REGISTRATION REPORT

Part B

Section 6

Mammalian Toxicology

Detailed summary of the risk assessment

Product code: ADM.09050.H.1.A

Product name(s): **STEMPER**

Chemical active substance:

Trinexapac-ethyl, 175 g/L

Central Zone

Zonal Rapporteur Member State: Poland

CORE ASSESSMENT

(authorization)

Applicant: **ADAMA**

Submission date: May 2022

Evaluation date: March 2023

Version history

When	What
January 2021	dRR version 1 submitted by applicant
March 2023	Version evaluated by zRMS PL

DATA PROTECTION CLAIM

Under Article 59, Regulation 1107/2009/EC, on behalf of the Sponsor Company the applicant claims data protection for these studies. The data protection status and corresponding justification as valid for the respective country will be confirmed in the respective PART A

STATEMENT FOR OWNERSHIP

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6 Mammalian Toxicology (KCP 7)

6.1 Summary

Table 6.1-1: Information on ADM.09050.H.1.A*

Product name and code	ADM.09050.H.1.A
Formulation type	Emulsifiable concentrate [Code: EC]
Active substance(s) (incl. content)	Trinexapac-ethyl, 175 g/L
Function	Plant growth regulator
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 ADM.09050.H.1.A 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 ADM.09050.H.1.A according to Regulation (EC) No 1272/2008

Hazard class(es), categories:	Skin irritation Category 2 Eye irritation Category 2 Skin sensitization Category 1 STOT RE 2, H373 (GI tract)
Hazard pictograms or Code(s) for hazard pictogram(s):	H315 H319 H317 H373 (GI tract)
Signal word:	GHS07 Warning
Hazard statement(s):	H315 Causes skin irritation H319 Causes serious eye irritation H317 May cause allergic skin reaction H373: May cause damage to organs (GI tract) through prolonged or repeated exposure
Precautionary statement(s):	~~Information can be found in Part A under Point 2.4~~ ~~**P102, P280, P302+P352, P305+P351+P338, P501**~~ P261 Avoid breathing spray. P264 Wash hands and face thoroughly after handling P272 Contaminated work clothing should not be allowed out of the workplace P280 Wear protective gloves/protective clothing/eye protection/face protection. P302 + P352 IF ON SKIN: Wash with plenty of soap and water P305 + P351 + P338 IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing. P337 + P313 If eye irritation persists: Get medical advice/attention P332 + P313 If skin irritation occurs: Get medical advice/attention. P362 Take off contaminated clothing and wash before reuse. P314 Get medical advice/attention if you feel unwell. P501 Dispose of contents/container to …in accordance with local/ regional/ national/international regulation
Additional labelling phrases:	~~Information can be found in Part A under Point 2.4~~ 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 ADM.09050.H.1.A

	Result	PPE / Risk mitigation measures
Operators	Acceptable	No specific PPE (Work wear)
Workers	Acceptable	No specific PPE (Work wear)
Bystanders	Acceptable	No Acute AOEL established, bystander exposure covered by resident exposure
Residents	Acceptable	None

No unacceptable risk for operators, workers, bystanders and residents was identified when the product is used as intended. No specific PPE is necessary.

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) a.s. 1 b) a.s. 2	**Water L/ha** **min / max**			**Operator**	**Worker**	**Bystander**	**Residents**
14	Winter barley	F	Spraying, LCTM	1	0.210	200 - 400	n/a	Critical GAP for Operator, worker and bystander/resident 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	A	A	A	A

* 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

Data gaps

Noticed data gaps are:

- None

6.2 Toxicological Information on Active Substance

Information regarding classification of the active substance 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)

Common Name	Trinexapac (variant evaluated trinexapac-ethyl)
CAS-No.	95266-40-3 (trinexapac-ethyl, enol form) 104273-73-6 (trinexapac, keto form) 143294-89-7 (trinexapac, enol form)
Classification and proposed labelling	
With regard to	None

toxicological endpoints (according to the criteria in Reg. 1272/2008, as amended)	Classification to be updated: Skin Sens. 1B, H317 STOT RE 2, H373 (GI tract) (RAC opinion adopted 5 Dec 2019, ~~Legal deadline for opinion adoption 14 Mar 2020~~)
Additional C&L proposal	Aquatic chronic 1, H410 (RAC opinion adopted 5 Dec 2019, ~~Legal deadline for opinion adoption 14 Mar 2020~~)
Agreed EU endpoints	
AOEL systemic	0.34 mg/kg bw/day
AAOEL	Not required
Reference	Peer review of the pesticide risk assessment of the active substance trinexapac (variant evaluated trinexapac-ethyl), EFSA Journal 2018;16(4):5229
Conditions to take into account/critical areas of concern with regard to toxicology	
Reference	Peer review of the pesticide risk assessment of the active substance trinexapac (variant evaluated trinexapac-ethyl), EFSA Journal 2018;16(4):5229 RAC opinion proposing harmonised classification and labelling at EU level of Trinexapac-ethyl (ISO); ethyl 4-[cyclopropyl(hydroxy)methylene]-3,5-dioxocyclohexane carboxylate adopted 5 Dec 2019 COMMISSION DELEGATED REGULATION (EU) 2021/849 of 11 March 2021 amending, for the purposes of its adaptation to technical and scientific progress, Part 3 of Annex VI to Regulation (EC) No 1272/2008 of the European Parliament and of the Council on classification, labelling and packaging of substances and mixtures

