (application rate: 1x100g/ha, once each year), the metabolite RPA 202248 causes significant consumer risk for human health and does not meet the conditions of product approval. **5. The new calculation for metabolite RPA 202248 was provided by the Applicant (application rate: 80 g isoxaflutole/ha, once every three years). The results indicate that the concentration of the metabolite RPA 202248 does not exceed drinking water limit of 0.1 µg/L for such scenario.** **Conclusions: Only the minimum application rate of 80 g of the product /ha can be**

	accepted. The product can be used once every three years. RPA 203328: 1. According to EFSA Journal 2016;14(2):4416, the consumer risk assessment resulting from consumption of drinking water could not be finalized although the nature of the residues in drinking water following water treatment had not been addressed. Taking into account toxicological data, the metabolite RPA 203328 possess low oral acute toxicity and has no genotoxic potential. 2. Since isoxaflutole is classified as Repr. 2, H361d, convincing evidence must be provided to demonstrate that the metabolite RPA 203328 does not qualify for the same classification. Taking into account the mechanism of reproduction toxicity of the parent substance, the toxicological data obtained for RPA 203328 indicate lack of such effect. 3. The results of consumer risk calculations in regards to the metabolite RPA 203328 indicate that the use of CHR/H/TERIZ 650 WG according to the list of intended uses presented in GAP Table, causes no significant risk for health of the adults, toddlers and infants.

The following data on metabolites with the potential to reach the groundwater in concentrations above 0.1 µg/L and requiring relevance assessment were submitted. Note that the relevance assessment of the metabolites is reported in Part B.10; the submitted toxicological studies are summarized in this document.

6.4.1 MT1 - desethyl terbuthylazine- terbuthylazine metabolite`

For metabolite MT1 (desethyl terbuthylazine)' simulations gave PECgw values in the range from <0.001 to 0.59µg/l (peak concentration with FOCUS PEARL Hamburg, 400 g a.s./ha). The results represent conservative first tier exposure estimates. **According to the Monitoring Studies for Tebuthylazine in ground water and EFSA Journal 2011; 9(1):1969:**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.

Data on MT1 (desethyl-terbuthylazine) was also presented in the original DAR (Section B.9.9.1.2. See also Attachment 1) 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). 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.

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).
MT1 was identified as a rat metabolite of terbuthylazine by both Notifiers (11U: Syngenta, M1: Oxon). It was identified as a metabolite in urine, bile and faeces, although not at very high levels in the studies by Syngenta (≤6.2%; DAR Table B.6.18) and Oxon (8.44-8.85%, DAR Table B.6.19). This metabolite is, however, proposed to be the initial metabolite in the metabolic pathways proposed by both Notifiers (DAR Figures B.6.9 and B.6.10), therefore systemic exposure to the metabolite is therefore likely to be considerably greater than these levels. Consumer exposure to MT1 in drinking water is therefore considered to be adequately covered by the ADI proposed for terbuthylazine.
MT1 is not considered to be a 'relevant metabolite'.

Table 6.4-1: Summary of the results of toxicity studies for MT1 Desethyl-terbuthylazine (GS26379)

Type of test, species	Result	Acceptability	Reference*
Acute oral - RAT	300-500 mg/kg bw	N/A	xxx (2004)
Bacterial mutagenicity (TA1535, TA1537, TA98, TA100, WP2*uvr*A)	Negative	N/A	Verspeek-Rip C.M. (2004)
Gene Mutation Assay- Mouse L5178Y TK+/- cells	Weakly positive	N/A	xxx (2004)
in vivo micronucleus test (rat bone marrow)	Negative	N/A	xxx (2006)
in vivo unscheduled DNA synthesis (rat liver)	Negative	N/A	xxx (2006)
90 day study (rat)	Reduced bodyweight gain Total WBC reduced	N/A	xxx (1971)

No new studies are necessary.

6.4.2 MT13 (hydroxy terbuthylazine) – terbuthylazine metabolite

For metabolite MT13 (2-hydroxy terbuthylazine), simulations gave PECgw values in the range from 0.29 to 14.96 µg/l (peak concentration with FOCUS PEARL Hamburg, 400 g a.s./ha). In the simulations, which used a more conservative formation fraction highest PEC was 14.95 µg/l. 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. **According to the Monitoring Studies for Tebuthylazine in ground water and EFSA Journal 2011; 9(1):1969:**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 conservative approach represent a very conservative assessment and such high concentrations are unlikely to be encountered under realistic use conditions.

Data on biological activity for MT13 (GS23158) have previously been assessed in the original DAR 2008 (Section B.9.9.1.2) and are copied at Attachment 1 of this document for convenience. It was concluded that these metabolites are not herbicidally active.

No new studies have been provided for MT13 in the resubmission(2010). 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.

Table 6.4-2: Summary of the results of toxicity studies for MT13 hydroxy-terbuthylazine (GS 23158)

Type of test, species	Result	Acceptability	Reference*
Acute oral - RAT	LD50 > 2000 mg/kg bw.	N/A	xxx 2001
90-day dietary rats	M: NOAEL and LOAEL of 16.7 and 34.1 mg/kg bw/day, based on decreased bodyweight, changes in clinical chemistry and urinalysis parameters and organ weight effects F: NOAEL and LOAEL of 0.7 and 7.6 mg/kg bw/day, based on altered oestrus cycle length and prolonged oestrus and/or dioestrus	N/A	xxx, 2002
Mutagenicity in bacterial cells (TA1535, TA1537, TA98, TA100, TA102, WP2uvrA	negative	N/A	xxx, 2001
Mouse micronucleus assay (L5178Y cells (TK)	Negative	N/A	xxx, 2001
Clastogenicity (Human lumphocytes)	Negative	N/A	xxx, 2002

No studies are necessary.

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 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.

6.4.3 MT14 desethyl-hydroxy terbuthylazine-terbuthylazine metabolite

For metabolite MT14 (desethyl-hydroxy terbuthylazine), simulations gave PECgw values up to 3.45 µg/l (peak concentration with FOCUS PEARL Hamburg, 400 g a.s./ha) Results represent conserva-

tive first tier exposure estimates. In the field leaching study in Northern Italy, annual average concentrations were found up to 0.38µg/l. In addition, this metabolite was only detected in two wells at concentrations between 0.05 to 0.06µg/l in an extensive and targeted German groundwater program. **According to the Monitoring Studies for Tebuthylazine in ground EFSA Journal 2011; 9(1):1969**:On the basis of the additional information from field leaching and German groundwater monitoring program, it is clear that the first tier FOCUS groundwater exposure assessment represents a very conservative assessment and such high concentrations are unlikely to be encountered under realistic use conditions.

An overview of the results of the accepted toxicological studies for groundwater metabolite MT14 is given in the following table. Full summaries of studies on the metabolite that have not previously been considered within an EU peer review process are described in detail in Appendix 2 (A 2.11 Other/Special Studies).

Table 6.4-3: Summary of the results of toxicity studies for MT14 desethyl-hydroxy terbuthylazine

Type of test, species	Result	Acceptability	Reference*
Acute oral LD50 (rats)	LD50> 2000 mg/kg bw.	N/A	xxx 2000
90-day dietary rats	NOAEL and LOAEL of 10.3 and 45.7 mg/kg bw/day, based on increased mortality and water consumption, changes in haematology, clinical chemistry and urinalysis parameters and increased kidney weight, renal (histo)pathology secondary to chronic renal failure.	N/A	xxx 2001
Mutagenicity in bacterial cells	negative	N/A	xxx 2000
Clastogenicity in CHO (Chinese Hamster Ovary) cells	negative.	N/A	xxx 2001
Mouse Lymphoma assay	negative	N/A	xxx 2000

* indicates that a study was reviewed at EU level

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.

6.4.4 LM1-terbuthylazine metabolite

The Notifiers have studies ongoing with this metabolite. The metabolite does not possess any struc-tural 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 resubmiss on so has not been evaluated.
LM1 also known as ammelide is a mammalian metabolite of melamine. Melamine has a long histo-ry of use in a range of products i.e. in combination with formaldehyde to produce melamine resin as durable thermosetting plastics, and melamine foam, a polymeric cleaning product. Other end products include

countertops, fabrics, glues and flame retardants. It is also a major component of pigment yellow 150 (colorant for inks and plastics), fertilizers, and derivatives of arsenical drugs for the treatment of African sleeping sickness (trypanosomiasis).

Melamine is a metabolite of cyromazine (an Annex I listed active substance see EFSA Scientific Report (2008) 168, 1-94 Conclusion on the peer review of cyromazine). The RMS produced an extensive review of the published literature on melamine and concluded melamine was found to have no toxicological relevance for groundwater according to the guidance document on groundwa-ter metabolites. The RMS proposed to set an ADI of 0.063 mg/kg bw/day for melamine based on the review, however the meeting considered that the ADI of the parent (cyrom zine) should be con-sidered relevant for melamine risk assessment. The ADI for cyromazine was set at 0.06 mg/kg bw/day. Based on this it is likely toxicity of metabolite LM1 is less than that of terbuthylazine and the tested metabolites

6.4.5 LM2-terbuthylazine metabolite

The Notifiers have studies ongoing with this metabolite. 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 Ames test is also available but was concluded too late to be included in the resubmission so has not been considered.

LM2 contains an additional carboxylic acid functional group when compared to terbuthylazine and is a hydroxyl metabolite. Also it does not contain any additional functional groups that are not pre-sent 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 LM2 is less than that of terbuthylazine and the tested metabolites.

6.4.6 LM3-terbuthylazine metabolite

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 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.

6.4.7 LM4-terbuthylazine metabolite

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 me-tabolites (including metabolites MT1, MT13, MT14 and M20 which have been tested for genotoxi-city) and is structurally very similar to MT13 and MT14. An Ames assay is also available but was concluded too late to be included in the resubmission so have not been considered.
The metabolite does not contain any additional functional groups that are not present in ter-buthylazine or its metabolites (including metabolites MT1, MT13, MT14 and M20 which have been tested for genotoxicity) and is structurally very similar to MT13 and MT14 which have been tested for toxicity. Deleted comment assessment relies on consumer assessment below.

6.4.8 LM5-terbuthylazine metabolite

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 con-cluded too late to be included in the resubmission so have not been considered.
The metabolite does not contain any additional functional groups that are not present in ter-buthylazine 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.

6.4.9 LM6-terbuthylazine metabolite

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 conside ed non-genotoxic. The metabolite does not possess any structural alerts for genotoxicity according to DEREK and is structurally similar to MT13 and MT14.
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.

6.4.10 RPA 202248 – Isoxaflutole metabolite

The metabolites of concern, the diketonitrile metabolite (RPA 202248) and the benzoic acid metabolite (RPA 203328) contain a substituted phenyl ring and therefore are not automatically of no concern.

An overview of the results of the accepted toxicological studies for groundwater metabolite RPA202248 is given in the following table. Full summaries of studies on the metabolite that have not previously been considered within an EU peer review process are described in detail in Appendix 2 (A 2.11 Other/Special Studies).

Table 6.4-10: Summary of the results of toxicity studies for RPA 202248

Type of test, species	Result	Acceptability	Reference*
Acute oral toxicity (male & female Sprague-Dawley rats)	LD50 > 5000 mg/kg bw	N/A	-, (1995a)
Bacterial mutagenicity (*Salmonella typhimurium)*	Negative	N/A	xxx, 1995

6.4.11 RPA 203328 – Isoxaflutole metabolite

Table 6.4-11: Summary of the results of toxicity studies for RPA 203328

Type of test, species	Result	Acceptability	Reference
Acute oral toxicity (Rat)	LD50 > 5000 mg/kg	N/A	-, (1995b)

Type of test, species	Result	Acceptability	Reference
	bw		
14-day gavage study (Rat)	NOAEL = 100 mg/kg bw/day LOAEL = 300 mg/kg bw/day	N/A	-, 1994
28-day dietary study (Rat)	NOAEL = 15000 ppm (1117.8/1268.7 mg/kg bw/day, M/F)	N/A	-, 1995
90-day dietary study (Rat)	NOAEL = 12000 ppm (769 / 952 mg/kgbw/day, M / F)	N/A	-,1998
In vitro bacterial reverse mutation Salmonella typhimurium (TA98, TA100, TA1535 and TA1537)	Negative	N/A	xxx, 1994
In vitro chromosomal aberrations (Chinese Hamster Ovary cells)	Negative	N/A	xxx, 1998
In vitro gene mutation (Chinese Hamster Ovary CHO-K1-BH4 cell line)	Negative	N/A	xxx, 1998
In vivo micronucleus MN (Crl:CD-l (ICR) BR mouse bone marrow)	Negative	N/A	-, 1998
Developmental toxicity (Sprague Dawley Crl: CD (SD) BR rat)	Fetal NOAEL = 750 mg/kg bw/day, highest dose tested Maternal NOAEL = 75 mg/kg bw/day	N/A	-, 1999

6.4.12 MNBA – Mesotrione metabolite

An overview of the results of the accepted toxicological studies for groundwater metabolite MNBA is given in the following table. Full summaries of studies on the metabolite that have not previously been considered within an EU peer review process are described in detail in Appendix 2 (A 2.11 Other/Special Studies).

Table 6.4-12: Summary of the results of toxicity studies for MNBA

Type of test, species	Result	Acceptability	Reference
Acute oral toxicity to the rat	LD50 > 5000 mg/kg bw	N/A	-, (1996)
acute dermal toxicity in rats	LD50 > 2000 mg/kg bw	N/A	-, (1996)
28 day oral toxicity study in rats	NOAEL= 1000 mg/kg bw/d	N/A	-,1998
90 day dietary toxicity study in rats	A NOAEL of 650 ppm for males (equivalent to 51 mg/kg bw/d) and 3000	N/A	-,2000

Type of test, species	Result	Acceptability	Reference
	ppm for females (equivalent to 264 mg/kg bw/d) based on decreased bodyweight and food consumption in males at the top dose level of 3000 ppm.		
skin irritation to the rabbit	MNBA was found to be a mild skin irritant in the rabbit.	N/A	-, (1996)
eye irritation to the rabbit	MNBA was found to be a moderate eye irritant.	N/A	-, (1996)
local lymph node assayusing CBA/Ca/Ola/Hsd mice	The application of MNBA at 3 and 10% w/v resulted in an increase in isotope incorporation in excess of 3 times the control value (the laboratory criterion for a positive result). MNBA is therefore considered to be a potential skin sensitiser. Positive results for hexylcinnamaldehyde were seen at all three concentrations,confirming the validity of the assay.	N/A	-, (1996)
An evaluation of mutagenic potential using S.Typhimurium and E.Coli	Negative	N/A	xxx, 1996a
In vitro cytogenetic assay in human lymphocytes	A significant increase in the number of aberrant cells was seen in the absence of S9 at the highest concentration tested, however this finding was not reproducible. No evidence of clastogenicity was seen in this study.	N/A	xxx, 2000a
In vivo rat liver unscheduled DNA synthesis assay	MNBA was not shown to be genotoxic under the conditions of this study	N/A	-, 2000
Rat bone marrow micronucleus test	MNBA was not shown to be genotoxic under the conditions of this study. The use of a single sex is considered to be acceptable	N/A	-, 2000b
Effects of MNBA, a metabolite of ZA1296 on p-Hydroxyphenylpyruvate dioxygenase (HPPD) activity	MNBA was found to cause only slight inhibition of HPPD at the highest concentration investigated in this study.	N/A	Elcombe BM and Meadowcroft S (1998)

Following EU expert discussion (PRAPeR 134) proposed classification for mesotrione asReproduction Cat 2 for developmental effects. Based on this proposal, all groundwater metabolites present at >0.1µg/L are considered as relevant unless it can be demonstrated that they would not produce the effects initiating the classification.

The RMS considers the developmental effects to be related to marked disturbances of tyrosine metabolism. The tyrosine disturbance is secondary to inhibition of p-hydroxyphenylpyruvate dioxygenase (HPPD). In a study of relative potency of HPPD inhibition, MNBA was several orders of magnitude less potent than mesotrione. It is considered that MNBA will not produce disturbance of tyrosine metabolism of sufficient magnitude to induce classifiable developmental effects. It is concluded that MNBA at >0.1 µg/L, in a single scenario, is not a relevant groundwater metabolite of mesotrione.

6.4.13 AMBA– Mesotrione metabolite

An overview of the results of the accepted toxicological studies for groundwater metabolite AMBA is given in the following table.

Table 6.4-13: Summary of the results of toxicity studies for AMBA

Type of test, species	Result	Acceptability	Reference
Acute oral toxicity to the rat	LD50 > 5000 mg/kg bw	N/A	-, (1996)
An evaluation of mutagenic potential using S.Typhimurium and E.Coli	Negative	N/A	xxx, 1996b
In vitro cytogenetic assay in human lymphocytes	No evidence of cytotoxicity was seen in this study A significant increase in the number of aberrant cells in the absence of metabolic activation at an intermediate dose in the initial assay and highest dose in the confirmatory assay.	N/A	xxx (2000c)
Effects of AMBA, a metabolite of ZA1296 on p-Hydroxyphenylpyruvate dioxygenase (HPPD) activity	AMBA was found to cause only slight inhibition of HPPD at the highest concentration investigated in this study	N/A	Elcombe BM and Meadowcroft S (1998)
local lymph node assayusing CBA/Ca/Ola/Hsd mice	The application of MNBA at 3 and 10% w/v resulted in an increase in isotope incorporation in excess of 3 times the control value (the laboratory criterion for a positive result). MNBA is therefore considered to be a potential skin sensitiser. Positive results for hexylcinnamaldehyde were seen at all three concentrations,confirming the validity of the assay.	N/A	-, (1996)

AMBA is of low acute oral toxicity and did not present mutagenic potential in an Ames test; however its genotoxic potential in vivo could not be ruled out due to positive results obtained in an in vitro cytogenetic assay, and no in vivo genotoxicity follow up testing; repeated dose toxicity would also have to be addressed as this metabolite is relevant to consumer risk assessment (see Section 3). As a groundwater metabolite, AMBA is relevant according to stage 3 of step 3 of the guidance document on the assessment of the relevance of metabolites in groundwater (European Commission, 2003a) due to its genotoxic potential and based on the classification of the parent mesotrione as Repr. 2 by the peer review. The RMS disagreed in considering the genotoxic potential of AMBA a critical area of concern.

6.4.14 RPA 202248 – Isoxaflutole metabolite

The metabolites of concern, diketonitrile metabolite (RPA 202248) and benzoic acid metabolite (RPA 203328) contain a substituted phenyl ring and therefore are not automatically of no concern.

An overview of the results of the accepted toxicological studies for groundwater metabolite RPA202248 is given in the following table. Full summaries of studies on the metabolite that have not previously been considered within an EU peer review process are described in detail in Appendix 2 (A 2.11 Other/Special Studies).