6.3 (RAC opinion adopted 5 Dec 2019Toxicological Evaluation of Plant Protection Product

A summary of the toxicological evaluation for ADM.09050.H.1.A (= AG-T3-175 EC1) is given in the following table.

Detailed compositions of ADM.09050.H.1.A (= AG-T3-175 EC1) and AG-T3-175 EC as well as a justification for the bridging between the two compositions are provided in Part C.

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 ADM.09050.H.1.A

Type of test, species, model system (Guideline)	Result	Acceptability	Classification (acc. to the criteria in Reg. 1272/2008)	Reference
LD_{50} oral, rat (OECD 423)	> 2000 mg/kg bw	Yes	None	xxxxxxxxx 2008a
LD_{50} dermal, rat (OECD 402)	> 2000 mg/kg bw	Yes	None	xxxxxxxxx 2008b
LC_{50} inhalation, rat (OECD 403)	Not required (Classification not required based on calculation method)			
Skin irritation, rabbit (OECD 404)	Irritating	Yes	Skin Irrit.2, H315	xxxxxxxx 2008c
Eye irritation, rabbit (OECD 405)	Irritating	Yes	Eye Irrit. 2, H319	xxxxxxxx 2008d

Skin sensitisation, Guinea pig (OECD 406)	sensitising	Yes	Skin Sens. 1, H317	xxxxxxxxxx 2008e
Supplementary studies for combinations of plant protection products	No data – not required	-	-	-

Table 6.3-2: Additional toxicological information relevant for classification/labelling of ADM.09050.H.1.A

	Substance (Concentration in product, % w/w)	**Classification of the substance (acc. to the criteria in Reg. 1272/2008)**	**Reference**
Toxicological properties of active substance(s) (relevant for classification of product)	Trinexapac-ethyl 17.24%	STOT RE 2, H373 (GI tract).	RAC opinion proposing harmonised classification and labelling at EU level of Trinexapac-ethyl (ISO); ethyl 4-[cyclopropyl(hydroxy) methylene]-3,5-dioxocyclohexane carboxylate adopted 5 Dec 2019
Toxicological properties of non-active substance(s) (relevant for classification of product)	Information can be found in the confidential dossier of this submission (Registration Report - Part C)		
Further toxicological information	No data – not required		

* 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

All metabolite concentrations are predicted to stay below 0.1 µg/L – no groundwater assessment is required. Reference is made to Part B section 10.

6.5 Dermal Absorption (KCP 7.3)

A summary of the dermal absorption rates for the active substances in ADM.09050.H.1.A (= AG-T3-175 EC1) are presented in the following table.

Table 6.5-1: Dermal absorption rates for active substances in ADM.09050.H.1.A

	Value	**Reference**
Concentrate	3.1%	xxxxxx 2018 (study reported in Appendix 2)
Dilution (dilution factor 1600)	66 %	

6.5.1 Justification for proposed values – Trinexapac-ethyl

Proposed dermal absorption rates for trinexapac-ethyl are based on dermal absorption study on the formulationADM.09050.H.1.A (previous code = AG-T3-175 EC1) on human skin. The study results are summarized in the following table. A full study summary is presented in Annex 2.

Table 6.5-2: Summary of the results of submitted dermal absorption studies for Trinexapac-ethyl

Test	Concentrate	Spray dilution (dilution factor 1600)	Formulation in study	Acceptability of study	Justification provided on representativity of study formulation for current product	Acceptability of justification	Reference
In vitro (human)	3.1 %	66 %	ADM.09050.H.1.A (= AG-T3-175 EC1)	YES	Yes (see Appendix A 2.10)	YES	xxxxxxx 2018

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	ADM.09050.H.1.A
Formulation type	EC
Category	Plant growth regulator
Active substance(s) (incl. content)	**Trinexapac-ethyl** 175 g/L
AOEL systemic	0.34 mg/kg bw/d
Inhalation absorption	100 %
Oral absorption	>96 %
Dermal absorption	Concentrate: 3.1 % Dilution: 66 % (Dilution rate: 1600)

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 Central EU is given in Part B, Section 0.