Table 6.4-14: Summary of the results of toxicity studies for RPA 202248

Type of test, species	Result	Acceptability	Reference*
Acute oral toxicity (male & female Sprague-Dawley rats)	LD50 > 5000 mg/kg bw		-, (1995a)
Bacterial mutagenicity (*Salmonella typhimurium)*	Negative		xxx, 1995

6.4.15 RPA 203328 – Isoxaflutole metabolite

An overview of the results of the accepted toxicological studies for groundwater metabolite RPA203328 is given in the following table. Full summaries of studies on the metabolite that have not previously been considered within an EU peer review process are described in detail in Appendix 2 (A 2.11 Other/Special Studies).

The mutagenic potential of RPA 203328 was assessed in an Ames assay using Salmonella typhimurium strains TA98, TA100, TA1535 and TA 1537 (xxx, 1995 M-170821-01-1). The material was tested in triplicate at concentrations of 100, 250, 500, 1000, 2500 and 5000 µg/plate in the presence and absence of a metabolic activation system (S9 mix) obtained from livers of rats pre-treated with Aroclor 1254. A cytotoxic effect, as indicated by a thinning of the bacterial background lawn, was noted on a majority of plates containing 2500 and 5000 µg/plate. RPA 203328 did not induce any concentration-dependent, significant increases in the numbers of revertants of any strain at any of the concentrations studied. RPA 203328 was considered non-mutagenic under the conditions of this test.
The mutagenic potential of RPA 203328 was also assessed in two mutagenicity studies using Chinese hamster ovary cells (xxx, 1998 M-157884-01-1, and xxx, 1998 M-189726-01-2), in which the material was tested at concentrations of up to 2700 µg/ml in both the presence and the absence of metabolic activation. There was some cytotoxicity observed in some cultures, but there was no indication of mutagenic activity of RPA 203328 at any concentration. RPA 203328 was therefore considered non-mutagenic un-

der the conditions of this test.

RPA 203328 has very low acute toxicity. The LD50 value for this compound was determined to be greater than the limit value of 5000 mg/kg (xxx, 1995 M-170815-01-1). Additionally, the signs observed during this study are not different from those observed in acute oral toxicity studies performed with other substances, in which the LD50 is greater than the limit dose of 5000 mg/kg.
In the 28-Day Repeated-Dose study with RPA 203328, there were no mortalities, and no treatment-related clinical signs were observed during the study. No effects were seen in body weight, food consumption, or ophthalmological parameters (xxx, 1995 M-170705-01-1). No changes were noted in hematology, clinical chemistry, or urinalysis. At necropsy, no changes were observed macroscopically or in organ weights. Upon histological examination, no changes attributable to RPA 203328 administration were observed in any of the 46 tissues examined. Specifically, there were no signs of hepatic necrosis, hypertrophy, changes in liver enzymes such as AST and ALT, or other adverse findings. The No Observed Effect Level was found to be 15,000 ppm, indicating that the toxicity of RPA 203328 is much lower than the parent and is unlikely to be associated with long-term liver effects. In addition, the lack of liver effects in this study (coupled with the high water solubility of RPA 203328) indicates that RPA 203328 is unlikely to induce hepatic cytochrome P-450 enzymes. This is in contrast to the parent isoxaflutole, which caused hepatocellular hypertrophy, increased liver weight, and induction of both cytochrome P450 and Phase II enzymes.
In a battery of genotoxicity tests conducted using isoxaflutole as the test substance, no evidence of mutagenicity was noted either with or without metabolic activation. The presence of the metabolic activation system would be expected to convert isoxaflutole to its two primary metabolites, RPA 202248 and RPA 203328. The formation of RPA 203328 is an oxidation reaction typically carried out by hepatic enzymes such as the cytochrome P-450 family.
Furthermore, in the 90-day study conducted with RPA 203328 (xxx, 1998 M-240662-01-1), there were no mortalities, clinical signs, or changes in body weight or body weight gain in either males or females, and no effects on either hematological or clinicochemical parameters. There were also no effects of administration of RPA 203328 at doses of up to 12000 ppm on organ weights or histopathology in either sex. At necropsy, there were some findings (dark or yellowish liver, marked lobular liver, and / or dark kidneys) noted in some animals, however there was no consistency of findings between sexes and there were no histopathological correlates to these gross findings. The No Observed Adverse Effect level was found to be 12000 ppm (768.9 mg/kg bw/day in males, 952.4 mg/kg bw/day in females), in contrast to the 90-day study conducted with the parent isoxaflutole, in which the NOEL was established at 3 mg/kg bw/day.
A developmental toxicity study was conducted in the rat with RPA 203328 (xxx, 1999 M-189848-01-1), using doses of 0, 75, 250, and 750 mg/kg bw/day administered by oral gavage on gestation days 6 through 20. Maternal food consumption and body weight gain was decreased at 250 and 750 mg/kg bw/day. Gestation rate, implantation rate, pre- and post-implantation mortality, the number of viable young, and sex ratio were unaffected by administration of RPA 203328. At examination of the fetuses, there was no effect of treatment on fetal body weight, or on external, visceral, or skeletal observations. The maternal NOAEL was 75 mg/kg bw/day, while the fetal NOAEL was 750 mg/kg bw/day, the highest dose tested.
Therefore, RPA 203328 is not capable of causing the fetal effects observed with isoxaflutole, and does not warrant any reproductive classification.
Following the provisions given RPA 203328 cannot be considered as relevant. An exposure and/or risk assessment has to be conducted.

Table 6.4-15: Summary of the results of toxicity studies for RPA 203328

Type of test, species	Result	Acceptability	Reference
Acute oral toxicity (Rat)	LD50 > 5000 mg/kg bw		-, (1995b)
14-day gavage study (Rat)	NOAEL = 100 mg/kg bw/day LOAEL = 300 mg/kg		-, 1994

Type of test, species	Result	Acceptability	Reference
	bw/day		
28-day dietary study (Rat)	NOAEL = 15000 ppm (1117.8/1268.7 mg/kg bw/day, M/F)		-, 1995
90-day dietary study (Rat)	NOAEL = 12000 ppm (769 / 952 mg/kgbw/day, M / F)		-,1998
In vitro bacterial reverse mutation Salmonella typhimurium (TA98, TA100, TA1535 and TA1537)	Negative		xxx, 1994
In vitro chromosomal aberrations (Chinese Hamster Ovary cells)	Negative		Murli, 1998
In vitro gene mutation (Chinese Hamster Ovary CHO-K1-BH4 cell line)	Negative		Cifone, 1998
In vivo micronucleus MN (Crl:CD-l (ICR) BR mouse bone marrow)	Negative		-, 1998
Developmental toxicity (Sprague Dawley Crl: CD (SD) BR rat)	Fetal NOAEL = 750 mg/kg bw/day, highest dose tested Maternal NOAEL = 75 mg/kg bw/day		-, 1999

6.5 Dermal Absorption (KCP 7.3)

A summary of the dermal absorption rates for the active substances in CHR/H/TERIZ are presented in the following table.

Table 6.5-1: Dermal absorption rates for active substances in CHR/H/TERIZ

	Terbuthylazine		Mesotrione		Isoxaflutole	
	Value	Reference	Value	Reference	Value	Reference
Concentrate	10 % default value	Guidance on Dermal Absorption EFSA Journal 2017;15(6):4873	10 % default value	Guidance on Dermal Absorption EFSA Journal 2017;15(6):4873	10 % default value	Guidance on Dermal Absorption EFSA Journal 2017;15(6):4873
Dilution	50 % default value	Guidance on Dermal Absorption EFSA Journal 2017;15(6):4873	50 % default value	Guidance on Dermal Absorption EFSA Journal 2017;15(6):4873	50 % default value	Guidance on Dermal Absorption EFSA Journal 2017;15(6):4873

6.5.1 Justification for proposed values - Terbuthylazine

No data on dermal absorption for Terbuthylazine in CHR/H/TERIZ is available. Justifications for default values according to Guidance on Dermal Absorption (EFSA Journal 2017;15(6):4873) are presented in the following table.

Table 6.5-2: Default dermal absorption rates for Terbuthylazine

	Value	Justification for value	Acceptability of justification
Concentrate	10 % default value	Guidance on Dermal Absorption EFSA Journal 2017;15(6):4873	Accepted
Dilution	50 % default value	Guidance on Dermal Absorption EFSA Journal 2017;15(6):4873	Accepted

* indicates that a study was reviewed at EU level

6.5.2 Justification for proposed values - Mesotrione

No data on dermal absorption for Mesotrione in CHR/H/TERIZ is available. Justifications for default values according to Guidance on Dermal Absorption (EFSA Journal 2017;15(6):4873) are presented in the following table.

Table 6.5-3: Default dermal absorption rates for Mesotrione

	Value	Justification for value	Acceptability of justification
Concentrate	10 % default value	Guidance on Dermal Absorption EFSA Journal 2017;15(6):4873	Acccepted
Dilution	50 % default value	Guidance on Dermal Absorption EFSA Journal 2017;15(6):4873	Accepted

* indicates that a study was reviewed at EU level

6.5.3 Justification for proposed values – Isoxaflutole

No data on dermal absorption for Isoxaflutole in CHR/H/TERIZ is available. Justifications for de-fault values according to Guidance on Dermal Absorption (EFSA Journal 2017;15(6):4873) are presented in the following table.

Table 6.5-4: Default dermal absorption rates for Isoxaflutole

	Value	Justification for value	Acceptability of justification
Concentrate	10 % default value	Guidance on Dermal Absorption EFSA Journal 2017;15(6):4873	Accepted
Dilution	50 % default value	Guidance on Dermal Absorption EFSA Journal 2017;15(6):4873	Accepted

* indicates that a study was reviewed at EU level

6.6 Exposure Assessment of Plant Protection Product (KCP 7.2)

Table 6.6-1: Product information and toxicological reference values used for exposure assessment

Product name and code	CHR/H/TERIZ		
Formulation type	WG		
Category	Herbicide		
Container size(s), short description	500-10000 g, HDPE, bottels/container		
Active substance(s) (incl. content)	**Terbuthylazine** 400 g/kg	**Mesotrione** 150 g/kg	**Isoxaflutole** 100 g/kg
AOEL systemic	0.0032 mg/kg bw/d	0.005 mg/kg bw/d	0.012 mg/kg bw/d
AAOEL	NA	NA	0.03 mg/kg bw
Inhalation absorption	100 %	100 %	100 %
Oral absorption	79% (acc. to EFSA Journal 2014;12(10):3874, p.5.6)	~~100 %~~ 50% (acc. to EFSA Journal 2014;12(10):3874, p.5.6)	60% (acc. to EFSA Journal 2014;12(10):3874, p.5.6)
Dermal absorption	New data on dermal absorption were provided (May, 2019): Concentrate: 1.73% Dilution: 15.3%	Concentrate: 10% Dilution: 50 % (default value)	Concentrate: 10% Dilution: 50 % (default value)

6.6.1 Selection of critical use(s) and justification

The critical GAP used for the exposure assessment of the plant protection product is shown in Table 6.1-4. A list of all intended uses within the zone is given in Part B, Section 0.

6.6.2 Operator exposure (KCP 7.2.1)

Comments of zRMS:	The results of the exposure estimations presented by the Applicant are accepted. **Summary of operator exposure to CHR/H/TERIZ (**Undito 650 WG, Jotamun 650 WG, Metodus 650 WG**):** - Isoxaflutole: The results of the exposure estimations suggest that the use of CHR/H/TERIZ according to the list of intended uses presented in GAP Table, causes **no health risk for the operator if appropriate PPE is used** according to AOEM. - Mesotrione: The results of the exposure estimation suggest that the use of CHR/H/TERIZ according to the list of intended uses presented in GAP Table, causes **no risk for operator using appropriate PPE** according to AOEM. - Terbuthylazine (evaluation acc. to data contained in the Appendix 5): the results

	of the exposure estimation indicate that the use of CHR/H/TERIZ **causes no risk for operator using appropriate PPE** according to AOEM. **Conclusions:** Taking into account data presented above, the use of CHR/H/TERIZ (Undito 650 WG, Jotamun 650 WG, Metodus 650 WG) according to the list of intended uses presented in GAP Table, causes acceptable exposure risk for operator assuming appropriate PPE is used. Based on all of the **exposure data** and the **classification** of CHR/H/TERIZ (Undito 650 WG, Jotamun 650 WG, Metodus 650 WG), the following sentence regarding the use of PPE (gloves and protective clothing) is recommended by the evaluator to be placed in the **section of precautions for operator:** *Stosować rękawice ochronne oraz odzież ochronną zabezpieczającą przed oddziaływaniem środków ochrony roślin i odpowiednie obuwie w trakcie przygotowywania cieczy użytkowej oraz w trakcie wykonywania zabiegu.* Wear protective gloves, protective clothing and sturdy footwear during mixing and loading and during application.

6.6.2.1 Estimation of operator exposure

A summary of the exposure models used for estimation of operator exposure to the active substances during application of CHR/H/TERIZ according to the critical use(s) is presented in Table 6.6-2. Outcome of the estimation is presented in Table 6.6-3. Detailed calculations are in Appendix 3.

Table 6.6-2: Exposure models for intended uses

Critical use	Maize (max. 1 kg product/ha)
Model	"EFSA Model" version 30,03.2015

Table 6.6-3: Estimated operator exposure

Terbuthylazine			
Model data	**Level of PPE**	**Total absorbed dose (mg/kg/day)**	**% of systemic AOEL**
Tractor mounted boom spray application outdoors to low crops Application rate: 0.4 kg a.s./ha			
EFSA Model	no PPE	0.0798	2495
	+PPE (gloves and workwear at mixing/loading)	0.0416	1301
	+ PPE (gloves,workwear and head and respiratory	0.0032	100%

	PPE at mixing/loading and gloves, clothing and head and respiratory PPE during application)		
Mesotrione			
Model data	**Level of PPE**	**Total absorbed dose (mg/kg/day)**	**% of systemic AOEL**
Tractor mounted boom spray application outdoors to low crops Application rate: 0.15 kg a.s./ha			
EFSA Model	no PPE	0.0348	695
	+PPE (gloves and workwear at mixing/loading and gloves during application)	0.0030	60
	+ PPE (gloves,workwear and head and respiratory PPE at mixing/loading and gloves, clothing and head and respiratory PPE during application)	0.002	41
Isoxaflutole			
Model data	**Level of PPE**	**Total absorbed dose (mg/kg/day)**	**% of systemic AOEL**
Tractor mounted boom spray application outdoors to low crops Application rate: 0.1 kg a.s./ha			
EFSA Model	no PPE	0.0182	151.61
	+PPE (gloves and workwear at mixing/loading)	0.0045	37.32
	+ PPE (gloves and workwear at mixing/loading and gloves during application)	0.0014	11.76

* no PPE: Operator wearing T-shirt and shorts

** no PPE: Operator wearing long sleeved shirt, long trousers (“permeable”) but no gloves

The predicted exposure values according to EFSA model for Terbuthylazine, Mesotrione and Isoxaflutole without using PPE and with using PPE at mixing loading are above 100 % AOEL, but with using PPE at mixing/loading and during application are significantly below 100% of systemic AOEL and therefore exposure of the operator is acceptable for mesotrione and isoxaflutole.

AOEL for terbuthylazine with full protective clothing to minimize the risk is close to 100 %. However measurement of operator exposure for terbuthylazine was performed during Annex I Inclusion for EC and SC formulation, which causes more risk to the operator than WG formulation. Please refere to point 6.6.3.

Accordingly, in this case it is advisable to use full protective clothing to minimize the risk.

6.6.3 Measurement of operator exposure

Since the operator exposure estimations for isoxaflutole and mesotrione carried out indicated that the acceptable operator exposure level (AOEL) will not be exceeded under conditions of intended uses and considering above mentioned personal protective equipment (PPE), a study to provide measurements of operator exposure was not necessary and was therefore not performed.

Since operator exposure estimations for terbuthylazine carried out indicated that the acceptable operator exposure level (AOEL) was exceeded under conditions of intended uses, below we refer to the study presented in Additional Report to the DAR, public version, Volume 3, Annex B, part 2, B.6, February 2010, point B.6.14.1.2 Measurement of Exposure. A summary of the study is presented below.

"B.6.14.1.2 Measurement of Exposure (page 151)
A number of operator exposure studies were evaluated for the original submission of Terbuthylazine. Of these, a single study was considered to adequately reflect the proposed conditions of use foe Terbuthylazine products, i.e. that involving the mixing/loading and application of the prosulfocarb product, "Boxer 800 EC" (Tribolet, 2004). The exposure study, conducted in the North-East of Germany, involved the monitoring of exposure for 12 operators mixing/loading and applying the product, which is an emulsifiable concentrate formulation containing 800 g a.s/L. All of the study participants were either professional farm employees, farmers or spray contractors. Applications took place over a 2 week period, covering the end of September to the beginning of October.

The product was applied at the label recommended rate (2.5-5 l product/ha) in water volumes ranging from 100-250 l/ha. Where rates below the maximum individual dose were applied (due to crop requirements), the work rate was increased to achieve an approximate daily volume of product handled and applied of 250 l/day (i.e. equivalent to 5 l/ha x 50ha).

Both trailed and self-propelled sprayers, having a tank capacity 2400 litres to 4000 litres, were used. All vehicles were fitted with closed cabs, although in one case the windows of the cab were open when the spray was applied. Ten of the twelve sprayers were filled using induction bowls during mixing and loading. Nine of the sprayers were re-filled in the field, the other tree from an on farm water supply. The boom width ranged from 18-36m.

In addition to monitoring exposure during the mixing and loading and spray application tasks, any clean-up and repair procedures which were required during the monitoring period were included. Application parameters for the 12 workers are summarised below.

Table B.6.62

Worker number (body weight kg)	Number of mix/load operations	Total time taken mix. and load. (minutes)	Total time taken applying spray (minutes)	Application rate (kg a.s./ha)	Approx. area treated (ha)	Vehicle cab
1 (90)	3	40	206	4	50	Closed
2 (102)	2	52	221	3.9	51	Closed
3 (85)	4	55	316	2.4	80	Closed
4 (115)	4	35	238	2	80	Closed
5 (104)	3	47	254	3.2	60	Closed
6 (67)	4	62	250	2.4	80	Closed
7 (95)	2	37	238	4	53	Closed
8 (100)	2	46	206	4	47	Closed
9 (82)	5	56	354	4	50	Closed
10 (70)	5	49	337	4	50	Closed
11 (103)	4	42	521	3.2	56	Closed
12 (85)	4	85	387	3.2	78	Closed*

*window open

Workers wore standardised sampling garments. The outer dosimeter consisted of a cotton/polyester (long sleeved) coverall. The inner dosimeters consisted of full length cotton underwear (long sleeved T-shirt and long johns) covering the arms, legs and torso. Any additional clothing (worn for warmth) was worn underneath the inner dosimeter. The clothing was unused and issued to the workers prior to the start of the monitoring. Exposure to the head was monitored using face/neck wipes taken at the end of the monitoring period.