Justification

ADM.09050.H.1.A is applied in small grain cereals and in grass for seed productions. The maximum recommended use rate is 1.2 L/ha for both crop types.

Critical GAP considered for the operator exposure and for worker exposure risk assessment (1.2 L product applied) covers the maximum application rate intended for the use of ADM.09050.H.1.A in cereals or in grass for seed production.

The critical GAP has been defined following evaluation of the individual GAPs for each crop in each relevant Member State and takes into account the maximum application rate applied in the minimum water volume as relevant for this zone.

The critical GAP considered for the resident/bystander risk assessment covers the maximum application rate (1.2 L product applied in 200 L water/ha) intended for the use of ADM.09050.H.1.A in cereals.

Thus, the use of ADM.09050.H.1.A (1.2 L/ha) in cereals is considered as critical GAP for all relevant exposure scenarios and for all intended uses.

6.6.2 Operator exposure (KCP 7.2.1)

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 ADM.09050.H.1.A according to the critical use 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(s)	Cereals (max. 1.2 L product/ha)
Model(s)	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 calculator version: 30/03/2015

Table 6.6-3: Estimated operator exposure

		Trinexapac-ethyl	
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: 0.210 kg a.s./ha			
EFSA Operator Model (75th quantile regression) Body weight: 60 kg	Potential exposure (no clothing)	0.0526	15.5%
	+ Work Wear (arms, body, legs covered)	0.0337	9.9%

Results
The estimated operator exposure for an operator wearing normal work wear accounts for about 10% of the established AOEL even when not considering the use of protective gloves during mixing/loading or application.

Therefore, it is concluded that the use of ADM.09050.H.1.A is at an acceptable risk for the operator.

6.6.3 Measurement of operator exposure

Since the operator exposure estimations 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 neces-

sary and was therefore not performed.

zRMS:
The potential exposure to Trinexapac-ethyl of operator not wearing a work clothing (long sleeved shirt, long trousers) and applying formulation ADM.09050.H.1.A (STEMPER) on cereals at maximal dose of 1.2 L product/ha (0.210 kg a.s./ha) using tractor-mounted/trailed boom sprayer, calculated with the EFSA AOEM amounted to 15.5% of AOEL. In case the operator is using a work clothing (long sleeved shirt, long trousers) during mixing/loading and application the exposure to Trinexapac-ethyl is reduced to 9.9% of AOEL.

Since the potential systemic exposures and systemic exposure of operator wearing a work clothing (long sleeved shirt, long trousers) during mixing/loading and application to active substance expressed as percentage of its AOEL is well below 100%, the application of product STEMPER (ADM.09050.H.1.A) according to its intended use within good agricultural practice does not pose an unacceptable risk to the health of operator

Since the product STEMPER (ADM.09050.H.1.A) is classified as Skin Irrit. 2, Eye Irrit. 2 and Skin Sens. 1 the operator should wear protective clothing covering body, legs and arms, sturdy shoes, protective gloves and eye protection/face protection during loading/mixing operations or when directly contacting surface of equipment contaminated with concentrated product.

6.6.4 Worker exposure (KCP 7.2.3)

6.6.4.1 Estimation of worker exposure

Table 6.6-4 shows the exposure model used for estimation of worker exposure after entry into a previously treated area or handling a crop treated with ADM.09050.H.1.A according to the critical use. 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)	Cereals (max. 1.2 L /product/ha)
Model	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

Table 6.6-5: Estimated worker exposure

		Trinexapac-ethyl	
Model data	**Level of PPE**	**Total absorbed dose (mg/kg/day)**	**% of systemic AOEL**
Number of applications and application rate:		1 x 0.210 kg a.s./ha	
EFSA Worker Model **Body weight: 60 kg,** **DFR: 3 µg/cm²/kg a.s./ha** 2 hours/day Body weight: 60 kg	Potential(1) TC:12500 cm^2/person/h	0.1733	51%
	Work cloth (2) TC: 1 400 cm^2/person/h	0.0194	5.7%

(1) Potential exposure: no clothing considered
(2) Work cloth: Worker wearing long sleeved shirt, long trousers (“permea ble”) but no gloves

The risk for worker is acceptable for the active substance when wearing a work wear only. No further refinement is necessary.

Therefore, it is concluded that there is no unacceptable risk, when a worker re-enters crops treated with ADM.09050.H.1.A.

6.6.4.2 Refinement of generic DFR value (KCP 7.2)

Since the worker exposure estimations 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.

6.6.4.3 Measurement of worker exposure

Since the worker exposure estimations 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.

zRMS:
The potential exposure to Trinexapac-ethyl of worker not wearing a work clothing (long sleeved shirt, long trousers) and entering for 2 hours inspection a field of cereals treated with formulation ADM.09050.H.1.A (STEMPER) at maximal dose of 1.2 L product/ha (0.210 kg a.s./ha) using tractor-mounted/trailed boom sprayer, calculated with the EFSA AOEM amounted to 51% of AOEL. In case the worker is wearing a work clothing (long sleeved shirt, long trousers) the exposure to Trinexapac-ethyl is reduced to 5.7% of AOEL.

Since the potential systemic exposures and systemic exposure of worker wearing a work clothing (long sleeved shirt, long trousers) during 2 hrs inspection to active substance expressed as percentage of its AOEL is well below 100%, the application of product STEMPER (ADM.09050.H.1.A) according to its intended use within good agricultural practice does not pose an unacceptable risk to the health of worker.

6.6.5 Bystander and resident exposure (KCP 7.2.2)

6.6.5.1 Estimation of resident exposure

Table 6.6-6 shows the exposure model(s) used for estimation of resident exposure to trinexapac-ethyl. Outcome of the estimation is presented in Table 6.6-7. Detailed calculations are given in Appendix 3.

Table 6.6-6: Exposure models for intended uses

Critical use(s)	Cereals (max. 1.2 L /product/ha)
Model	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 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

Table 6.6-7: Estimated resident exposure

	Trinexpac-ethyl	
Route of exposure	**75th centile (mg/kg bw/day)**	**in % of AOEL (RVNAS)**
Tractor mounted boom spray application outdoors to low crops (cereals) Application rate: 0.21 kg trinexapac-ethyl/ha water volume 200 L/ha Drift rate: 5.60/4.10 % Buffer zone: 2-3 (m) Drift reduction technology: no DT_{50}: 30 days; DFR: 3 µg/cm²/kg a.s./ha		
Resident child (body weight 10 kg)		
Spray drift	0.0186	5.47%
Vapour	0.0011	0.31%
Surface deposits	0.0022	0.64%
Entry into treated crops (= exposure to soil borne residues)	0.0234	6.88%
Sum of all pathways: Mean	0.0316	9.28%
Resident adult (body weight 60 kg)		
Spray drift[1]	0.0045	1.31%
Vapour	0.0002	0.07%
Surface deposits	0.0009	0.28%
Entry into treated crops (= exposure to soil borne residues)	0.0130	3.82%
Sum of all pathways: Mean	0.0134	3.94%

The calculated total systemic exposure for residents are below the AOEL for children and adults with the active substance trinexapac-ethyl.

Therefore, it is concluded that resident exposure to ADM.09050.H.1.A is acceptable in cereals.

6.6.5.2 Estimation of bystander exposure

According to the EFSA-OPEX guidance, a bystander risk assessment is required for plant protection products that have significant acute toxicity or the potential to exert toxic effects after a single exposure, based on the 95th percentile data values.
For Trinexapac-ethyl no AAOEL and no ARfD have been established. Therefore, a risk assessment for bystanders was not performed. The chronic risk for bystanders, however, is covered by the chronic risk assessment for residents.

6.6.5.3 Measurement of bystander and/or resident exposure

Since the resident exposure estimations carried out indicated that the acceptable operator exposure level (AOEL) for trinexapac-ethyl 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.

zRMS:
The exposure estimation of resident (adult and child) to Trinexapac-ethyl, an active substance of a product STEMPER (formulation ADM.09050.H.1.A) applied on a field of cereals at maximal dose of 1.2 L product/ha (0.210 kg a.s./ha) as foreseen in GAP, using tractor-mounted/trailed boom sprayer, calculated with the EFSA AOEM demonstrates that such a exposure for adult resident is 3.94 % of AOEL and for child resident 9.28 %% of AOEL, therefore the risk would be acceptable, and no risk refinement is needed using relevant risk management measures such as increased buffer zone or drift reduction technology.

No bystander acute exposure estimation for Trinexapac-ethyl is required since no acute acceptable operator exposure value (AAOEL) has be set for any of this active substance. Therefore, as indicated in the EU guidance (SANTE-10832-2015 rev. 1.7; 24 January 2017), no unacceptable risk is expected for bystanders due to short-term single exposure to Trinexapac-ethyl as a result of application of a product STEMPER (formulation ADM.09050.H.1.A) with accordance with intended use within good agricultural practice.

Summing up application of a product STEMPER (formulation ADM.09050.H.1.A) in line with GAP on low crops at maximal dose of 1.2 L product/ha, using tractor-mounted/trailed boom sprayer does not pose an unacceptable health risk for residents and bystanders.

6.6.6 Combined exposure

Not relevant. The product contains only one active substance.