Hand exposure (actual) was measured using a hand wash procedure. Hand washes were conducted after each mixing/loading cycle and after each application task. Protective gloves (as recommended on the product label) were worn during mixing/loading. A further set of gloves was issued to workers to use for maintenance and/or repair work during application. Deposit on the protective gloves was measured to determine potential hand exposure.

Inhalation exposure was monitored using personal air sampling equipment. Sampling pumps were calibrated to a sample flow rate of approximately 1.5 l/minute. The air sampler, fitted with XAD-2/OVS sampling tubes was positioned in the breathing zone by attaching it to the collar of the worker.

[...]

Analysis:
Dermal exposure:
Dermal exposure was assessed by analysis of the clothing, gloves and hand wash solutions. The coveralls worn by workers were sectioned prior to analysis. Potential dermal exposure was calculated from exposure on the coveralls, inner dosimeter, face/neck wipes, gloves and hand wash. Actual dermal exposure was represented by the inner dosimeter, face/neck wipes and hand wash.
Inhalation exposure:
Potential inhalation exposure was determined by analysis of the glass fibre filter and first XAD-2 layer (front layer) and the polyurethane foam and second XAD-2 layer (back layer). The front and back sampling layers were analysed separately to show if breakthrough had occurred.
Method of analysis:
Sample of the outer and inner dosimeter and face/neck wipes were extracted using hexane. Hand wash solutions were partitioned with hexane. The hexane was evaporated and the residues resuspended in a acidified methanol before analysis by HPLC-MS/MS. Protective glove sample were extracted using methanol, resuspended in methanol and aqueous formic acid before analysis by HPLC-MS/MS. Glass fibre and XAD air samplers were extracted with acetonitrile then diluted with aqueous formic acid before analysis by HPLC-MS/MS.
Field /travel recovery:
Field fortifications were prepared for each of the 5 days of exposure monitoring. […] The whole body dosimeter samples were exposed to field conditions for the exposure monitoring period in an upwing locations, away from possible contamination.[…]

Observation of work and hygiene practices
[…] All of the workers complied with the directions given on the product label (i.e. gloves to be worn when mixing/loading). The workers followed good occupational hygiene by wearing (new) protective gloves when performing repairs or maintenance tasks during applications of the spray solution. Whilst several of these workers were required to perform some sort of repair or maintenance, these were of a minor nature and no significant equipment failures were reported.
Significant foaming during filling was reported for two of the workers (11 and 12), with the external surface of both spray tanks becoming contaminated as foam flowed out from the top of the tank.[…] These incidents and the subsequent contamination of the sprayers are expected to have been significant contamination events for both workers, noting that both had high hand and coverall exposures compared to the other workers.

It appeared that unseasonable weather was responsible for worker 12 choosing to open the cab windows during spraying. In addition, this worker exposed the inner dosimeter by opening the front of his coveralls and also attempting to roll up the sleeves and legs of the coveralls. These observations provide some possible explanations for the high ADE values measured for this worker.

Results:

Procedural recovery

Clothing dosimeter fortified at 0.5-2500 µg, nitrole gloves at 5-2500 µg, wipes at 0.5-100 µg, hand wash solutions at 0.0005-0.1 mg/l and air sampling tube matrix at 0.05-10 µg gave acceptable procedural recoveries (averages in the range 93-103 %, n-78). The appropriately validated levels of quantitation were 5 µg (outer dosimeter, nitrile gloves), 0.5 µg (inner dosimeter, wipes), 0.005 µg/l (hand wash solution) and 0.05 µg (air sampling adsorbent).

[…]

Operator exposure

A summary of the potential dermal exposure (PDE), actual dermal exposure (ADE) and potential inhalation exposure (PIE) for each operator is presented below.[…] This is the value given for light work which includes mixing/loading with containers of less than 23 kg. The PIE results have therefore been revised to reflect this slightly higher breathing rate.

Table B.6.65 Summary of operator exposure for prosulfocarb

Operator	Body weight (kg)	Total PDE (mg/person)	Total ADE (mg/person)	PIE (mg/person)
1	90	43.90	0.165	0.003
2	102	31.34	0.045	0.002
3	85	205.03	1.190	0.030
4	115	35.60	0.101	0.005
5	104	318.9	0.812	0.014
6	67	62.76	0.130	0.020
7	95	32.56	0.019	0.005
8	100	50.07	0.233	0.025
9	82	100.66	0.473	0.014
10	70	31.83	0.191	0.007
11	103	346.74	1.719	0.011
12	85	809.3	7.823	0.071

1.Potential dermal exposure in calculated from exposure on the coveralls, inner dosimeter, face/neck wipes, gloves and hand wash.
2.Actual dermal exposure is calculated from inner dosimeter, face/neck wipes and hand wash.
3.PIE is calculated from the average sampling rate of 1.48 litres/minute and a breathing rate of 16.7 litres/minute.

Discussion:

Levels of potential dermal exposure, which reflect protective coveralls and gloves worn when mixing/loading and when performing any maintenance and/or repairs during spraying, range from 31 mg per person to 809 mg per person. As expected, the outer dosimeter (coverall) and protective gloves worn during mixing/loading contribute most towards the total PDE for each operator (66% to <90%). Worker 12 had the highest levels of PDE. Most of this exposure was measured on the protective gloves worn during mixing/loading. It is noted that this worker operated a sprayer which required tank top loading and that the extremal surfaces of the spray tank became contaminated (by foam). These factors are expected to have contributed to the high levels of glove exposure for this worker. Worker 3 has the highest coverall exposure. From the limited information on worker practice provided there is no obvious explanation for this result.

Acute dermal exposure for all workers was significantly lower that then respective PDE values (<1% for all workers). It is noted that new clothing and gloves had been issued to these workers, hence these ADE

values reflect the higher level of protection provided by such items PPE. Worker 12 also had the highest ADE value (7.8 mg)[…]. It is reported that this worker opened the front of their coverall and sprayed with the cab windows open.[…] Worker 11 has the highest hand exposure (at mixing/loading). This is possibly attributes to the foaming incident experienced when filing the sprayer. For inhalation exposure, the mixing/loading and application tasks were monitored separately. Levels of PIE during mixing/loading and application were generally lower than those measured during application of the spray.[…] Whilst level of PIE were low in comparison with levels of ADE, as dermal absorption for prosulfocarb is low (0.1% for the concentrate and 2% for the spray dilution), PIE contributes significantly to the total absorbed dose calculated for each worker (24% to 93%).
[…]

Potential Dermal Exposure (PDE) is calculated from exposure on the coveralls, inner dosimeter, face/neck wipes, protective gloves and hand wash.

Actual dermal exposure (ADE) mixing/loading is calculated from the hand wash during mixing/loading. ADE application is calculated from exposure on the inner dosimeter and face/neck wipes (mixing/loading and application) and from the hand washes taken after the application task.

Potential inhalation exposure (PIE) in calculated from the average sampling rate of 1.48 litres/minute and a breathing rate of 16.7 litres/minute.

Whilst the application rate used in the prosulfocarb study (4 kg a.s/ha) is significantly higher than the rates of use proposed for "Terbuthylazine 500 SC" and "AC9476C" (844-850 g a.s/ha), as it is uncertain for these data whether exposure is directly proportional to the amount of a.s applied, the exposure values have not been normalised. Systemic exposure for operators applying the Terbuthylazine containing products is predicted assuming the relevant dermal absorption values for each. The extrapolated data are presented in tables B.6.67. and B.6.68. […]."

According to Final Addendum to the Additional Report, public version for Terbuthylazine, September 2010, Addendum 3 to Volume 3 to the AR, values AOEL was changed from 0.004 mg/kg bw/d to 0.0032 mg/kg bw/d. Therefore, in the tables below are the results with regard to the current AOEL.

"B.6.14 Exposure data (page 93)
In the meeting of experts (PRAPeR 81), it was agreed that the proposed AOEL of 0.004 mg/kg bw/d should be amended in light of the lower oral absorption of 79%. The new value is **0.0032 mg/kg bw/d.**

B.6.14.1 Operator exposure
The exposures predicted for the Additional Report still apply, but need to be compared with the new AOEL.
[…]

Table B.6.13 Extrapolated exposure to terbuthylazine for 'Terbuthylazine 500SC', based on the study with 'Boxer 800EC'

Operator	Body weight (kg)	Total PDE (mg/person)	Total ADE (mg/person)	PIE (mg/person)	Systemic exposure (ADE+PIE) (mg/kg bw/day)	Absorbed dose as a % of the AOEL
1	90	43.90	0.165	0.003	0.0001	3%
2	102	31.34	0.045	0.002	0.00003	1%
3	85	205.03	1.190	0.030	0.0007	22%
4	115	35.60	0.101	0.005	0.0001	3%
5	104	318.9	0.812	0.014	0.0003	9%
6	67	62.76	0.130	0.020	0.0003	9%

7	95	32.56	0.019	0.005	0.0001	3%
8	100	50.07	0.233	0.025	0.0003	9%
9	82	100.66	0.473	0.014	0.0003	9%
10	70	31.83	0.191	0.007	0.0002	6%
11	103	346.74	1.719	0.011	0.0003	9%
12	85	809.3	7.823	0.071	0.0031	97%
MAX		809.33	7.823	0.071	0.0031	97%

PDE Potential dermal exposure (as. determined from outer dosimeter)
ADE Actual dermal exposure (as. determined from inner dosimeter)
PIE Potential inhalation exposure (as. determined from personal air sampler)

Table B.6.14 Extrapolated exposure to terbuthylazine for 'AC9476C, based on the study with 'Boxer 800EC'

Operator	Body weight (kg)	Total PDE (mg/person)	Total ADE (mg/person)	PIE (mg/person)	Systemic exposure (ADE+PIE) (mg/kg bw/day)	Absorbed dose as a % of the AOEL
1	90	43.90	0.165	0.003	0.0001	3%
2	102	31.34	0.045	0.002	0.00003	1%
3	85	205.03	1.190	0.030	0.0005	16%
4	115	35.60	0.101	0.005	0.0001	3%
5	104	318.9	0.812	0.014	0.0002	6%
6	67	62.76	0.130	0.020	0.0003	9%
7	95	32.56	0.019	0.005	0.0001	3%
8	100	50.07	0.233	0.025	0.0003	9%
9	82	100.66	0.473	0.014	0.0003	9%
10	70	31.83	0.191	0.007	0.0001	3%
11	103	346.74	1.719	0.011	0.0002	6%
12	85	809.3	7.823	0.071	0.0021	66%
MAX		809.33	7.823	0.071	0.0021	66%

PDE Potential dermal exposure (as. determined from outer dosimeter)
ADE Actual dermal exposure (as. determined from inner dosimeter)
PIE Potential inhalation exposure (as. determined from personal air sampler)

For a relatively small surrogate dataset, it is appropriate to consider the maximum exposure values, especially in light of the fact that the maximum values was used during the Annex I review of prosulfocarb and the activities of the operator for whom these exposures were obtained were not considered to be out of the ordinary. For both products, it is evident that these maximum predicted exposures are within the AOEL."

The study of determination of dermal and inhalation exposure to operators during mixing/loading and application (Tribolet R, 2004. Determination of dermal and inhalation exposure to operators during mixing/loading and application using Boxer 800 EC (Amplifiable Concentrate formulation of 800 g/l prosulfocarb, A 8545) with vehicle mounted ground boom sprayer in cereals. RCC Ltd, Environmental Chemistry & Pharmanalytics, Switzerland. RCC Study Number: 856713.) was conducted on the formulation of EC, than extrapolated to formulation SC.
Both the EC formulation and the SC formulation are a liquid formulations, which is expected to be more toxic than solid formulations, eg. WG. Additionaly, in product "Terbuthylazine 500 SC" the content of a.s is 500 g/l (application rate 850 g terbuthylazine/ha, 1.7 L product/ha), in product CHR/H/TERIZ 650 WG the content of a.s. is 400 g/kg (application rate 400 g terbuthylazine/ha, 1 kg product/ha). The predicted exposure values according to German model with using PPP at mixing/loading and during application are below 100% of systemic AOEL and therefore exposure of the operator is acceptable. Therefore, we as-

sume that presented study are the worst case, and thus the product CHR/H/TERIZ is in the risk envelope and the predicted exposure for operators are acceptable.

6.6.4 Worker exposure (KCP 7.2.3)

Comments of zRMS:	The results of worker exposure estimations to terbuthylazine* (400 g.kg), isoxaflutole (100 g/kg) and mesotrione (150 g/kg) contained in the formulation CHR/H/TERIZ presented by the Applicant are accepted. **Conclusions:** The results of the exposure estimations based on EUROPOEM II suggest that the use of CHR/H/TERIZ (Undito 650 WG, Jotamun 650 WG, Metodus 650 WG) according to the list of intended uses presented in GAP Table, causes **no health risk for the worker** assuming: - the workwear (arms, body and legs covered) and protective gloves are used, - the time of worker activities (inspection) is limited to 2 hours. Following sentence regarding the use of PPE is recommended by the evaluator to be placed in the **section of precautions for the workers:** „*Stosować rękawice ochronne oraz odzież roboczą (długie spodnie, koszula z długim rękawem) oraz ograniczyć czas inspekcji terenu poddanego opryskowi do 2 godzin.* “Wear protective gloves and workwear (long trousers, long-sleeve shirt) and limit the time of inspection of treated area to 2 hours”. **The exposure assessment using refined DFR for foliar deposits of terbuthylazine is not accepted in case of the use on the bare soil (BBCH 00) /previous evaluation provided in 2017 and finished in 2019/. Assuming the inspection time is limited to 2 hours, the exposure to terbuthylazine contained in CHR/H/TERIZ is acceptable because it amounts to 96% of AOEL for this active substance.*

Only new data for isoxaflutole is presented.

6.6.4.1 Estimation of worker exposure

Table 6.6-4 shows the exposure model(s) used for estimation of worker exposure after entry into a previously treated area or handling a crop treated with CHR/H/TERIZ according to the critical use(s). Outcome of the estimation is presented in Table 6.6-5. Detailed calculations are in Appendix 3.

Table 6.6-4: Exposure models for intended uses

Critical use(s)	Maize (max. 1 kg product/ha)
Model	EUROPEM II

Table 6.6-5: Estimated worker exposure

		Terbuthylazine	
Model data	**Level of PPE**	**Total absorbed dose (mg a.s /day)**	**% of systemic AOEL**
Number of applications and application rate:		0.4 kg a.s./ha	
2 hours/day (1), TC: 2500 cm^2/person/h (2) Body weight: 60 kg DFR 30mg a.s/m2. (default)	no PPE (3)	3.000	~~1667~~1563
	with PPE (gloves)	0.600	~~333~~313

		Terbuthylazine	
Model data	**Level of PPE**	**Total absorbed dose (mg a.s /day)**	**% of systemic AOEL**
Number of applications and application rate:		0.4 kg a.s./ha	
2 hours/day (1), TC: 2500 cm^2/person/h (2) Body weight: 60 kg DFR 2.34 mg a.s/m2. Based on DT50 2.8 days for foliar deposits on maize. Cross reference: Terbuthylazine – Additional report Annex B6 page 167. And Additional report Annex B9 B.9.1.3.3.2.i	no PPE (3)	0.234	~~130~~122
	with PPE (gloves)	0.047	~~26~~24

		Mesotrione	
Model data	**Level of PPE**	**Total absorbed dose (mg a.s /day)**	**% of systemic AOEL**
Number of applications and application rate:		0.15 kg a.s./ha	
2 hours/day (1), TC: 2500 cm^2/person/h (2) Body weight: 60 kg DFR 30mg a.s/m2. (default)	no PPE (3)	1.125	375
	with PPE (4)	0.225	75

		Isoxaflutole	
Model data	**Level of PPE**	**Total absorbed dose (mg a.s /day)**	**% of systemic AOEL**
Number of applications and application rate:		0.1 kg a.s./ha	
8 hours/day (1), TC: 2500 cm^2/person/h (2) Body weight: 60 kg DFR 30mg a.s/m2. (default)	no PPE (3)	0.0625	520.83
	with PPE (4)	0.007	58.33

(1) 8 h/day hours for harvesting and maintenance type activities and 2h/day for crop inspection and irrigation-type activities
(2) Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products, EFSA Journal 2014;12(10):3874
(3) no PPE: Worker wearing long sleeved shirt, long trousers ("permeable"), covered body, but no gloves
(4) with PPE: type of PPE / see 'Instructions for use'

Having regard to the above values, the predicted exposure values for terbuthylazine,mesotrione and isoxaflutole without PPP are above 100%, but with using PPP are significantly below 100% of systemic AOEL and therefore exposure of the worker with using PPP is acceptable.
The use of CHR/H/TERIZ 650 WG pose no risk to worker.

6.6.4.2 Refinement of generic DFR value (KCP 7.2)

Based on DT50 2.8 days for foliar deposits on maize for terbuthylazine the DFR was calculated to be DFR 2.34 mg a.s/m2 based on the equation:

$$DFR(t) = DFR \times e^{(-\ln(2)/DT50) \times t} = 2.34\ \mu g/cm^2/kg\ a.s./ha$$

Cross reference: Terbuthylazine – Additional report Annex B6 page 167. And Additional report Annex B9 B.9.1.3.3.2.i

6.6.4.3 Measurement of worker exposure

Since the worker exposure estimations for carried out indicated that the acceptable operator exposure level (AOEL) will not be exceeded under conditions of intended uses and considering above mention PPE, a study to provide measurements of worker exposure was not necessary and was therefore not performed.

6.6.5 Bystander and resident exposure (KCP 7.2.2)

Comments of zRMS:	Terbuthylazine and mesotrione: According to the current guidelines of Polish Authorities, the preferred calculation model for bystander and resident exposure estimation is AOEM (for all applications submitted or updated after the 1th of March 2017). The calculations for mesotrione and terbuthylazine presented in the table 6.6 7 has been corrected by the evaluator in the previous evaluation (provided in 2017 and finished in 2019). The summary and conclusions are presented below. Isoxaflutole: The reference value acutely toxic active substance (RVAAS/AAOEL) for isoxaflutole is allocated and amounts to 0.03 mg/kg bw[1,2]. Thus, the calculation of bystander exposure has

	been provided by the Applicant. The presented calculations for bystander and resident are accepted. The reference values acutely toxic active substance (RVAAS) for the terbuthylazine and mesotrione in CHR/H/TERIZ are not allocated. Consequently, it is assumed that the estimation of bystander exposure is covered by the calculation of resident exposure towards these active substances. **Summary of bystander/resident exposure to CHR/H/TERIZ**: - **Mesotrione** and **terbuthylazine**: The results of the exposure estimations suggest that the use of CHR/H/TERIZ according to the list of intended uses presented in GAP Table, causes **unacceptable health risk for bystander and resident (both adult and child)** according AOEM (**minimal buffer zone: 5m**). However, it should be noted that the majority of the exposure is supposed to occur if the resident/bystander enters into the treated area. Thus, the incidental short-time exposure of bystander and resident (children and adult) to mesotrione is acceptable if the **warning boards** preventing from resident/bystander entry into treated area are installed and remain till the end of cultivation. - **Isoxaflutole**: The results of the exposure estimations suggest that the use of CHR/H/TERIZ according to the list of intended uses presented in GAP Table, **causes acceptable health risk for bystander and resident adult and child (buffer zone: 5m).** **Conclusions:** **1.** The exposure of resident and bystander (children and adult) to isoxaflutole contained in the CHR/H/TERIZ causes acceptable risk to human health. **2.** The exposure to isoxaflutole contained in the CHR/H/TERIZ causes **acceptable risk to human health** when: - **warning boards preventing from bystander entry into treated area are installed** and remain till the end of cultivation - **5-meter buffer zone** is kept during spraying, - **drift-reduction** nozzles are used. [1] *SANTE/11653/2017 Rev 2, 22 March 2019* [2] *EFSA Journal 2017;15(2):4731*

Only new data for isoxaflutole is presented.

6.6.5.1 Estimation of bystander and resident exposure

Table 6.6-6 shows the exposure model(s) used for estimation of bystander and resident exposure to terbuthylazine, mesotrione and isoxaflutole. Outcome of the estimation is presented in Table 6.6-7. Detailed calculations are in Appendix 3.

Table 6.6-6: Exposure models for intended uses

Critical use(s)	maize (max. 1/ kg product/ha)
Model	„German model" (Estimation of bystander and resident exposure(adults and children).

Table 6.6-7: Estimated bystander and resident exposure

	Terbuthylazine		**Mesotrione**		**Isoxaflutole (in EFSA MODEL)**	
Model data	**Total absorbed dose (mg/kg/day)**	**% of systemic AOEL**	**Total absorbed dose (mg/kg/day)**	**% of systemic AOEL**	**Total absorbed dose (mg/kg/day)**	**% of systemic AOEL**
Tractor mounted boom spray application outdoors to low crops						
Application rate:	0.4 kg a.s./ha		0.15 kg a.s./ha		0.1 kg a.s./ha	
Bystanders (adult) Drift rate: 0.57 % (5 m) Body weight: 60 kg	0.0019000	59.43	0.0007132	14.26	0.0042	35.27%
Bystanders (children) Drift rate: 0.57 % (5 m) Body weight:16.5 kg	0.0014824	46.45	0.0005574	11.15	0.0092	76.30%
Residents (adult) Drift rate: 0.57 % (5 m) Body weight: 60 kg	0.0004149	12.96	0.0003282	6.56	0.0042	35.27%
Residents (children) Drift rate: 0.57 % (5 m) Body weight:16.5 kg	0.0007334	22.92	0.0005966	11.93	0.0092	76.30%

After the renewal of isoxaflutole, AAOEL of 0.03 mg/kg bw was allocated. Therefore, risk assessment of bystander exposure was calculated.

Table 6.6-8: Estimated bystander exposure

	Isoxaflutole (AOEM)			
Model data	**Total absorbed dose (mg/kg/day)**	**% of systemic AOEL**	**Total absorbed dose (mg/kg/day)**	**% of systemic AOEL**
	child		**adult**	
Tractor mounted boom spray application outdoors to low crops Buffer strip: 5 m				
Application rate:	0.1 kg a.s./ha			
Spray drift	0.0098815	32.94%	0.0019515	6.51%
Vapour	0.0010700	3.57%	0.0002300	0.77%

Surface deposits	0.0009975	3.33%	0.0004229	1.41%
Entry into treated crops	0.0084375	28.13%	0.0046875	15.63%

6.6.5.2 Measurement of bystander and/or resident exposure

Since the bystander and resident exposure estimations carried out indicated that the acceptable operator exposure level (AOEL) for terbuthylazine, mesotrione and isoxaflutole will not be exceeded under conditions of intended uses and considering above mentioned risk mitigation measures, a study to provide measurements of bystander/resident exposure was not necessary and was therefore not performed.

6.6.6 Combined exposure

The product is a mixture of three active substances.
From a scientific point of view it is regarded necessary to take into account potential combination effects. However, the evaluation of cumulative or synergistic effects as requested by Art. 4 (3b) of Regulation (EC) No. 1107/2009 should only be performed when harmonised “scientific methods accepted by the Authority to assess such effects are available.”

6.6.6.1 Exposure Assessment of terbuthylazine, mesotrione and isoxafutole in CHR/H/TERIZ.

From a scientific point of view it is regarded necessary to take into account potential combination effects. However, the evaluation of cumulative or synergistic effects as requested by Art. 4 (3b) of Regulation (EC) No. 1107/2009 should only be performed when harmonised “scientific methods accepted by the Authority to assess such effects are available.”

Appendix 1 Lists of data considered in support of the evaluation

List of data submitted by the applicant and relied on

Data point	Author(s)	Year	Title Company Report No. Source (where different from company) GLP or GEP status Published or not	Vertebrate study Y/N	Owner
KCP 7.1.1	xxx	2016	CHR/H/TERIZ 650 WG Acute oral toxicity study on rats – fixed dose method. xxx, xxx, Poland Study code: PO-7/16 GLP - yes Unpublished	Y	Chemirol
KCP 7.1.2	xxx	2016	CHR/H/TERIZ 650 WG Acute dermal toxicity study on rats. xxx, xxx, Poland Study code: DER-8/16 GLP – yes Unpublished	Y	Chemirol
KCP 7.1.4	xxx	2016	CHR/H/TERIZ 650 WG *In vitro* skin corrosion: Transcutaneous electrical resistance test (TER)	Y	Chemirol

Data point	Author(s)	Year	Title Company Report No. Source (where different from company) GLP or GEP status Published or not	Vertebrate study Y/N	Owner
			xxx, Poland Study code: OES-14/16 GLP – yes Unpublished		
KCP 7.1.4	Andres I.	2016	Determination of skin irritation potential of CHR/H/TERIZ 650 WG in the reconstructed human epidermis (RHE) LAUS GmbH, Kirrweiler, Germany Study code: GLP – yes Unpublished	N	Chemirol
KCP 7.1.5	xxx	2016	CHR/H/TERIZ 650 WG Isolated Chicken Eye Test Method for Identifying i) Chemicals Including Serious Eye Damage and ii) Chemicals Not Requiring Classifications for Eye Irritation or Serious Eye Damage xxx, Poland Study code: ICE-14/16 GLP – yes Unpublished	Y	Chemirol
KCP 7.1.5	xxx	2016	CHR/H/TERIZ 650 WG Acute eye irritation/corrosion study on rabbits.	Y	Chemirol

Data point	Author(s)	Year	Title Company Report No. Source (where different from company) GLP or GEP status Published or not	Vertebrate study Y/N	Owner
			xxx, Poland Study code: ODR-10/16 GLP – yes Unpublished		
KCP 7.1.6	xxx	2016	CHR/H/TERIZ 650 WG Skin Sensitization Study. xxx, Poland Study code: AL-4/16 GLP – yes Unpublished	Y	Chemirol

List of data submitted or referred to by the applicant and relied on, but already evaluated at EU peer review

Data point	Author(s)	Year	Title Company Report No. Source (where different from company) GLP or GEP status Published or not	Vertebrate study Y/N	Owner
KCP 7.2.1.1	Tribolet R.	2004	Determination of dermal and inhalation exposure to operators during mixing/loading and application using Boxer 800 EC (Amplifiable Concentrate formulation of 800 g/l prosulfocarb, A 8545) with vehicle mounted ground boom sprayer in cereals. RCC Ltd, Environmental Chemistry & Pharmanalytics,	N	SYN

			Switzerland. RCC Study Number: 856713. Additional Report to the DAR, public version, Volume 3, Annex B, part 2, B.6, February 2010 GLP Published		
KCP 7.0/01	Verspeek-Rip. C.M.	2002	EVALUATION OF THE MUTAGENIC ACTIVITY OF 2-HYDROXY-TERBUTHYLAZIONE IN THE SALMONELLA TYPHIMURIUM REVERSE MUTATION ASSAY AND THE ESCHERICHIA COLI REVERSE MUTATION ASSAY (WITH INDEPENDENT REPEAT) Notox B.V s'Hertogenbosch, The Netherlands Report N. 335543 Oxon Italia S.p.A, Pero, Italy GLP: yes published: no	N	OXN
KCP 7.0/02	Verspeek-Rip. C.M.	2002	EVALUATION OF THE MUTAGENIC ACTIVITY OF 2-HYDROXY-TERBUTHYLAZINE IN AN *IN VITRO* MAMMALIAN CELL GENE MUTATION TEST WITH L5178Y MOUSE LYMPHOMA CELLS (WITH INDEPENDENT REPEAT) Notox B.V s'Hertogenbosch, The Netherlands Report N. 335554 Oxon Italia S.p.A, Pero, Italy GLP: yes published: no	N	OXN
KCP 7.0/03	xxx	2002	ASSESSMENT OF ACUTE ORAL TOXICITY WITH 2-HYDROXY-TERBUTHYLAZINE IN THE RAT (ACUTE CLASS METHOD) [redacted] Report N. 335532 Oxon Italia S.P.A, Pero, Italy GLP: yes published: no	Y	OXN

KCP 7.0/04	Meerts I.	2002	EVALUATION OF THE ABILITY OF 2-HYDROXY-TERBUTHYLAZINE TO INDUCE CHROMOSOME ABERRATIONS IN CULTURED PERIPHERAL HUMAN LYMPHOCYTES Notox B.V s'Hertogenbosch, The Netherlands Report N. 335565 Oxon Italia S.p.A, Pero, Italy GLP: yes published: no	N	OXN
KCP 7.0/05	xxx	2003	2-HYDROXY-TERBUTHYLAZINE: REPEATED DOSE 90 DAY ORAL TOXICITY STUDY IN WISTAR RATS [redacted] Report N. 3345-01 Oxon Italia S.p.A, Pero, Italy GLP: yes published: no	Y	OXN
KCP 7.0/06	xxx	2001	GS 28620 TECH. (METABOLITE OF GS 13529) - 90-DAY ORAL TOXICITY STUDY IN RATS (ADMINISTRATION IN FOOD), [redacted] [redacted]20001005, 14.12.2001	Y	OXN (SYN access)
KCP 7.0/07	xxx	2001	GS 23158 (METABOLITE OF GS 13529): L5178Y TK+/- MOUSE LYMPHOMA MUTATION ASSAY,[redacted] CTL/VV0268/REG/REPT / 20011055, 12.12.2001	Y	OXN (SYN access)
KCP 7.0/08	Deparade E.	2000	GS 28620 (METABOLITE OF GS 13529) - SALMONELLA AND ESCHERICHIA/MAMMALIAN-MICROSOME MUTAGENICITY TEST, Novartis Crop Protection AG, Stein, Switzerland, 20001001, 21.08.2000	N	OXN (SYN access)

KCP 7.0/09	Deparade E.	2001	GS 23158 TECH. (METABOLITE OF GS 13529) - SALMONELLA AND ESCHERICHIA/MAMMALIAN-MICROSOME MUTAGENICITY TEST, Syngenta Crop Protection Ag, Stein, Switzerland, 20011054, 12.12.2001	N	OXN (SYN access)
KCP 7.0/10	Fox V.	2002	GS 23158: IN VITRO CYTOGENETIC ASSAY IN HUMAN LYMPHOCYTES, Central Toxicology Laboratory (CTL), Cheshire, United Kingdom, CTL/SV1087/REG/REPT, 18.01.2002	N	OXN (SYN access)
KCP 7.0/11	Lloyd M.	2000	GS 28620 (METABOLITE OF GS 13529): MUTATION AT THE THYMIDINE KINASE (TK) LOCUS OF MOUSE LYMPHOMA L5178Y CELLS (MLA) USING THE MICROTITRE FLUCTUATION TECHNIQUE, [redacted] 252/268-D5140 / 20001002, 16.05.2000	N	OXN (SYN access)
KCP 7.0/12	Marshall R.	2001	GS 28620 (METABOLITE OF GS 13529): INDUCTION OF CHROMOSOME ABERRATIONS IN CULTURED CHINESE HAMSTER OVARY (CHO) CELLS, Covance Laboratories, North Yorkshire, United Kingdom, 252/269-D6172 / 20001003, 07.03.2001	N	OXN (SYN access)
KCP 7.0/13	xxx	2000	GS 28620 TECH. (METABOLITE OF GS 13529) - ACUTE ORAL TOXICITY IN THE RAT (LIMIT TEST), [redacted] 20001004, 03.02.2000	Y	OXN (SYN access)
KCP 7.0/14	xxx	2001	GS 23158 TECH. (METABOLITE OF GS 13529) - ACUTE ORAL TOXICITY IN THE RAT (LIMIT TEST), [redacted] 20011053, 25.04.2001	Y	OXN (SYN access)

KCP 7.0/15	xxx	2002	GS 23158 TECH. (METABOLITE OF GS 13529) - 90-DAY ORAL TOXICITY STUDY IN RATS (ADMINISTRATION IN FOOD), [redacted]20011058, 18.12.2002	Y	OXN (SYN access)
KCP 7.0/16	xxx	2000	GS 28620 tech. (Metabolite of GS 13529) – Acute oral toxicity in the rat (Limit test) Novartis Crop Protection AG, Basel, Switzerland [redacted] [redacted]Report No 20001004 GLP Not Published Syngenta File N° GS28620/0005	Y	SYN
KCP 7.0/17	xxx	2001	GS 28620 tech. (Metabolite of GS 13529) – 90-Day oral toxicity study in rats (Administration in food) Syngenta Crop Protection AG, Basel, Switzerland [redacted] [redacted]Report No 20001005 GLP Not Published Syngenta File N° GS28620/0012	Y	SYN
KCP 7.0/18	Deparade E.	2000	GS 28620 (Metabolite of GS 13529) – Salmonella and Escherichia/mammalian-microsome mutagenicity test Novartis Crop Protection AG, Basel, Switzerland Novartis Crop Protection AG, Stein, Switzerland, Report No 20001001 GLP Not Published Syngenta File N° GS28620/0010	N	SYN

KCP 7.0/19	Lloyd. M	2000	GS 28620 (Metabolite of GS 13529): Mutation at the thymidine kinase (tk) locus of mouse lymphoma L5178Y cells (MLA) using the microtitre fluctuation technique Novartis Crop Protection AG, Basel, Switzerland [redacted] [redacted] Report No 252/268-D5140 / 20001002 GLP Not Published Syngenta File N° GS28620/0007	N	SYN
KCP 7.0/20	Marshall R.	2001	GS 28620 (Metabolite of GS 13529): Induction of chromosome aberrations in cultured Chinese hamster ovary (CHO) cells Syngenta Crop Protection AG, Basel, Switzerland Covance Laboratories, North Yorkshire, United Kingdom, Report No 252/269-D6172 / 20001003 GLP Not Published Syngenta File N° GS28620/0011	N	SYN
KCP 7.0/21	xxx	2001	GS 23158 tech. (Metabolite of GS 13529) – Acute oral toxicity in the rat (Limit test) Syngenta Crop Protection AG, Basel, Switzerland [redacted] [redacted] Report No 20011053 GLP Not Published Syngenta File N° GS23158/0010	Y	SYN

KCP 7.0/22	xxx	2002	GS 23158 tech. (Metabolite of GS 13529) – 90-day oral toxicity study in rats (Administration in food) Syngenta Crop Protection AG, Basel, Switzerland [redacted] Report No 20011058 GLP Not Published Syngenta File N° GS23158/0020	Y	SYN
KCP 7.0/23	Deparade E.	2001	GS 23158 tech. (Metabolite of GS 13529) – Salmonella and Escherichia/mammalian-microsome mutagenicity test Syngenta Crop Protection AG, Basel, Switzerland Syngenta Crop Protection AG, Stein, Switzerland, Report No 20011054 GLP Not Published Syngenta File N° GS23158/0012	N	SYN
KCP 7.0/24	Fox V.	2002	GS 23158: In vitro cytogenetic assay in human lymphocytes Syngenta Crop Protection AG, Basel, Switzerland Central Toxicology Laboratory (CTL), Cheshire, United Kingdom, Report No CTL/SV1087/REG/REPT GLP Not Published Syngenta File N° GS23158/0013	N	SYN

KCP 7.0/25	Clay P.	2001	GS 23158 (Metabolite of GS 13529): L5178Y TK+/- mouse lymphoma mutation assay Syngenta Crop Protection AG, Basel, Switzerland [redacted] [redacted] Report No CTL/VV0268/REG/REPT / 20011055 GLP Not Published Syngenta File N° GS23158/0011	N	SYN
KCP 7.0/26	xxx	1991	G28273 – Acute oral toxicity study in rats. Novartis Crop Protection AG, Basel, Switzerland [redacted] Report No 7801-91 GLP Not Published Syngenta File N° G28273/0034	Y	SYN
KCP 7.0/27	xxx	1991	G28273 Diaminochlorotriazine – 90-day oral toxicity study in rats Novartis Crop Protection AG, Basel, Switzerland [redacted] [redacted] Report No F-00006 GLP Not Published Syngenta File N° G28273/0017	Y	SYN
KCP 7.0/28	Deparade E.	1987	G 28273 tech. – Salmonella/mammalian-microsome mutagenicity test Novartis Crop Protection AG, Basel, Switzerland Ciba-Geigy Ltd., Basel, Switzerland, Report No 871372 GLP Not Published Syngenta File N° G28273/0007	N	SYN

KCP 7.0/29	Strasser F.	1988	G28273 technical – Micronucleus test, mouse Novartis Crop Protection AG, Basel, Switzerland [redacted] Report No 871369 GLP Not Published Syngenta File N° G28273/0006	N	SYN
KCP 7.0/30	xxx	2003	GS26379: Acute Oral Toxicity Study in the Rat – Up and Down Procedure Syngenta Crop Protection AG, Basel, Switzerland [redacted] Report No AR7315 GLP Not Published Syngenta File N° GS26379/0020	Y	SYN
KCP 7.0/31	Callander R.	2003	GS26379: Bacterial Mutation Assay in S.Typhimurium and E.Coli Syngenta Crop Protection AG, Basel, Switzerland Central Toxicology Laboratory (CTL), Cheshire, United Kingdom, Report No YV6393 GLP Not Published Syngenta File N° GS26379/0021	N	SYN