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 7.1.1/01	xxxxxxxxxx	2008a	Trinexapac-ethyl 175 EC – Acute Oral Toxicity Study in Rats Report No. B92790 xxxxxxxxxxxx GLP unpublished	Y	Celsius Property B.V.
KCP 7.1.2/01	xxxxxxxxx	2008b	Trinexapac-ethyl 175 EC – Acute Dermal Toxicity Study in Rats Report No. B92801 xxxxxxxxxxxxxxxx GLP unpublished	Y	Celsius Property B.V.
KCP 7.1.4/01	xxxxxxxxx	2008c	Trinexapac-ethyl 175 EC – Primary Skin Irritation Study in Rabbits (4 –Hour Semi-Occlusive Application) Report No. B92812 xxxxxxxxxxxxxxx GLP unpublished	Y	Celsius Property B.V.
KCP 7.1.5/01	xxxxxxxxx	2008d	Trinexapac-ethyl 175 EC – Primary Eye Irritation Study in Rabbits Report No. B92823 xxxxxxxxxxxxxxxxxxxx GLP unpublished	Y	Celsius Property B.V.
KCP 7.1.6/01	xxxxxxxxx	2008e	Trinexapac-ethyl 175 EC – Contact Hypersensitivity in Albino Guinea Pigs, Maximisation –Test Report No. B97187 xxxxxxxxxxxxxxxxxx	Y	Celsius Property B.V.

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*
			GLP unpublished		
KCP 7.3/01	xxxxxxxx	2018	*In vitro* percutaneous absorption of Trinexapac-ethyl, formulated as AG-T3-175 EC1, through human skin Report V21000/22; 90020905 xxxxxxxxxxxxxxxxxxxxxxxxxxx GLP unpublished	N	ADAMA Agan Ltd

*Celsius Property B.V. is a member of the ADAMA group.

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

None.

The following tables are to be completed by MS

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

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

Appendix 2 Detailed evaluation of the studies relied upon

A 2.1 Statement on bridging possibilities

For the bridging of the acute toxicity studies from AG-T3-175 EC to ADM.09050.H.1.A please refer to Part C.

Comments of zRMS:	The change in the composition of formulation ADM.09050.H.1.A in comparison with composition of formulation Trinexapac-ethyl 175 EC used for toxicity testing is considered as non-significant according to criteria of Guidance document on significant and non-significant changes of the chemical composition of authorised plant protection products under Regulation (EC) No 1107/2009 of the EU Parliament and Council on placing of plant protection products on the market and repealing Council Directives 79/117/EEC and 91/414/EEC, therefore the results of this testing can be used for assessment of toxicity of formulation ADM.09050.H.1.A (see part C)

A 2.2 Acute oral toxicity (KCP 7.1.1)

Comments of zRMS:	The study performed according to relevant OECD guidelines and in GLP conditions is acceptable. The results indicate that LD_{50} is > 2000 mg/kg bw, thus above the classification criteria for category 4 (300 < Category 4 ≤ 2 000 mg/kg bw), therefore the formulation Trinexapac-ethyl 175 EC/ ADM.09050.H.1.A (STEMPER) does not require classification for acute oral toxicity according to criteria of the Regulation 1272/2008 as Acute Tox. 4; H302.

Reference:	**KCP 7.1.1/01**
Report	Trinexapac-ethyl 175 EC – Acute Oral Toxicity Study in Rats. xxxxxx (2008a); Document No B92790
Guideline(s):	OECD 423 equivalent to Council Regulation (EC) 440/2008 B.1 Tris
Deviations:	Yes (no step-wise testing procedure)
GLP:	Yes
Acceptability:	Yes
Duplication (if vertebrate study)	No. The study was already performed in 2008. It is an existing report, and the study was not conducted for this submission.

Materials and methods

Test material (Lot/Batch No.)	Trinexapac-ethyl 175 EC (Batch D-I0703)
Species	Rat, Han:Wistar
No. of animals (group size)	3 female rat/group, 2 groups
Dose(s)	2000 mg/kg bw
Exposure	Once by gavage
Vehicle/Dilution	deionized water

Post exposure observation period	14 days
Remarks	Purity analysed

Results and discussions

Table A2.2-1: Results of acute oral toxicity study in rats of Trinexapac-ethyl 175 EC

Dose (mg/kg bw)	Toxicological results *	Duration of signs	Time of death	LD50 (mg/kg bw) (14 days)
Female rats				
2000	0/6	No signs	na	> 2000

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

Table A2.2-2: Summary of findings of acute oral toxicity study in rats of Trinexapac-ethyl 175 EC

Mortality:	No mortality occurred.
Clinical signs:	No clinical signs of toxicity were observed.
Body weight:	Body weight gain was considered to be normal.
Macroscopic examination:	The necropsies performed at the end of the study revealed no apparent findings.

Conclusion

Under the experimental conditions, the oral LD_{50} of Trinexapac-ethyl 175 EC is 2000 mg/kg bw in rats. Thus, no classification is required according to Regulation (EC) No. 1272/2008.

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

Comments of zRMS:	The study performed according to relevant OECD guidelines and in GLP conditions is acceptable. The results indicate that LD_{50} is > 2000 mg/kg bw, thus above the classification criteria for category 4 (1000 mg/kg bw < Category 4 ≤ 2 000 mg/kg bw), therefore the formulation Trinexapac-ethyl 175 EC/ ADM.09050.H.1.A (STEMPER) does not require classification for acute dermal toxicity according to criteria of the Regulation 1272/2008.

Reference:	**KCP 7.1.2/01**
Report	Trinexapac-ethyl 175 EC – Acute Dermal Toxicity Study in Rats. xxxxxxx (2008b); Document No B92801
Guideline(s):	OECD 402 equivalent to Council Regulation (EC) 440/2008 B.3
Deviations:	Yes (no step-wise testing procedure)
GLP:	Yes
Acceptability:	Yes
Duplication (if vertebrate study)	No. The study was already performed in 2008. It is an existing report, and the study was not conducted for this submission.

Materials and methods

Test material (Lot/Batch No.)	Trinexapac-ethyl 175 EC (Lot/Batch No. D-I0703)
Species	e.g. Rat, Han:Wistar
No. of animals (group size)	5 rats/sex
Dose(s)	2000 mg/kg bw
Exposure	24 hours (dermal, semi-occlusive)
Vehicle/Dilution	deionized water
Post exposure observation period	14 days
Remarks	None

Results and discussions

Table A2.3-1: Results of acute dermal toxicity study in rats of Trinexapac-ethyl 175 EC

Dose (mg/kg bw)	Toxicological results *	Duration of signs	Time of death	LD50 (mg/kg bw) (14 days)
Male rats				
2000	5/5	During observation period	na	> 2000
Female rats				
2000	5/5	During observation period	na	> 2000

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

Table A 2.3-2: Summary of findings of acute dermal toxicity study in rats of Trinexapac-ethyl 175 EC

Mortality:	No mortality occurred.
Clinical signs:	Yes - Observed skin reactions were slight to moderate erythema and scaling that resolved in most of the animals in the middle of the observation period, but in few animals persisted until the end of observation. Slight oedema were observed in the first days after treatment but resolved afterwards. Necrosis was found in two animals and slight fissures in three animals.
Body weight:	Two animals did not gain weight and one animal slightly lost weight (<2%) during the first week after treatment, but those animals recovered until end of observation.
Macroscopic examination:	The necropsies performed at the end of the study revealed no apparent findings

Conclusion

Under the experimental conditions, the dermal LD_{50} of Trinexapac-ethyl 175 EC is 2000 mg/kg bw in rats. Thus, no classification is required according to Regulation (EC) No. 1272/2008.

A 2.4 Acute inhalation toxicity (KCP 7.1.3)

No inhalation toxicity study was required since the active ingredient trinexapac has a vapour pressure of 2.3×10^{-3} Pa at 25°C, which is well below the trigger value of 1×10^{-2} Pa at 25°C, and the use of ADM.09050.H.1.A will not result in any significant generation of inhalable particles or droplets (< 50 µm).

Comments of zRMS:	None of the component of formulation Trinexapac-ethyl 175 EC/ ADM.09050.H.1.A (STEMPER) is classified for acute inhalation toxicity, therefore in line with calculation method described in Regulation 1272/2008 the whole mixture does not require classification for acute inhalation toxicity

A 2.5 Skin irritation (KCP 7.1.4)

Comments of zRMS:	The study performed according to relevant OECD guidelines and in GLP conditions is acceptable. According to Regulation 1272/2008 in order to be classified as Skin Irrit. 2 a substance or mixture has to induced in a standard test the effects meeting the following criteria; (1) Mean value of ≥ 2,3 - ≤ 4,0 for erythema/eschar or for (or oedema in at least 2 of 3 tested animals from gradings at 24, 48 and 72 hours after patch removal or, if reactions are delayed, from grades on 3 consecutive days after the onset of skin reactions; or (2) Inflammation that persists to the end of the observation period normally 14 days in at least 2 animals, particularly taking into account alopecia (limited area), hyperkeratosis, hyperplasia, and scaling; or (3) In some cases where there is pronounced variability of response among animals, with very definite positive effects related to chemical exposure in a single animal but less than the criteria above. The score for erythema or oedema were of lower than those defined in the classification criteria in all three animals, thus the first criterion was not met. However, in all three animals erythema was still visible at the end of the 14 days of observation, (in 2 animals with score of 2) thus inflammation was persistent, therefore the classification criteria are met and formulation Trinexapac-ethyl 175 EC/ ADM.09050.H.1.A (STEMPER) warrant classification as Skin Irrit. 2, H315: Causes skin irritation