KCP 7.0/32	Fox V.	2003	GS 26379: In Vitro Cytogenetic Assay in Human Lymphocytes Syngenta Crop Protection AG, Basel, Switzerland Central Toxicology Laboratory (CTL), Cheshire, United Kingdom, Report No SV1196 GLP Not Published Syngenta File N° GS26379/0022	N	SYN
KCP 7.0/33	xxx	1995	2-year dietary chronic toxicity /oncogenicity study with G34048 technical in rats. [redacted] Report No. F-00125 GLP: Yes Published: No Syngenta file No. G34048/0046	Y	SYN
KCP 7.0/34	xxx	2004	Assessment of acute oral toxicity with terbuthylazine-desethyl in the rat (acute class method) Oxon Italia S.p.A. GLP, not published File No GS13529_10043	Y	OXON
KCP 7.0/35	Verspeek-Rip C.M.	2004	Evaluation of the mutagenic activity of terbuthylazine-desethyl in the Salmonella Typhimurium reverse mutation assay and the Escherichia Coli reverse mutation assay (with independent repeat) Oxon Italia S.p.A. NOTOX B.V., Hertogenbosch, Netherlands, 400826 GLP, not published File No GS13529_10044	N	OXON

KCP 7.0/36	Jones E.	2004	GS 26379: L5178Y TK+/- Mouse Lymphoma Mutation Assay Syngenta Crop Protection AG, Basel, Switzerland Central Toxicology Laboratory (CTL), Cheshire, United Kingdom, VV0297-REG GLP, not published File No GS26379/0024	N	SYN: oxon has data access
KCP 7.0/37	xxx	2006	GS26379: Rat Bone Marrow Micronucleus Test Syngenta Crop Protection AG, Basel, Switzerland [redacted] GLP, not published File No GS26379/0026	Y	SYN: oxon has data access
KCP 7.0/38	xxx	2006a	GS26379: In Vivo Rat Liver Unscheduled DNA Synthesis Assay Syngenta Crop Protection AG, Basel, Switzerland [redacted] GLP, not published File No GS26379/0025	Y	SYN: oxon has data access
KCP 7.0/39	xxx	1971	90-Day subacute oral toxicity study with GS 26`379 technical in albino rats. Novartis Crop Protection AG, Basel, Switzerland [redacted] Not GLP, not published File No GS26379/0001	Y	SYN: oxon has data access

KCP 7.0/40	Verspeek-Rip C.M.	2002a	Evaluation of the mutagenic activity of 2-hydroxy-terbuthylazione in the *Salmonella typhimurium* reverse mutation assay and the *Escherichia coli* reverse mutation assay (with independent repeat) Notox B.V s'Hertogenbosch, The Netherlands Report N. 335543 Oxon Italia S.p.A, Pero, Italy GLP: Yes published: No	N	OXON (SYN access)
KCP 7.0/41	Verspeek-Rip C.M.	2002b	Evaluation of the mutagenic activity of 2-hydroxy-terbuthylazine in an *in vitro* mammalian cell gene mutation test with l5178y mouse lymphoma cells (with independent repeat) Notox B.V s'Hertogenbosch, The Netherlands Report N. 335554 Oxon Italia S.p.A, Pero, Italy GLP: Yes published: No	N	OXON (SYN access)
KCP 7.0/42	xxx	2002	Assessment of acute oral toxicity with 2-hydroxy-terbuthylazine in the rat (acute class method) [redacted] Report N. 335532 Oxon Italia S.P.A, Pero, Italy GLP: Yes Published: No	Y	OXON (SYN access)
KCP 7.0/43	Meerts I.	2002	Evaluation of the ability of 2-hydroxy-terbuthylazine to induce chromosome aberrations in cultured peripheral human lymphocytes. Notox B.V s'Hertogenbosch, The Netherlands Report N. 335565 Oxon Italia S.p.A, Pero, Italy GLP: Yes published: No	N	OXON (SYN access)

KCP 7.0/44	xxx	2003	2-Hydroxy-terbuthylazine: repeated dose 90 day oral toxicity study in Wistar rats. [redacted] Report N. 3345-01 GLP: Yes Published: No	Y	OXON (SYN access)
KCP 7.0/45	Moxon M.	2003	GS 13529: Subchronic Neurotoxicity Study in Rats Syngenta Crop Protection AG, Basel, Switzerland [redacted] [redacted] Report No PR1228 GLP Not Published Syngenta File N° GS13529/1839	N	SYN
KCP 7.0/46	xxx	1995	RPA202248 - Oral limit test in the rat Report No.: R005369, Edition Number: M-170825-01-1 GLP Not published	Y	Bayer CropScience
KCP 7.0/47	Percy, A. J.	1995	Salmonella typhimurium reverse mutation assay (Ames test) RPA202248 Rhone-Poulenc Agro, Sophia Antipolis, France Report No.: R005367, Edition Number: M-170821-01-1 Date: 1995-11-10 GLP Not published	N	not disclosed's
KCP 7.0/48	xxx	1995	RPA203328 - Oral limit test in the rat Report No.: R005364, Edition Number: M-170815-01-1 EPA MRID No.: 43904812 GLP Not published	Y	Bayer CropScience

KCP 7.0/49	xxx	1995	28-day toxicity study in the rat by dietary administration RPA203328 (a metabolite of RPA201772) Report No.: R005242, Edition Number: M-170705-01-1 GLP Not published	Y	not disclosed's
KCP 7.0/50	Percy, A. J.	1995	Reverse mutation assay (Ames test) Salmonella typhimurium RPA203328 Report No.: R005218, Edition Number: M-170668-01-1 GLP Not published	N	Bayer CropScience
KCP 7.0/51	xxx	1994	RPA 203328 - Exploratory 14-day toxicity study in the rat by gavage Report No.: C027126, Edition Number: M-212732-01-1 GLP Not published	Y	Bayer CropScience
KCP 7.0/52	xxx	1998	RPA 203328: 90-Day Toxicity Study in the Rat by Dietary Administration Report No.: B003642, Report includes Trial Nos.: SA 98129 Edition Number: M-240662-01-1 GLP Not published	Y	Bayer CropScience
KCP 7.0/53	Murli, H.	1998	Mutagenicity test on RPA203328 - Measuring chromosomal aberrations in Chinese hamster ovary (CHO) cells Report No.: R000093, Edition Number: M-157884-01-1 EPA MRID No.: 44545301 GLP Not published	N	Bayer CropScience
KCP 7.0/54	Cifone, M. A.	1998	Mutagenicity test on RPA203328 in the CHO/HGPRT forward mutation assay with duplicate cultures and a confirmatory assay Report No.: M-189726-01-2,	N	Bayer CropScience

			Edition Number: M-189726-01-2 EPA MRID No.: 44545303 GLP Not published		
KCP 7.0/55	xxx	1998	Mutagenicity test on RPA 203328 in the in vivo mouse micronucleus assay Report No.: C026351, Report includes Trial Nos.: 19201 Edition Number: M-211247-01-1 GLP Not published	Y	Bayer CropScience
KCP 7.0/56	not disclosed's	1999	Developmental toxicology study in the rat by gavage RPA203328 Report No.: R014875, Edition Number: M-189848-01-1 GLP Not published	Y	Bayer CropScience
KCP 7.0/57	xxx	1999	Developmental toxicology study in the rat by gavage RPA203328 Report No.: R014875, Edition Number: M-189848-01-1 GLP Not published	Y	not disclosed's
KCP 7.0/58	not disclosed's	1996a	AMBA (2- Amino-4- Methylsulfonyl Benzoic Acid: Acute Oral Toxicity to the Rat Report No. /P/5282 GLP Not published	Y	Synenta
KCP 7.0/59	Fox, V	2000c	AMBA In vitro cytogenetic assay in human lymphocytes Zeneca Central Toxicology Laboratory Report No. CTL/SV0989 GLP Not published	N	Synenta
KCP 7.0/60	Elcombe , B.M.	1998a	ZA1296: Effects of AMBA, a metabolite of ZA1296 on phydroxy phenyl pyruvate dioxygenase (HPPD) activity. Zeneca Central Toxicology Laboratory	N	Synenta

			Report No. CTL/R/1361 GLP -not Not published		
KCP 7.0/61	Callande r, R.D.	1996b	AMBA AMBA (2-Amino-4-Methylsulfonyl Benzoic Acid): An Evaluation of Mutagenic Potential Using S.Typhimurium and E.Coli. Zeneca Central Toxicology Laboratory Report No. CTL/P/5226 GLP Not published	N	Synenta
KCP 7.0/62	not disclosed's	1996b.	MNBA: Acute Dermal Toxicity Study in Rats. Report No. /P/4963 GLP Not published	Y	Synenta
KCP 7.0/63	not disclosed's	1996c	MNBA: Skin Irritation to the Rabbit. Report No. /P/4964 GLP Not published	Y	Synenta
KCP 7.0/64	not disclosed's	1996d	MNBA: Eye Irritation to the Rabbit. Report No. /P/4965 GLP Not published	Y	Synenta
KCP 7.0/65	not disclosed's	1996e	MNBA: Local Lymph Node Assay. Report No. /P/4966 GLP Not published	N	Synenta
KCP 7.0/66	not disclosed's	1998	MNBA: 28 Day Oral Toxicity Study in Rats. Report No. /P/5578 GLP Not published	Y	Synenta
KCP 7.0/67	not disclosed's	2000	MNBA: 90 day dietary toxicity study in rats. Report No. /PR1155 GLP	Y	Synenta

			Not published		
KCP 7.0/68	not disclosed's	2000	MNBA: Biotransformation in the rat. Report No. /P/6326 GLP Not published	Y	Synenta
KCP 7.0/69	not disclosed's	2000b	MNBA: Rat bone marrow micronucleus test Report No. /SR1043 GLP Not published	N	Synenta
KCP 7.0/70	Elcombe , B.M.	1998b	ZA1296: Effects of MNBA, a metabolite of ZA1296 on phydroxy phenyl pyruvate dioxygenase (HPPD) activity. Zeneca Central Toxicology Laboratory Report No. CTL/R/1367 GLP -not Not published	N	Synenta

List of data submitted by the applicant and not relied on

Data point	**Author(s)**	**Year**	**Title** **Company Report No.** **Source (where different from company)** **GLP or GEP status** **Published or not**	**Vertebrate study Y/N**	**Owner**
KCP XX	Author	YYYY	Title Company Report N Source GLP/non GLP/GEP/non GEP Published/Unpublished	Y/N	Owner

List of data relied on not submitted by the applicant but necessary for evaluation

Data point	**Author(s)**	**Year**	**Title** **Company Report No.** **Source (where different from company)** **GLP or GEP status** **Published or not**	**Vertebrate study** **Y/N**	**Owner**
KCP XX	Author	YYYY	Title Company Report N Source GLP/non GLP/GEP/non GEP Published/Unpublished	Y/N	Owner

Appendix 2 Detailed evaluation of the studies relied upon

A 2.1 Statement on bridging possibilities

Not required.

Comments of zRMS:	

A 2.2 Acute oral toxicity (KCP 7.1.1)

Comments of zRMS:	The studies were evaluated and accepted during the evaluation completed in 2017. No re-evaluation is required.

Reference:	6.3
Report	CHR/H/TERIZ 650 WG Acute Oral Toxicity Study on Rats – Fixed Dose Method; xxx., 2016,Study code: PO-7/16
Guideline(s):	OECD Guideline No 420 / EU Method B.1.BIS
Deviations:	Yes. During the experiment, the air temperature exceed 25°C a few times, and the relative air humidity dropped below 30%, and exceed 70% a few times. These changes were temporary and did not influence the study course and results. No other deviations from the Study Plan were observed.
GLP:	Yes
Acceptability:	Yes
Duplication (if vertebrate study)	No (investigated formulation has no equivalent on the market, there are no studies available on the subject formulation)

Materials and methods

Test material (Lot/Batch No.)	CHR/H/TERIZ 650 WG, batch number: 54191-74; stable till August 2017.
Species	the Wistar female rats (Cmdb: WI; outbred)
No. of animals (group size)	10 rats – one animal was used to preliminary experimnet; four animals used in the main experiment (with dose 2000 mg/kg b.w.). The animal from the preliminary experiment was included in the main experiment. Then next 5 animal used in experiment with dose 300 mg/kg b.w.
Dose(s)	In the sighting study the product was administered at 2000 mg/kg bw. The dose was selected based on toxicity data on the active substance of test item. In the main study the product was administered at 2000 mg/kg bw. After the death 3 of four animals, the next animals was treated with the test item at a dose of 300 mg/kg b.w.
Vehicle/Dilution	The test item was administered with the aid of a metal stomach tube of animals in the form of an aqueous suspension at volume 0.5 mL per 100 g bw.
Post exposure observation period	14 days
Remarks	After the 14-day observation period, the animals were euthanized and subjected to a detailed gross examination.

Results and discussions

Table A 1: Results of acute oral toxicity study in rats of CHR/H/TERIZ

Dose (mg/kg bw)	Toxicological results *	Duration of signs	Time of death	LD50 (mg/kg bw) (14 days)
Male rats				
Preliminary experiment				
2000 mg/kg bw	0/1/1	the day of administration, and on the 1st day after administration	-	>2000
Main experiment				
2000 mg/kg bw	3/4/4	the day of administration the test item	24 hours after administration the test item	<2000
300 mg/kg bw	0/5/5	the day of administration the test item	-	>300

* Number of animals which died/number of animals with clinical signs/number of animals used

Table A 2: Summary of findings of acute oral toxicity study in rats of CHR/H/TERIZ

Mortality:	Three of four animals died after the administration of the test item at a dose of 2000 mg/kg b.w.
Clinical signs:	Preliminary experiment: rounded back, slightly decreased of locomotor activity, and accelerated respiration was observed on the day of administration, and on the 1st day after administration the test item. The animal survived the experiment. Main experiment: - Dose 2000 mg/kg b.w.: to four animals rounded back, slightly decreased of locomotor activity, and accelerated respiration was observed on the day of administration the test item in all animals. Moreover, respiratory murmurs was observed on the day of administration the test item in one animal (no. 5). - Dose 300 mg/kg b.w.: rounded back, and slightly decreased of locomotor activity was observed on the day of administration the test item in all animals. Moreover, seizures, dejection, animal could be very easy to catch, bristled coat, and accelerated respiration were observed on the day of administration the test item in one animal (no. 1).
Body weight:	Preliminary experiment - during the first week of the experiment, slight body weight loss was observed. During the 14-day experiment, the body weight of the animal increased. Main experiment - during the first week of the experiment, slight body weight loss in one animal (no. 3 – dose 2000 mg/kg b.w.) was observed. During the 14-day experiment, the body weight of all the animals increased.
Macroscopic examination:	Preliminary experiment - the animal did not exhibit any pathological changes. Main experiment - the animal did not exhibit any pathological changes.

Conclusion

Under the experimental conditions, the oral LD50 of the CHR/H/TERIZ for rats is greater than 300 mg/kg bw but below than 2000 mg/kg bw.
According to the Regulation (EC) No. 1272/2008 of the European Parliament and of the Council of December 16, 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, the

test item, i.e. CHR/H/TERIZ can be classified to categorie 4: Acute Tox. 4, H302 .

A 2.3 Acute percutaneous (dermal) toxicity (KCP 7.1.2)

Comments of zRMS:	The study was evaluated and accepted during the evaluation completed in 2017. No re-evaluation is required.

A 2.3.1 Acute dermal toxicity on rats

Reference:	6.3
Report	CHR/H/TERIZ 650 WG Acute Dermal Toxicity Study on Rats; xxx., 2016, Study code: DER-8/16
Guideline(s):	OECD Guideline No. 402 / EU Method B.3.
Deviations:	During the experiment, the air temperature exceed 25°C a few times, and the relative air humidity dropped below 30%, and exceed 70% a few times. These changes were temporary and did not influence the study course and results. No other deviations from the Study Plan were observed.
GLP:	Yes
Acceptability:	Yes
Duplication (if vertebrate study)	No (investigated formulation has no equivalent on the market, there are no studies available on the subject formulation)

Materials and methods

Test material (Lot/Batch No.)	CHR/H/TERIZ 650 WG, batch number: 54191-74; stable till August 2017.
Species	the Wistar male and female rats (Cmdb: WI; outbred)
No. of animals (group size)	5 males, 5 females
Dose(s)	Single dose of 2000 mg/kg bw
Exposure	24 hour
Vehicle/Dilution	The test item was applied to gauze patches, at a single dose of 2000 mg/kg b.w. was applied to the dorsal area of the trunks. After 24 hours, the band and the gauze patches were taken off, and the residual test item was removed using water.
Post exposure observation period	14 days
Remarks	After the 14-day observation period, the animals were euthanized, dissected, and subjected to detailed gross examinations.

Results and discussions

Table A 3: Results of acute dermal toxicity study in rats of CHR/H/TERIZ

Dose (mg/kg bw)	Toxicological results *	Duration of signs	Time of death	LD50 (mg/kg bw) (14 days)
Male rats				
2000 mg/kg b.w.	0/5/5	from the 1st to the	-	> 2000

Dose (mg/kg bw)	Toxicological results *	Duration of signs	Time of death	LD50 (mg/kg bw) (14 days)
		10th day		
Female rats				
2000 mg/kg b.w.	0/5/5	from the 1st to the 6th day	-	> 2000

* Number of animals which died/number of animals with clinical signs/number of animals used

Table A 4: Summary of findings of acute dermal toxicity study in rats of CHR/H/TERIZ

Mortality:	No
Clinical signs:	Following single application of the test item, the animals did not exhibit any general clinical signs. Males: erythema, and skin dryness, was observed on the treated skin in all males; in two males (no. 1, and no. 3): edema, and desquamation of epidermis; in three males (no. 1, 2, 3): scabs. Females: erythema, desquamation of epidermis, and skin dryness was observed on the treated skin in all females.
Body weight:	During the first week of the experiment, slightly body weight loss was observed in two females (no. 1, and no. 5). During the 14-day experiment, the body weight of all the animals increased.
Macroscopic examination:	Gross examinations did not reveal any pathological changes in the examined animals.

Conclusion

On the grounds of the study results, it may be concluded that the median lethal dose (LD50) of CHR/H/TERIZ 650 WG is greater than 2000 mg/kg b.w.
According to the Commission Regulation (EU) No. 286/2011 of March 10, 2011 amending, for the purposes of its adaptation to technical and scientific progress, Regulation (EC) No. 1272/2008 of the European Parliament and of the Council on classification, labelling, and packaging of substances and mixtures, it may be concluded that the test item, i.e. CHR/H/TERIZ 650 WG is beyond categorization.