Reference:	**KCP 7.1.4/01**
Report:	Trinexapac-ethyl 175 EC – Primary Skin Irritation Study in Rabbits (4 – Hour Semi-Occlusive Application). xxxxxxx (2008c); Document No B92812
Guideline(s):	OECD 404 equivalent to Council Regulation (EC) 440/2008 B.4
Deviations:	Yes (no initial test using one animal)
GLP:	Yes
Acceptability:	Yes
Duplication (if vertebrate study)	No. The study was already performed in 2008. It is an existing report, and the study was not conducted for this submission.

Materials and methods

Test material (Lot/Batch No.)	Trinexapac-ethyl 175 EC (Lot/Batch No. D-I0703)
Species	Rabbit, New Zealand White
No. of animals (group size)	3 animals (1 male, 2 females)
Initial test using one animal	No

Exposure	0.5 mL (4 hours, semi-occlusive)
Vehicle/Dilution	None
Post exposure observation period	14 days
Remarks	None

Results and discussions

Table A 2.5-1: Skin irritation of Trinexapac-ethyl 175 EC

Animal No.		Scores after treatment *				Mean scores (24-72 h)	Reversible (day)
		1 h	24 h	48 h	72 h		
1	Erythema Oedema	2 1	2 1	2 1	1 1	1.67 1	Still observed at day 14 7
2	Erythema Oedema	2 1	2 2	2 2	2 2	2 2	Still observed at day 14 10
3	Erythema Oedema	2 1	2 2	2 1	2 1	2 1.33	Still observed at day 14 7

* scores in the range of 0 to 4

Clinical signs:	Yes - Mild to moderate erythema was observed after end of treatment (in all animals, up to max. grade 2). Oedema resolved in the last animal by 10 days after application, while erythema decreased in severity, but were visible until the end of the observation period.

Conclusion

Under the experimental conditions, Trinexapac-ethyl 175 EC is a skin irritant. Thus, classification with 'H315: Causes Skin Irritation'is required according to Regulation (EC) No. 1272/2008.

A 2.6 Eye irritation (KCP 7.1.5)

Comments of zRMS:	The study performed according to relevant OECD guidelines and in GLP conditions is acceptable. According to Regulation 1272/2008 in order to be classified as Eye Irrit. 2 a substance or mixture if, when applied to the eye of an animal, produces at least in 2 of 3 tested animals, a positive response of: — corneal opacity ≥ 1 and/or — iritis ≥ 1, and/or — conjunctival redness ≥ 2 and/or — conjunctival oedema (chemosis) ≥ 2 calculated as the mean scores following grading at 24, 48 and 72 hours after installation of the test material, and which fully reverses within an observation period of 21 days. Since the formulation Trinexapac-ethyl 175 EC/ ADM.09050.H.1.A (STEMPER) has induced in three rabbits the conjunctival redness with a score of 2 as a mean of grading at 24, 48 and 72 hours and all eye effects were reversible within 14 days after instillation the formulation Trinexapac-ethyl 175 EC/ ADM.09050.H.1.A (STEMPER) **should be classified as Eye Irrit. 2**

Reference: **KCP 7.1.5/01**

Report Trinexapac-ethyl 175 EC – Primary Eye Irritation Study in Rabbits.

	xxxxxxxx (2008d); Document No B92823
Guideline(s):	OECD 405
Deviations:	Yes (no *in vitro* tests and no test in one animal only)
GLP:	Yes
Acceptability:	Yes
Duplication (if vertebrate study)	No. The study was already performed in 2008. It is an existing report, and the study was not conducted for this submission.

Materials and methods

Test material (Lot/Batch No.)	Trinexapac-ethyl 175 EC (Lot/Batch No. D-I0703)
Species	Rabbit, New Zealand White
No. of animals (group size)	3 animals (1 male, 2 females)
Initial test using one animal	No
Exposure	0.1 mL (single instillation in conjunctival sac)
Irrigation (time point)	No
Vehicle/Dilution	None
Post exposure observation period	14 days
Remarks	None