A 2.4 Acute inhalation toxicity (KCP 7.1.3)

Comments of zRMS:	According to the Regulation 284/2013, the inhalation study shall be carried out where the plant protection product: (a) is a gas or liquefied gas; (b) is a smoke generating plant protection product or fumigant; (c) is used with fogging/misting equipment; (d) is a vapour releasing plant protection product; (e) is supplied in an aerosol dispenser; (f) is in a form of a powder or granules containing a significant proportion of particles of diameter < 50 μm (> 1 % on a weight basis); (g) is to be applied from aircraft in cases where inhalation exposure is relevant; (h) contains an active substance with a vapour pressure > 1 × 10–2 Pa and is to be used in enclosed spaces such as warehouses or glasshouses; (i) is to be applied by spraying. However, the study shall not be required if the applicant can justify an alternative approach under Regulation (EC) No 1272/2008, where applicable. Consequently, the inhalation toxicity of CHR/H/TERIZ can be determined by calculation from the data for all relevant ingredients (additivity formula). Taking into account the analysis of the classification of all ingredients of CHR/H/TERIZ and intended method of application (medium sprayer), the

	classification in regards to acute inhalation toxicity is not required.

Inhalation study on CHR/H/TERIZ is not required based on Council Directive 91/414/EC, Annex III, point 7.1.3., (COMMISSION REGULATION (EU) No 545/2011of 10 June 2011 implementing Regulation (EC) No 1107/2009 of the European Parliament and of the Council as regards the data requirements for plant protection products) since the preparation:

- is not used with fogging equipment,
- is not an aerosol,
- is not a powder containing a significant proportion of particles of diameter < 50 micrometre (> 1 % on a weight basis),
- is not to be applied from aircraft in cases where inhalation exposure is relevant,
- is not to be applied in a manner which generates a significant proportion of particles or droplets of diameter < 50 micrometre (> 1 % on a weight basis),
- contains a volatile component at greater than 10 %.

A 2.5 Skin irritation (KCP 7.1.4)

Comments of zRMS:	The study was evaluated and accepted during the evaluation completed in 2017. No re-evaluation is required.

A 2.5.1 In vitro Skin Corrosion

Reference:	6.3
Report	CHR/H/TERIZ 650 WG In Vitro Skin Corrosion: Transcutaneous Electrical Resistance Test (TER); xxx., 2016, Study code: OES-14/16
Guideline(s):	OECD Guideline No. 430 / EU Method B.40.
Deviations:	During quarantine relative humidity exceed 70% a few times. The animals had the "Labofeed H Standard" standard laboratory fodder produced by Zo-fia xxx", Kcynia instead Murigran" standard granulated fodder produced by Wytwórnia Koncentratów i Mieszanek Paszowych AGROPOL, Motycz as it was written in the Study Plan. These changes had no impact on the course and results of the study. No other deviations from the Study Plan were stated.
GLP:	Yes
Acceptability:	Yes
Duplication (if vertebrate study)	No (investigated formulation has no equivalent on the market, there are no studies available on the subject formulation)

Materials and methods

Test material (Lot/Batch No.)	CHR/H/TERIZ 650 WG, batch number: 54191-74; stable till August 2017.
Animals/species	the WISTAR female rats (outbred)
Materials for studys	11 skin discs obtained from each two 30-days old rat - two of them were used to control the quality of the procedure, whereas the remaining nine were used for the purpose of the experiment.
Application and exposure	The test item (ground to a powder) was applied evenly to the disc and moistened with 150 µL of distilled water (three skin discs obtained from each animal were used for the test item and three for control item - positive 36%

	hydrochloric acid and negative distilled water). Test item was applied for 24 hours at 21-22 °C. The test item were removed by washing with a jet of tap water at up to 30°C and the electrical resistance was measured and made an overall assessment. The dye binding procedure was not necessary in this case since all TER values for the test item were higher than 5 kΩ and there were not any visible changes on the skin discs.
Time of exposure	24 h
Remarks	The experiment was performed in duplicate, because the classification of the test items was unequivocal.

Results and discussions

- Mean TER results for the skin discs treated with the test item were equal: 8.76 kΩ (animal No. 1) and 11.17 kΩ (animal No. 2). They can be accepted because the concurrent positive and negative control values fell within the acceptable ranges for the method.
- The concurrent mean values for the positive and negative controls were as follows: for 36% HCl – 0.92 kΩ (animal no. 1) and 0.90 kΩ (animal no. 2), and for distilled water – 18.13 kΩ (animal no. 1) and 13.62 kΩ (animal no. 2). These values fell within the acceptable ranges for the method.
- Gross examinations of the skin discs treated with the test item did not reveal any pathological changes.
- The test item is considered to be non-corrosive to skin if:
  - the mean TER value obtained for the test item is greater than 5 kΩ, or
  - the mean TER value is less than or equal to 5 kΩ, and the skin discs show no obvious damage.

Conclusion:
On the grounds of the results, it may be stated that the test item, i.e. CHR/H/TERIZ 650 WG belongs to a group of substances which do not lead to skin corrosion/severe irritation. The mean TER values for the test item were higher than 5 kΩ and there were not any visible changes on the skin discs. Performance of skin irritation/corrosion study is justified.

A 2.5.2 In vitro skin irritation

Reference:	6.3
Report	Determination of skin irritation potential of CHR/H/TERIZ 650 WG in re-constructed human epidermis (RHE), I. Anders, 2016, Study no.: 16090807G840
Guideline(s):	OECD 439, EU Method B.46
Deviations:	No
GLP:	Yes
Acceptability:	Yes
Duplication (if vertebrate study)	No (investigated formulation has no equivalent on the market, there are no studies available on the subject formulation)

Materials and methods

Test material (Lot/Batch No.)	CHR/H/TERIZ 650 WG, batch number: 54191-74; stable till August 2017.

Materials for studys	Three tissues of the human skin model EpiDermTM
Application and exposure	The test item was applied directly to each tissue and spread to match the tissue size (0.63 cm2; as indicated by supplier) for 60 minutes. DPBS-buffer was used as negative control, 5 % SDS solution was used as positive control. The test consists of a topical exposure of the neat test item to a human reconstructed epi-dermis model followed by a cell viability test. The percentage reduction of cell viability in comparison of untreated negative controls is used to predict skin irritation potential.
Remarks	Skin irritation potential of the test item is assessed as given in the following : ≤ 50 % of negative control - Irritant to skin (GHS Category 2 for Skin Irritation); > 50 % of negative control - Non skin irritant (no Category for Skin Irritation).

Findings:

- After the treatment with the test item, the relative absorbance values were reduced to 3.7 %. This value is below the threshold for irritation potential (50%).
- After treatment with the negative control, the absorbance values were within the required acceptability criterion of 0.8 ≤ mean OD ≤ 2.8, OD was 1.5. The positive control showed clear irritating effects. Relative absorbance was reduced to 3.3% (required: < 20%). Variation within tissues was acceptable (required: ≤ 18%).

Conclusion

Under the experimental conditions, CHR/H/TERIZ 650 WG is considered as skin irritant in the Human Skin Model Test. According to study results and the Regulation (EC) No. 1272/2008 of the European Parliament and of the Council of December 16, 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, product CHR/H/TERIZ is **Skin Irrit. 2, H315**. Hence, an acute skin irritation/corrosion study on rabbits, based on the OECD Guideline for the Testing of Chemicals No. 404/EU Method B.4, will not be performed.

A 2.5.3 Acute eye irritation/corrosion study on rabbits

Based on study: "Determination of skin irritation potential of CHR/H/TERIZ 650 WG in reconstructed human epidermis (RHE)" Andres I. et al., 2016; showed, that test item is considered as skin irritant. Hence, an acute skin irritation/corrosion study on rabbits has not been conducted.

A 2.6 Eye irritation (KCP 7.1.5)

Comments of zRMS:	The study was evaluated and accepted during the evaluation completed in 2017. No re-evaluation is required.

A 2.6.1 In vitro eye corrosion

Reference: 6.3

Report CHR/H/TERIZ 650 WG Isolated Chicken Eye Test Method for Identifying i) Chemicals Inducing Serious Eye Damage and ii) Chemicals Not Requiring Classifications for Eye Irritation or Serious Eye Damage; xxx, 2016, Study

	code: ICE-14/16
Guideline(s):	OECD Guideline No. 438 / EU Method B.48.
Deviations:	No
GLP:	Yes
Acceptability:	Yes
Duplication (if vertebrate study)	No (investigated formulation has no equivalent on the market, there are no studies available on the subject formulation)

Materials and methods

Test material (Lot/Batch No.)	CHR/H/TERIZ 650 WG, batch number: 54191-74; stable till August 2017.
Biological material:	9 eyeballs; three eyeballs were used for negative control, positive control and for the test item
Exposure	The test item (ground to a powder) and the items used in the positive (imidazole) were applied in the amount of 0.03 g, whereas the item used in the negative control (physiological saline) was applied in a volume of 0.03 mL., for 10 second. Then, they were rinsed from the eye with 20 mL of physiological salt at ambient temperature.
Observation	At all observation time points, corneal opacity and swelling were evaluated, whereas morphological changes of the corneal surface were recorded. The quantitative determination of fluorescein retention was performed only once, i.e. 30 minutes after the end of the exposure.
Post exposure observation period	The corneas treated with the test item and the control items were evaluated pretreatment and starting at 30, 75, 120, 180, and 240 minutes (± 5 minutes) after the post-treatment rinse.
Remarks	The study was conducted in two runs. The first study led to a GHS NC outcome, so a second run of nine eyeballs was conducted to confirm or discard the negative outcome.

Results and discussions

Table A 6: Eye irritation in Isolated Chicken Eye Test of CHR/H/TERIZ

Dose (g)	Fluorescein retention score	Corneal opacity score	Corneal swelling score	Gross evaluation of cornea	Histopathological evaluation of cornea	Conclusion
Isolated chicken eyes						
1st run						
0.03	0.7	1.7-2.0	3.8-21.0	the test item was observed on the cornea surface of all examined eyeballs	vacuolation, erosions, necrosis of the superficial layer of the anterior corneal epithelium, karyopyknosis of the anterior corneal epithelium, local dissection of the anterior corneal epithelium, dissection of the corneal stroma	CHR/H/TERIZ did not cause serious eye damage

2nd run						
0.03	2.3	1.7-2.3	6.8-17.1	the test item was observed on the cornea surface of all examined eyeballs	dissection, necrosis and erosions of the superficial layer of the anterior corneal epithelium, karyopyknosis of the anterior corneal epithelium, dissection of the corneal stroma	CHR/H/TERIZ did not cause serious eye damage

Findings:

- In the first run the mean fluorescein retention value for the eyeballs treated with the test item was equal to 0.7 (ICE class II). The mean fluorescein retention values for the concurrent positive and negative controls were 3.0 (ICE class IV) for imidazole and 0.0 (ICE class I) for physiological saline.
- In the second run the mean fluorescein retention value for the eyeballs treated with the test item was equal to 2.3 (ICE class III). The mean fluorescein retention values for the concurrent positive and negative controls were 3.0 (ICE class IV) for imidazole and 0.0 (ICE class I) for physiological saline.
- In the first run the mean corneal opacity values for the eyeballs treated with the test item were from 1.7 (ICE class III) to 2.0 (ICE class III). In the first run the mean corneal opacity values for the concurrent positive and negative controls were 4.0 (ICE class IV) for imidazole and 0.0 (ICE class I) for physiological saline. These values fell within the acceptable ranges for the method.
- In the second run the mean corneal opacity values for the eyeballs treated with the test item were from 1.7 (ICE class III) to 2.3 (ICE class III). The mean corneal opacity values for the concurrent positive and negative controls were 4.0 (ICE class IV) for imidazole and 0.0 (ICE class I) for physiological saline.
- In the first run the mean corneal swelling values for the eyeballs treated with the test item were from 3.8 % (ICE class I) to 21.0 % (ICE class III). The mean corneal swelling values for the positive control (imidazole) were from 54.3 % (ICE class IV) to 92.8 % (ICE class IV). As for the concurrent negative control samples (physiological saline), there was no corneal swelling detected (ICE class I).
- In the second run the mean corneal swelling for the eyeballs treated with the test item were from 6.8 % (ICE class II) to 17.1 % (ICE class II). Additionally, the corneal swelling after 75 minutes of study was equal 12,2 % (ICE class III). The mean corneal swelling values for the positive control (imidazole) were from 55.5% (ICE class IV) to 80.3 % (ICE class IV). As for the concurrent negative control samples (physiological saline), there was no corneal swelling detected (ICE class I).
- The test item was observed on the cornea surface of all examined eyeballs through the duration of the study in both runs. During the gross examination of the positive control treated eyeballs, roughening of the corneal surface were observed in both runs. The negative control eyeballs did not exhibit any changes of the corneal in both runs.
- Histopathological examinations in the first run: of the corneas treated with the test item revealed vacuolation (eyeball no.1), erosions (eyeball no. 3), and necrosis of the superficial layer of the anterior corneal epithelium (eyeballs no. 1, no. 2, no. 3), karyopyknosis of the anterior corneal epithelium (eyeball no. 1), local dissection of the anterior corneal epithelium (eyeball no. 2), dissection of the corneal stroma (eyeballs no. 1, no. 2). In second run: dissection (eyeball no. 3), necrosis and erosions of the superficial layer of the anterior corneal epithelium (eyeballs no. 1, no. 2, no. 3), karyopyknosis of the anterior corneal epithelium (eyeballs no. 1, no. 2, no. 3), dissection of the corneal stroma (eyeballs no. 1, no. 2).
- All values fell within the acceptable ranges for the method.

Conclusion:

On the grounds of the study results described in this Report and the overall in vitro Irritancy Classification, it may be stated that the test item, i.e. CHR/H/TERIZ 650 WG did not cause serious eye damage. According to UN GHS classification criteria "no prediction can be made", since the ICE Class combination of the 3 endpoints were 2 x III and 1 x II for first run and 2 x III, 1xII for second run. On the basis of the results obtained in the course of the histopathological evaluation it can be concluded that the test item can have a negative effect on the chicken cornea in the ICE test, however the test item cannot be put into category 1. Hence, an acute eye irritation/corrosion study on rabbits, based on the OECD Guideline for the Testing of Chemicals No. 405/EU Method B.5, will be performed.

A 2.6.2 Eye irritation

Reference:	6.3
Report	CHR/H/TERIZ 650 WG Acute eye irritation/corrosion study on rabbits; xxx, 2016, Study code: ODR-10/16
Guideline(s):	OECD Guideline No 405 / EU Method B.5.
Deviations:	During the experiment the temperature few times exceeded 23 °C and the humidity few times exceeded 70 %. The changes were temporary and did not influence on the study course. No other deviations from the Study Plan were found.
GLP:	Yes
Acceptability:	Yes
Duplication (if vertebrate study)	No (investigated formulation has no equivalent on the market, there are no studies available on the subject formulation)

Materials and methods

Test material (Lot/Batch No.)	CHR/H/TERIZ 650 WG, batch number: 54191-74; stable till August 2017.
Species	albino rabbits Imp: BN of the New Zealand strain
No. of animals (group size)	3 females
Initial test using one animal	Yes
Exposure	The test item in amount of 0.069 g was applied to the conjunctival sac of one eye of the animals after gently pulling the lower lid away from the eyeball. The lids were then gently held together for a moment in order to prevent loss of the material. The other eye, which remained untreated, served as a control.
Post exposure observation period	7 days – rabbit no. 1 and 2, 14 days – rabbit no. 3
Remarks	After the observation period, the animals were euthanized.

Results and discussions

Table A 7: Eye irritation of CHR/H/TERIZ

An-imal No.		Scores after treatment *						Mean scores (24-72 h)	Reversible (day)
		1 h	24 h	48 h	72 h	7 day	14 day		
1	Corneal opacity	0	0	0	0	0	-	0.0	-
	Iritis	0	0	0	0	0	-	0.0	-
	Redness conjunctivae	2	2	2	2	0	-	2.0	after 72 hours
	Chemosis conjunctivae	1	1	1	1	0	-	1.0	after 72 hours
2	Corneal opacity	0	0	0	0	0	-	0.0	-
	Iritis	0	0	0	0	0	-	0.0	-
	Redness conjunctivae	2	2	2	2	0	-	2.0	after 72 hours
	Chemosis conjunctivae	1	1	1	1	0	-	1.0	after 72 hours
3	Corneal opacity	0	0	0	0	0	0	0.0	-
	Iritis	0	0	0	0	0	0	0.0	-
	Redness conjunctivae	2	2	2	2	1	0	2.0	after 7th day
	Chemosis conjunctivae	2	2	2	1	0	0	1.7	after 72 hours

* scores in the range of 0 to 4 for cornea opacity and chemosis, 0 to 3 for redness of conjunctivae and 0 to 2 for iritis

Clinical signs:	No clinical signs of toxicity were observed.
Body weights	At the beginning of the experiment, rabbit no. 1 weighed 3.65 kg, rabbit no. 2 weighed 4.37 kg and rabbit no. 3 weighed 3.79 kg. On the last day of the experiment, the animals weighed 3.59 kg, 4.45 kg and 3.71 kg, respectively.

Conclusion

Under the experimental conditions, CHR/H/TERIZ 650 WG can be classified into the following categories:
- agents which do not irritate the rabbit eye – according to the Annex to the Regulation of the Minister of Health of August 10, 2012 on classification of chemical substances and their mixtures (Dz.U. poz. 1018),
- agents which are beyond categorization – according to the Comission Regulation (EU) No 286/2011 of 10 March 2011 amending, for the purposes of its adaptation to technical and scientific progress, Regulation (EC) No 1272/2008 of the European Parliament and of the Council on classification, labelling and packaging of substances and mixtures.

A 2.7 Skin sensitisation (KCP 7.1.6)

Comments of zRMS:	The study was evaluated and accepted during the evaluation completed in 2017. No re-evaluation is required.

A 2.7.1 Skin sensitization

Reference:	6.3
Report	CHR/H/TERIZ 650 WG Skin Sensitization Study; xxxx., 2016, Study code: Al-4/16
Guideline(s):	OECD Guideline No. 406 / EU Method B.6.

Deviations:	During the experiment, the air temperature exceeded 23°C a few times, and the relative air humidity exceeded 70%. These changes were temporary and did not influence the study course and results. No other deviations from the Study Plan were observed.
GLP:	Yes
Acceptability:	Yes
Duplication (if vertebrate study)	No (investigated formulation has no equivalent on the market, there are no studies available on the subject formulation)

Materials and methods

Test material (Lot/Batch No.)	CHR/H/TERIZ 650 WG, batch number: 54191-74; stable till August 2017.
Species	the Dunkin-Hartley male and female guinea pigs (outbred)
No. of animals (group size)	Preliminary experiment: 8 guinea pigs – 4 males, 4 females Main experiment: 20 guinea pigs - 10 males, 10 females
Range finding:	Yes / grading scale given in the OECD Guideline No. 406 / EU Method B.6: 0 - no visible changes 1 - discrete or patchy erythema 2 - moderate or confluent erythema 3 - intense erythema and swelling
Exposure (concentration(s), no. of applications)	**Intradermal inductione:** three pairs of intradermal injections of 0.1 mL volume were given to all 20 animals so that one of each pair of injections laid on each side of the midline (1% aqueous suspension) **Topical inductione:** 50% aqueous suspension of the test item in a volume of about 1 mL was applied to multilayered gauze patches for 48 h. **Challengee:** a 20% aqueous suspension of the test item in a volume of 0.5 mL was applied for 48 hours to the skin of right flank of animals. The medium (aqua pro injectione) was applied to the left flanks in the same manner.
Vehicle	aqua pro injectione
Pretreatment prior to topical application	Yes/ Aqueous suspensions of the test item at the appropriate concentrations in a volume of 0.5 mL in concentrations of 10%, 20%, 30%, 40% and 50%.
Reliability check	**Intradermal induction:** Three pairs of intradermal injections of 0.1 mL - a 1:1 mixture (v/v) FCA / aqua pro injectione, aqua pro injectione (medium), a 1:1 mixture (v/v) of the medium with a 1:1 mixture (v/v) FCA / aqua pro injectione. **Topical induction:** aqua pro injectione was applied to the skin in the sites of the intradermal injections. **Challenge:** A 20% aqueous suspension of the test item in a volume of 0.5 mL.
Remarks	After the observation period, the animals were euthanized and utilized.

Results and discussions

Table A 8: Results of skin sensitisation study of product CHR/H/TERIZ

	24 hours	48 hours	72 hours	Total number of animals affected
	After challenge			
CHR/H/TERIZ	0/20	0/20	0/20	0%
Test Vehicle Control Group	0/8	0/8	0/8	0%

* Number of animals with positive dermal response (scores of 1-3) /number of animals in dose group

Clinical signs: During the readings which took place 24, 48, and 72 hours after the end of the exposure, the treated group animals did not exhibit any pathological changes in the sites of the test item and the medium application.

Conclusion

Under the experimental conditions, CHR/H/TERIZ 650 WG caused no allergic skin reactions in treated animals. Therefore, it can be classified into the following categories:
- agents causing no sensitization – according to Magnusson and Kligman's classification [5],
- is beyond categorization – according to the Commission Regulation (EU) No. 286/2011 of March 10, 2011 amending, for the purposes of its adaptation to technical and scientific progress, Regulation (EC) No. 1272/2008 of the European Parliament and of the Council on classification, labelling, and packaging of substances and mixtures.

A 2.8 Supplementary studies for combinations of plant protection products (KCP 7.1.7)

Not available.

A 2.9 Data on co-formulants (KCP 7.4)

A 2.9.1 Material safety data sheet for each co- formulant

Information regarding material safety data sheets of the co-formulants can be found in the confidential dossier of this submission (Registration Report - Part C).

A 2.9.2 Available toxicological data for each co-formulant

Available toxicological data for each co-formulant can be found in the confidential dossier of this submission (Registration Report - Part C).

A 2.10 Studies on dermal absorption (KCP 7.3)

For the dermal absorption of the active substance the Applicant refers to Guidance on Dermal Absorption1 EFSA Panel on Plant Protection Products and their Residues (PPR), EFSA Journal 2012;10(4):2665.
Based on an evaluation of agreed dermal absorption values for a range of concentrated pesticide formulations and their dilutions, the following default values are recommended (see opinion section 4.1.1.for details).
A default dermal absorption value of 25% may be applied for products containing > 5% (50 g/kg for solids or 50 g/L for liquids) active substance.
A default value of 75% should be used for products or in use dilutions containing ≤ 5% active substance.
If log Pow < -1 or > 4 and MW > 500 a default dermal absorption value of 10% may be applied (de Heer et al., 1999).

Comments of zRMS:	According to the Guidance on Dermal Absorption EFSA Journal 2017;15(6):4873, the default value of dermal absorption of active substances of CHR/H/TERIZ are accepted;10% for concentrated and 50% for dilution. A new study on terbuthylazine absorption were provided in May 2019. The study of (Bernal J, 2019) is acceptable. However, it must be noticed that some minor deviations of the applied method were observed. According to the Guidance document for the conduct of skin absorption studies, Env/Jm/Mono(2004)2, the test substance ideally should be radio-labelled, in a metabolically stable position preferably with 14C, and of suitable radiochemical purity (ideally >98%). Noteworthy, in case of the study on terbuthylazine contained in CHR/H/TERIZ, the radiopurity was slightly lower. Nevertheless, the deviation should have not affect the result of the absorption study. **Conclusions:** Based on the results of (Bernal J, 2019) study, the absorption rate for terbuthylazine contained in CHR/H/TERIZ amounts to 1.73 and 15.3% for the concentrate and in-use dilution, respectively. Those values were considered for the estimation of operator, worker and bystander/resident exposure estimations (Appendix 5).

A 2.11 Other/Special Studies

Not available.

Appendix 3 Exposure calculations

A 3.1 Operator exposure calculations (KCP 7.2.1.1)

A 3.1.1 Calculations for terbuthylazine

Substance	terbuthylazine	Formulation = Wettable granules, soluble granules	Application rate-0.4 kg a.s. /ha	Spray dilution = 2 g a.s./l	Vapour pressure = low volatile substances having a vapour pressure of <5*10-3Pa
Scenario	Cereals / Outdoor / Downward spraying / Vehicle-mounted			Buffer = 2-3	Number applications = 1, Application interval = 365 days
Percentage Absoprtion	Dermal for product = 10	Dermal for in use diluation = 50	Oral = 100	Inhalation = 100	
RVNAS	0.0032 mg/kg bw/day		RVAAS	mg/kg bw/day	
DFR	3 µg a.s./cm2 per kg a.s./ha		DT50	30 days	

Operator Model		Mixing, loading and application AOEM			
Potential exposure	Longer term systemic exposure mg/kg bw/day		0.0798	% of RVNAS	2495.09%
	Acute systemic exposure mg/kg bw/day		0.4238	% of RVAAS	
Mixing and Loading		Gloves = Yes	Clothing = Work wear - arms, body and legs covered	RPE = FP2, P2 and similar	Soluble bags = No
Application		Gloves = Yes	Clothing = Work wear - arms, body and legs covered	RPE = Hood and visor	Closed cabin = Yes
Exposure (including PPE options above)	Longer term systemic exposure mg/kg bw/day		0.0032	% of RVNAS	101.42%
	Acute systemic exposure mg/kg bw/day		0.0467	% of RVAAS	

A 3.1.2 Calculations for mesotrione

Substance	mesotrione	Formulation = Wettable granules, soluble granules	Application rate-0.15 kg a.s. /ha	Spray dilution = 0.75 g a.s./l	Vapour pressure = low volatile substances having a vapour pressure of <5*10-3Pa
Scenario	Cereals / Outdoor / Downward spraying / Vehicle-mounted			Buffer = 2-3	Number applications = 1, Application interval = 365 days
Percentage Absoprtion	Dermal for product = 10	Dermal for in use diluation = 50	Oral = 100	Inhalation = 100	

RVNAS	0.005 mg/kg bw/day	RVAAS	mg/kg bw/day
DFR	3 µg a.s./cm2 per kg a.s./ha	DT50	30 days

Operator Model	Mixing, loading and application AOEM			
Potential exposure	Longer term systemic exposure mg/kg bw/day	0.0348	% of RVNAS	695.02%
	Acute systemic exposure mg/kg bw/day	0.2149	% of RVAAS	
Mixing and Loading	Gloves = Yes	Clothing = Work wear - arms, body and legs covered	RPE = FP1, P1 and similar	Soluble bags = No
Application	Gloves = Yes	Clothing = Work wear - arms, body and legs covered	RPE = FP2, P2 and similar	Closed cabin = No
Exposure (including PPE options above)	Longer term systemic exposure mg/kg bw/day	0.0020	% of RVNAS	40.66%
	Acute systemic exposure mg/kg bw/day	0.0393	% of RVAAS	

A 3.1.3 Calculations for isoxaflutole

Substance	isoxaflutole	Formulation = Wettable granules, soluble granules	Application rate-0.1 kg a.s. /ha	Spray dilution = 0.5 g a.s./l	Vapour pressure = low volatile substances having a vapour pressure of <5*10-3Pa
Scenario	Cereals / Outdoor / Downward spraying / Vehicle-mounted-Drift Reduction			Buffer = 5	Number applications = 1, Application interval = 365 days
Percentage Absoprtion	Dermal for product = 10	Dermal for in use diluation = 50	Oral = 60	Inhalation = 100	
RVNAS	0.012 mg/kg bw/day		RVAAS	mg/kg bw/day	
DFR	3 µg a.s./cm2 per kg a.s./ha		DT50	30 days	

Operator Model	Mixing, loading and application AOEM			
Potential exposure	Longer term systemic exposure mg/kg bw/day	0.0182	% of RVNAS	151.61%
	Acute systemic exposure mg/kg bw/day	0.1003	% of RVAAS	
Mixing and Loading	Gloves = Yes	Clothing = Work wear - arms, body and legs covered	RPE = None	Soluble bags = No
Application	Gloves = Yes	Clothing = Work wear - arms, body and legs covered	RPE = None	Closed cabin = No
Exposure (including PPE options above)	Longer term systemic exposure mg/kg bw/day	0.0014	% of RVNAS	11.76%
	Acute systemic exposure mg/kg bw/day	0.0067	% of RVAAS	

A 3.2 Worker exposure calculations (KCP 7.2.3.1)

A 3.2.1 Calculations for terbuthylazine

WORKER EXPOSURE			EUROPOEM II MODEL	
form	CHR/H/TERIZ		**Re-entry in the field**	
a.s.	terbuthylazine			
Parameter		**Value**	**Unit**	**References, comments**
Re-entry activities in the field				
AR	Application rate	0.4	kg a.s./ha	summary of intended uses
Worker				
Duration				
T		2	hours / day	default: 6 h (Europoem II)
Inhalation Exposure				without PPE
	no model available	-		
Dermal Exposure				
DFR	Dislodgeable foliar residue	2.34	mg a.s./m2/kg a.s./ha	default (Europoem II)
TC	Transfer coefficient	0.25	m2/ hour	vegetable (field): 0.25; ornamentals: 0.5; small fruit: 0.3; large fruit: 0.45 (Europoem II)
Dermal Exposure		**0.468**	mg a.s./ day	DE = DFR x AR x TC x T
Internal exposure				
DA	Dermal Absorption	50	%	
	PPE-factor dermal	5		gloves*
	AOEL	0.18	mg a.s./ day	based on 70 kg bw
		Without PPE	**With PPE**	
	Internal exposure	[mg a.s./ day]	[mg a.s./ day]	
	Inhalation	-	-	no model available
	Dermal	0.234	0.047	DE(int) = DE x (DA/100)
	Total	**0.234**	**0.047**	**sum**
	% AOEL			
	Inhalation	-	-	no model available
	Dermal	130	26	%AOEL = 100 x DE(int) / AOEL
	Total	**130**	**26**	**sum**

* It is assumed in the used TC values, that body exposure is already reduced by (protective) clothing. The use of gloves will result in an extra reduction factor of 5.

A 3.2.2 Calculations for mesotrione

WORKER EXPOSURE			EUROPOEM II MODEL	
form	CHR/H/TERIZ		**Re-entry in the field**	
a.s.	mesotrione			
Parameter		**Value**	**Unit**	**References, comments**
Re-entry activities in the field				
AR	Application rate	0.15	kg a.s./ha	summary of intended uses

Worker				
Duration				
T		2	hours / day	default: 6 h (Europoem II)
Inhalation Exposure				without PPE
	no model available	-		
Dermal Exposure				
DFR	Dislodgeable foliar residue	30	mg a.s./m2/kg a.s./ha	default (Europoem II)
TC	Transfer coefficient	0.25	m2/ hour	vegetable (field): 0.25; ornamentals: 0.5; small fruit: 0.3; large fruit: 0.45 (Europoem II)
Dermal Exposure		**2.25**	mg a.s./ day	DE = DFR x AR x TC x T
Internal exposure				
DA	Dermal Absorption	50	%	
	PPE-factor dermal	5		gloves*
	AOEL	0.3	mg a.s./ day	based on 70 kg bw

	Without PPE	**With PPE**	
Internal exposure	[mg a.s./ day]	[mg a.s./ day]	
Inhalation	-	-	no model available
Dermal	1.125	0.225	DE(int) = DE x (DA/100)
Total	**1.125**	**0.225**	**sum**
% AOEL			
Inhalation	-	-	no model available
Dermal	375	75	%AOEL = 100 x DE(int) / AOEL
Total	**375**	**75**	**sum**

* It is assumed in the used TC values, that body exposure is already reduced by (protective) clothing. The use of gloves will result in an extra reduction factor of 5.

A 3.2.3 Calculations for isoxaflutole

Worker - Inspection, irrigation	Potential exposure mg/kg bw/day	0.0625	% of RVNAS	520.83%
	Working clothing mg/kg bw/day	0.0070	% of RVNAS	58.33%
	Working clothing and gloves mg/kg bw/day		% of RVNAS	

A 3.3 Bystander and resident exposure calculations (KCP 7.2.2.1)

A 3.3.1 Calculations for terbuthylazine

Estimation of bystander exposure during/after application in Field Crops, Tractor Mounted (FCTM)

Input parameters considered for the estimation of bystander exposure:

Intended use(s):			**Drift (D):**	0.57	% (FCTM, 5 m)
Application rate (AR):	0.4	kg a.s./ha	**Exposed Body Surface Area (BSA):**	1	m² (adults)
				0.21	m² (children)

Body weight (BW):	60	kg/person (adults)	**Specific Inhalation Exposure (I*$_A$):**	0.001	mg/kg a.s. (6 hours, adults)
	16.15	kg/person (children)		0.00057	mg/kg a.s. (6 hours, children)
Dermal absorption (DA):	50.00	% ('worst case')	**Area Treated (A):**	20	ha/d (based on Field Crops, Tractor Mounted (FCTM))
Inhalation absorption (IA):	100	%	**Exposure duration (T):**	5	min
AOEL:	0.0032	mg/kg bw/d			

Bystander exposure towards terbuthylazine					
Adults			**Children**		
Bystander: Dermal exposure after application in (via spray drift)					
SDE_B = (AR x D x BSA x DA) / BW			SDE_B = (AR x D x BSA x DA) / BW		
(40 x 0.57% x 1 x 50%) / 60			(40 x 0.57% x 0.21 x 50%) / 16.15		
External exposure	0.228	mg/person	External exposure	0.04788	mg/person
External exposure	0.0038	mg/kg bw/d	External exposure	0.00296471	mg/kg bw/d
Absorbed dose:	**0.0019000**	**mg/kg bw/d**	**Absorbed dose:**	**0.0014824**	**mg/kg bw/d**
Bystander: Inhalation exposure after application in					
SIE_B = (I*$_A$ x AR x A x T x IA) / BW			SIE_B = (I*$_A$ x AR x A x T x IA) / BW		
(0,000 / 360 x 0.4 x 20 x 5 x 100%) / 60			(0,000 / 360 x 0.4 x 20 x 5 x 100%) / 16.15		
External exposure	0.00011111	mg/person	External exposure	6.3857E-05	mg/person
External exposure	1.8519E-06	mg/kg bw/d	External exposure	3.954E-06	mg/kg bw/d
Absorbed dose:	**0.0000019**	**mg/kg bw/d**	**Absorbed dose:**	**0.0000040**	**mg/kg bw/d**
Total systemic exposure: $SE_B = SDE_B + SIE_B$			Total systemic exposure: $SE_B = SDE_B + SIE_B$		
Total systemic exposure (absorbed dose)	0.11411111	mg/person	Total systemic exposure (absorbed dose)	0.02400386	mg/person
Total systemic exposure (absorbed dose)	**0.0019019**	**mg/kg bw/d**	**Total systemic exposure** (absorbed dose)	**0.0014863**	**mg/kg bw/d**
% of AOEL:	**59.43**	**%**	**% of AOEL:**	**46.45**	**%**

Estimation of resident exposure after application in Field Crops, Tractor Mounted (FCTM)

Input parameters considered for the estimation of resident exposure:

Intended use(s):			**Drift (D):**	0.57	% (FCTM, 5 m)
Application rate (AR):	0.4	kg a.s./ha	**Transfer coefficient (TC):**	7300	cm^2/h (adults)
				2600	cm^2/h (children)
Number of applications (NA):	1		**Turf Transferable Residues (TTR):**	5	%
Body weight (BW):	60	kg/person (adults)	**Exposure Duration (H):**	2	h
	16.15	kg/person (children)	**Airborne Concentration of Vapour (ACV):**	0.001	mg/m3
Dermal absorption (DA):	50.00	% ('worst case')	**Inhalation Rate (IR):**	16.57	m^3/d (adults),
Inhalation absorption (IA):	100	%		8.31	m^3/d (children)
Oral absorption (OA)	100	%	**Saliva Extraction Factor (SE):**	50	%

AOEL	0.0032	mg/kg bw/d	**Surface Area of Hands (SA):**	20	cm^2
			Frequency of Hand to Mouth (Freq):	20	events/h
			Dislodgeable foliar residues (DFR):	20	%
			Ingestion Rate for Mouthing of Grass/Day (IgR):	25	cm^2/d

Resident exposure towards terbuthylazine					
Adults			**Children**		
Residents: Dermal exposure after application in (via deposits caused by spray drift)					
SDE_R = (AR x NA x D x TTR x TC x H x DA) / BW			SDE_R = (AR x NA x D x TTR x TC x H x DA) / BW		
(0.004 x 1 x 0.57% x 5% x 7300 x 2 x 50%) / 60			(0.004 x 1 x 0.57% x 5% x 2600 x 2 x 50%) / 16.15		
External exposure	0.016644	mg/person	External exposure	0.005928	mg/person
External exposure	0.0002774	mg/kg bw/d	External exposure	0.00036706	mg/kg bw/d
Absorbed dose:	**0.0001387**	**mg/kg bw/d**	**Absorbed dose:**	**0.0001835**	**mg/kg bw/d**
Residents: Inhalation exposure to vapour					
SIE_R = (AC_V x IR x IA) / BW			SIE_R = (AC_V x IR x IA) / BW		
(0.001 x 16.57 x 100%) / 60			(0.001 x 8.31 x 100%) / 16.15		
External exposure	0.01657	mg/person	External exposure	0.00831	mg/person
External exposure	0.00027617	mg/kg bw/d	External exposure	0.00051455	mg/kg bw/d
Absorbed dose:	**0.0002762**	**mg/kg bw/d**	**Absorbed dose:**	**0.0005146**	**mg/kg bw/d**
			Residents: Oral exposure (hand-to-mouth transfer)		
			SOE_H = (AR x NA x D x TTR x SE x SA x Freq x H x OA) / BW		
			(0.004 x 1 x 0.57% x 5% x 50% x 20 x 20 x 2 x 100%) / 16.15		
			External exposure	0.000456	mg/person
			External exposure	2.8235E-05	mg/kg bw/d
			Absorbed dose	**0.0000282**	**mg/kg bw/d**
			Residents: Oral exposure (object-to-mouth transfer)		
			SOE_O = (AR x NA x D x DFR x IgR x OA) / BW		
			(0.004 x 1 x 0.57% x 20% x 25 x 100%) / 16.15		
			External exposure	0.000114	mg/person
			External exposure	7.0588E-06	mg/kg bw/d
			Absorbed dose	**0.0000071**	**mg/kg bw/d**
Total systemic exposure: $SE_R = SDE_R + SIE_R$			Total systemic exposure: $SE_R = SDE_R + SIE_R + SOE_H + SOE_O$		
Total systemic exposure (absorbed dose)	0.024892	mg/person	Total systemic exposure (absorbed dose)	0.011844	mg/person
Total systemic exposure (absorbed dose)	**0.0004149**	**mg/kg bw/d**	**Total systemic exposure** (absorbed dose)	**0.0007334**	**mg/kg bw/d**
% of AOEL:	**12.96**	**%**	**% of AOEL:**	**22.92**	**%**

Estimation of bystander exposure during/after application in Field Crops, Tractor Mounted (FCTM)

Input parameters considered for the estimation of bystander exposure:

Intended use(s):	6 – renewal of authorisation (isoxaflutole)		**Drift (D):**	0.57	% (FCTM, 5 m)
Applicant version			**Exposed Body Surface**	1	m² (adults)
Application rate (AR):	0.15	kg a.s./ha	**Area (BSA):**	0.21	m² (children)
Body weight (BW):	60	kg/person (adults)	**Specific Inhalation Exposure (I^*_A):**	0.001	mg/kg a.s. (6 hours, adults)
	16.15	kg/person (children)		0.00057	mg/kg a.s. (6 hours, children)
Dermal absorption (DA):	50.00	% ('worst case')	**Area Treated (A):**	20	ha/d (based on Field Crops, Tractor Mounted (FCTM))
Inhalation absorption (IA):	100	%	**Exposure duration (T):**	5	min
AOEL:	0.005	mg/kg bw/d			

Bystander exposure towards mesotrione					
Adults			**Children**		
Bystander: Dermal exposure after application in (via spray drift)					
SDE_B = (AR x D x BSA x DA) / BW			SDE_B = (AR x D x BSA x DA) / BW		
(15 x 0.57% x 1 x 50%) / 60			(15 x 0.57% x 0.21 x 50%) / 16.15		
External exposure	0.0855	mg/person	External exposure	0.017955	mg/person
External exposure	0.001425	mg/kg bw/d	External exposure	0.00111176	mg/kg bw/d
Absorbed dose:	**0.0007125**	**mg/kg bw/d**	**Absorbed dose:**	**0.0005559**	**mg/kg bw/d**
Bystander: Inhalation exposure after application in					
SIE_B = (I^*_A x AR x A x T x IA) / BW			SIE_B = (I^*_A x AR x A x T x IA) / BW		
(0,000 / 360 x 0.15 x 20 x 5 x 100%) / 60			(0,000 / 360 x 0.15 x 20 x 5 x 100%) / 16.15		
External exposure	4.1667E-05	mg/person	External exposure	2.3946E-05	mg/person
External exposure	6.9444E-07	mg/kg bw/d	External exposure	1.4827E-06	mg/kg bw/d
Absorbed dose:	**0.0000007**	**mg/kg bw/d**	**Absorbed dose:**	**0.0000015**	**mg/kg bw/d**
Total systemic exposure: $SE_B = SDE_B + SIE_B$			Total systemic exposure: $SE_B = SDE_B + SIE_B$		
Total systemic exposure (absorbed dose)	0.04279167	mg/person	Total systemic exposure (absorbed dose)	0.00900145	mg/person
Total systemic exposure (absorbed dose)	**0.0007132**	**mg/kg bw/d**	**Total systemic exposure** (absorbed dose)	**0.0005574**	**mg/kg bw/d**
% of AOEL:	**14.26**	**%**	**% of AOEL:**	**11.15**	**%**

Estimation of resident exposure after application in Field Crops, Tractor Mounted (FCTM)

Input parameters considered for the estimation of resident exposure:

Intended use(s):			**Drift (D):**	0.57	% (FCTM, 5 m)
Application rate (AR):	0.15	kg a.s./ha	**Transfer coefficient (TC):**	7300	cm^2/h (adults)
				2600	cm^2/h (children)
Number of applications (NA):	1		**Turf Transferable Residues (TTR):**	5	%
Body weight (BW):	60	kg/person (adults)	**Exposure Duration (H):**	2	h
	16.15	kg/person (children)	**Airborne Concentration of Vapour (ACV):**	0.001	mg/m3
Dermal absorption (DA):	50.00	% ('worst case')	**Inhalation Rate (IR):**	16.57	m^3/d (adults),
Inhalation absorption (IA):	100	%		8.31	m^3/d (children)
Oral absorption (OA)	100	%	**Saliva Extraction Factor (SE):**	50	%

AOEL	0.005	mg/kg bw/d	**Surface Area of Hands (SA):**	20	cm^2
			Frequency of Hand to Mouth (Freq):	20	events/h
			Dislodgeable foliar residues (DFR):	20	%
			Ingestion Rate for Mouthing of Grass/Day (IgR):	25	cm^2/d

Resident exposure towards mesotrione					
Adults			**Children**		
Residents: Dermal exposure after application in (via deposits caused by spray drift)					
SDE_R = (AR x NA x D x TTR x TC x H x DA) / BW			SDE_R = (AR x NA x D x TTR x TC x H x DA) / BW		
(0.0015 x 1 x 0.57% x 5% x 7300 x 2 x 50%) / 60			(0.0015 x 1 x 0.57% x 5% x 2600 x 2 x 50%) / 16.15		
External exposure	0.0062415	mg/person	External exposure	0.002223	mg/person
External exposure	0.00010403	mg/kg bw/d	External exposure	0.00013765	mg/kg bw/d
Absorbed dose:	**0.0000520**	**mg/kg bw/d**	**Absorbed dose:**	**0.0000688**	**mg/kg bw/d**
Residents: Inhalation exposure to vapour					
SIE_R = (AC_V x IR x IA) / BW			SIE_R = (AC_V x IR x IA) / BW		
(0.001 x 16.57 x 100%) / 60			(0.001 x 8.31 x 100%) / 16.15		
External exposure	0.01657	mg/person	External exposure	0.00831	mg/person
External exposure	0.00027617	mg/kg bw/d	External exposure	0.00051455	mg/kg bw/d
Absorbed dose:	**0.0002762**	**mg/kg bw/d**	**Absorbed dose:**	**0.0005146**	**mg/kg bw/d**
			Residents: Oral exposure (hand-to-mouth transfer)		
			SOE_H = (AR x NA x D x TTR x SE x SA x Freq x H x OA) / BW		
			(0.0015 x 1 x 0.57% x 5% x 50% x 20 x 20 x 2 x 100%) / 16.15		
			External exposure	0.000171	mg/person
			External exposure	1.0588E-05	mg/kg bw/d
			Absorbed dose	**0.0000106**	**mg/kg bw/d**
			Residents: Oral exposure (object-to-mouth transfer)		
			SOE_O = (AR x NA x D x DFR x IgR x OA) / BW		
			(0.0015 x 1 x 0.57% x 20% x 25 x 100%) / 16.15		
			External exposure	0.00004275	mg/person
			External exposure	2.6471E-06	mg/kg bw/d
			Absorbed dose	**0.0000026**	**mg/kg bw/d**
Total systemic exposure: $SE_R = SDE_R + SIE_R$			Total systemic exposure: $SE_R = SDE_R + SIE_R + SOE_H + SOE_O$		
Total systemic exposure (absorbed dose)	0.01969075	mg/person	Total systemic exposure (absorbed dose)	0.00963525	mg/person
Total systemic exposure (absorbed dose)	**0.0003282**	**mg/kg bw/d**	**Total systemic exposure** (absorbed dose)	**0.0005966**	**mg/kg bw/d**
% of AOEL:	**6.56**	**%**	**% of AOEL:**	**11.93**	**%**

A 3.3.2 Calculations for Mesotrione

A 3.3.3 Calculations for isoxaflutole

Resident - child	Spray drift (75th percentile) mg/kg bw/day	0.0022	% of RVNAS	18.61%
	Vapour (75th percentile) mg/kg bw/day	0.0011	% of RVNAS	8.92%
	Surface deposits (75th percentile) mg/kg bw/day	0.0002	% of RVNAS	1.33%
	Entry into treated crops (75th percentile) mg/kg bw/day	0.0084	% of RVNAS	70.31%
	All pathways (mean) mg/kg bw/day	0.0092	% of RVNAS	76.30%
Resident - adult	Spray drift (75th percentile) mg/kg bw/day	0.0004	% of RVNAS	3.39%
	Vapour (75th percentile) mg/kg bw/day	0.0002	% of RVNAS	1.92%
	Surface deposits (75th percentile) mg/kg bw/day	0.0001	% of RVNAS	0.58%
	Entry into treated crops (75th percentile) mg/kg bw/day	0.0047	% of RVNAS	39.06%
	All pathways (mean) mg/kg bw/day	0.0042	% of RVNAS	35.27%

A 3.4 Combined exposure calculations for mesotrione, tebuthylazine and isoxaflutole.

Not nessesery.

Appendix 4 Detailed evaluation of exposure and/or DFR studies relied upon (KCP 7.2, KCP 7.2.1.1, KCP 7.2.2.1, KCP 7.2.3.1)

Appendix 5 New data provided during the evaluation (May, 2019)

Operator, Worker, bystender/resident exposure assessment- CHR/H/TERIZ 650 WG

Dermal Absorption values

A summary of the dermal absorption rates for the active substances in CHR/H/TERIZ 650 WG are presented in the following table.

Dermal absorption rates for active substance Terbuthylazine in CHR/H/TERIZ 650 WG based on new dermal absorption study

	Terbuthylazine	
	Value	**Reference**
Concentrate	1.73%	Jeanne Bernal

	Terbuthylazine	
	Value	**Reference**
Dilution	15.3%	IN-VITRO HUMAN SKIN PENETRATION OF 14C-TERBUTHYLAZINE IN CHR/H/TERIZ TEST ITEM Eurofins Agroscience Services Chem SAS; 2019 Study code S19-01525

Exposure Assessment of Plant Protection Product CHR/H/TERIZ 650 WG based on active substance Terbuthylazine

Product information and toxicological reference values used for exposure assessment

Product name and code	CHR/H/TERIZ		
Formulation type	WG		
Category	Herbicide		
Container size(s), short description	500-10000 g, HDPE, bottels/container		
Active substance(s) (incl. content)	**Terbuthylazine** 400 g/kg		
Application rate	**1kg CHR/H/TERIZ 650 WG/ha equivalent to 400 g terbuthylazine/ha**		
AOEL systemic	0.0032 mg/kg bw/d		
Inhalation absorption	100 %		
Oral absorption	79% (acc. to EFSA Journal 2014;12(10):3874, p.5.6)		
Dermal absorption	Concentrate: 1.73% Dilution: 15.3 % From own study S19-01525		

OPERATOR EXPOSURE

Due to the new dermal absorption study IN-VITRO HUMAN SKIN PENETRATION OF 14C-TERBUTHYLAZINE IN CHR/H/TERIZ TEST ITEM; Eurofins 2019, new dermal absorption values were estimated. Therefore this section contains only updated Operator exposure assessment for Terbuthylazine.

Terbuthylazine			
Model data	**Level of PPE**	**Total absorbed dose (mg/kg/day)**	**% of systemic AOEL**
Tractor mounted boom spray application outdoors to low crops Application rate: 0.4 kg a.s./ha			
EFSA Model	no PPE	0.0122	382.32

	+PPE (gloves and workwear at mixing/loading)	0.0056	175.80
	+ PPE (gloves,workwear at mixing/loading and gloves, clothing and PPE during application)	0.0018	57.30

The predicted exposure values according to EFSA model for Terbuthylazine without using PPE and with using PPE at mixing loading are above 100 % AOEL, but with using PPE at mixing/loading and during application are significantly below 100% of systemic AOEL and therefore exposure of the operator is acceptable for terbuthylazine**.**

Accordingly, in this case it is advisable to use full protective clothing to minimize the risk.

Worker exposure

Due to the new dermal absorption study IN-VITRO HUMAN SKIN PENETRATION OF 14C-TERBUTHYLAZINE IN CHR/H/TERIZ TEST ITEM; Eurofins 2019, new dermal absorption values were estimated. Therefore this section contains only updated worker exposure assessment for Terbuthylazine.

Critical use(s)	Maize (max 400 g terbuthylazine/ha)
Model	EUROPEM II

Estimated worker exposure

		Terbuthylazine	
Model data	**Level of PPE**	**Total absorbed dose (mg a.s /day)**	**% of systemic AOEL**
Number of applications and application rate:		0.4 kg a.s./ha	
2 hours/day (1), TC: 2500 cm^2/person/h (2) Body weight: 60 kg DFR 30mg a.s/m2. (default)	no PPE (3)	0.918	478
	with PPE (gloves)	0.184	96
		Terbuthylazine	
Model data	**Level of PPE**	**Total absorbed dose (mg a.s /day)**	**% of systemic AOEL**
Number of applications and application rate:		0.4 kg a.s./ha	
8 hours/day (1), TC: 2500 cm^2/person/h (2) Body weight: 60 kg DFR 2.34 mg a.s/m2. Based on DT50 2.8 days for foliar deposits on maize. Cross reference: Terbuthylazine – Additional report Annex B6 page 167. And Additional report Annex B9 B.9.1.3.3.2.i	no PPE (3)	0.286	149
	with PPE (gloves)	0.057	30

Conclusions:

The results of the exposure estimations based on EUROPOEM II suggest that the use of CHR/H/TERIZ according to the list of intended uses presented in GAP Table, causes **no health risk for the worker** assuming:

- the workwear (arms, body and legs covered) and protective gloves are used,
- the time of worker activities (inspection) is reduced to 2 hours
- the worker is allowed to enter treated area earliest on the fourth day after PPP application.

Following sentence regarding the use of PPE is recommended by the evaluator to be placed in the **section of precautions for the workers:**

„*Stosować rękawice ochronne oraz odzież roboczą (długie spodnie, koszula z długim rękawem) oraz ograniczyć czas inspekcji terenu poddanego opryskowi: do 2 godzin. Wejście na teren poddany opryskowi możliwy jest nie wcześniej niż w czwartej dobie od wykonania oprysku".*

"Wear protective gloves and workwear (long trousers, long-sleeve shirt) and reduce the time of treated area inspection to 2 hours. The reentry into treated area is allowed not sooner than on the fourth day post-treatment".

Bystander and resident exposure

Due to the new dermal absorption study IN-VITRO HUMAN SKIN PENETRATION OF 14C-TERBUTHYLAZINE IN CHR/H/TERIZ TEST ITEM; Eurofins 2019, new dermal absorption values were estimated. Therefore this section contains only updated bystander/resident exposure assessment for Terbuthylazine.

Exposure models for intended uses

Critical use(s)	maize (max. 1/ kg product/ha)
Model	EFSA model

Estimated bystander and resident exposure for terbuthylazine with default DFR and DT50 values and drift reducing nozzels

Resident - child	Spray drift (75th percentile) mg/kg bw/day	0.0027	% of RVNAS	85.80%
	Vapour (75th percentile) mg/kg bw/day	0.0011	% of RVNAS	33.44%
	Surface deposits (75th percentile) mg/kg bw/day	0.0002	% of RVNAS	7.37%
	Entry into treated crops (75th percentile) mg/kg bw/day	0.0103	% of RVNAS	322.73%
	All pathways (mean) mg/kg bw/day	0.0110	% of RVNAS	344.01%
Resident - adult	Spray drift (75th percentile) mg/kg bw/day	0.0005	% of RVNAS	15.60%
	Vapour (75th percentile) mg/kg bw/day	0.0002	% of RVNAS	7.19%
	Surface deposits (75th percentile) mg/kg bw/day	0.0001	% of RVNAS	2.68%
	Entry into treated crops (75th percentile) mg/kg bw/day	0.0057	% of RVNAS	179.30%
	All pathways (mean) mg/kg bw/day	0.0051	% of RVNAS	160.31%

Refinement of generic DFR value

Based on DT50 2.8 days for foliar deposits on maize for terbuthylazine the DFR was calculated to be DFR 2.34 mg a.s/m2 based on the equation:

$$DFR\ (t) = DFR \times e^{(-\ln(2)/DT50) \times t} = 2.34\ \mu g/cm^2/kg\ a.s./ha$$

Cross reference: Terbuthylazine – Additional report Annex B6 page 167. And Additional report Annex B9 B.9.1.3.3.2.i

Estimated bystander and resident exposure for terbuthylazine with refined DFR and DT50 values and drift reducing nozzels

Resident - child	Spray drift (75th percentile) mg/kg bw/day	0.0027	% of RVNAS	85.80%
	Vapour (75th percentile) mg/kg bw/day	0.0011	% of RVNAS	33.44%
	Surface deposits (75th percentile) mg/kg bw/day	0.0002	% of RVNAS	7.37%
	Entry into treated crops (75th percentile) mg/kg bw/day	0.0081	% of RVNAS	251.73%
	All pathways (mean) mg/kg bw/day	0.0092	% of RVNAS	287.40%
Resident - adult	Spray drift (75th percentile) mg/kg bw/day	0.0005	% of RVNAS	15.60%
	Vapour (75th percentile) mg/kg bw/day	0.0002	% of RVNAS	7.19%
	Surface deposits (75th percentile) mg/kg bw/day	0.0001	% of RVNAS	2.68%
	Entry into treated crops (75th percentile) mg/kg bw/day	0.0045	% of RVNAS	139.85%
	All pathways (mean) mg/kg bw/day	0.0041	% of RVNAS	128.85%

The main exposure to resident/bystander is from entry into treated crops. Therefore as a risk mitigation it should be stated:

- Drift reducing nozzels
- Do not entry into treated area