Results and discussions

Table A 2.6-1: Eye irritation of Trinexapac-ethyl 175 EC

Animal No.		Scores after treatment *				Mean scores (24-72 h)	Reversible (day)
		1 h	24 h	48 h	72 h		
1	Corneal opacity	0	1	1	1	1	7
	Iritis	0	0	0	0	0	No effects
	Redness conjunctivae	2	2	2	2	2	7
	Chemosis conjunctivae	1	1	0	0	0.33	2
2	Corneal opacity	0	0	0	0	0	No effects
	Iritis	0	0	0	0	0	No effects
	Redness conjunctivae	2	2	2	2	2	10
	Chemosis conjunctivae	1	1	0	0	0.33	2
3	Corneal opacity	0	0	0	0	0	No effects
	Iritis	0	0	0	0	0	No effects
	Redness conjunctivae	2	2	2	2	2	2
	Chemosis conjunctivae	1	1	1	0	0.67	3

* 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:	Mild to moderate transient ocular changes (corneal opacity, reddening if conjunctiva and sclera, discharge and chemosis) were observed after end of treatment. No effects on the iris were noted. All observed effects resolved within the observation period of 14 days.

Conclusion

Under the experimental conditions, Trinexapac-ethyl 175 EC is an eye irritant. Thus, classification with

"H319: Causes Serious Eye Irritation" required according to Regulation (EC) No. 1272/2008.

A 2.7 Skin sensitisation (KCP 7.1.6)

Comments of zRMS:	The study performed according to relevant OECD guidelines and in GLP conditions is acceptable. According to Regulation 1272/2008 in order to be classified as Skin Sens. 1 a substance or mixture when tested in the adjuvant type guinea pig test method for skin sensitization should induce a positive response in at least 30 % of the animals tested. In this study 80% of animals have got skin sensitization therefore the formulation Trinexapac-ethyl 175 EC/ ADM.09050.H.1.A (STEMPER) should be classified as skin sensitizer. Since the product was used for intradermal induction in concentration above 1% the subcategorization is not possible, therefore formulation warrant classification as Skin Sens. 1 H317: May cause an allergic skin Reaction.

Reference:	**KCP 7.1.6/01**
Report	Trinexapac-ethyl 175 EC – Contact Hypersensitivity in Albino Guinea Pigs, Maximisation –Test. xxxxxxxxxx (2008e); Document no B97187
Guideline(s):	OECD 406, equivalent to Council Regulation (EC) 440/2008 B.6
Deviations:	None
GLP:	Yes
Acceptability:	Yes
Duplication (if vertebrate study)	No. The study was already performed in 2008. It is an existing report, and the study was not conducted for this submission.

Materials and methods

Test material (Lot/Batch No.)	Trinexapac-ethyl 175 EC (Lot/Batch No. D-I0703)
Species	Guinea pig, Hartley albino
No. of animals (group size)	Test substance group: 10 male guinea pigs Vehicle control goup: 5 male guinea pigs
Range finding:	Yes
Exposure (concentration(s), no. of applications)	Intradermal induction: 75%, 50% and 25% Topical induction: 100%, 75%, 50% 25% Challenge: 25%
Vehicle	1:1 Freund's complete adjuvant : physiological saline
Pretreatment prior to topical application	Yes (1:1 Freund's complete adjuvant : physiological saline)
Reliability check	Substance (15 % intradermal induction, 100 % topical induction and 25 % challenge)
Remarks	None

Results and discussions

Table A 2.7-1: Results of skin sensitisation study of Trinexapac-ethyl 175 EC

	24 hours	48 hours	
	After first challenge		After second challenge
Trinexapac-ethyl 175 EC	8/10	8/10	10/10
Test Vehicle Control Group	2/5	2/5	na

Positive control: study with alpha-hexylcinnamaldehyde performed APR/MAY 2008; 90% of the animals responded positively

Clinical signs:	No toxic signs were evident in the guinea pigs of the control or test group, no deaths occurred. Eight out of ten test animals and two out of five control animals showed skin reactions after the first challenge treatment with Trinexapac-ethyl 175 EC at 25 % in purified water. After the second challenge with Trinexapac-ethyl 175 EC at 25 % in purified water, the eight animals which had reacted in the first challenge and two additional animals (booster effect) showed skin reactions.

Conclusion

Under the experimental conditions, Trinexapac-ethyl 175 EC is a skin sensitiser. Thus, classification with 'H317: May Cause Allergic Skin Reaction' is required according to Regulation (EC) No. 1272/2008.

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

Not required

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)

Comments of zRMS:	The study performed on formulation AG-T3-175EC1 (ADM.09050.H.1.A) according to relevant OECD method and in GLP conditions is acceptable. The number of replicates for the concentrate was 8 and for dilution 8. According to EFSA Guidance on Dermal Absorption (EFSA Journal 2017;15(6):4873) the dermal absorption in an in vitro study is equal : mean value + ks, where k is multiplication factor and s is the sample standard deviation: **Concentrate** Mean absorption of the concentrate: 2.36 + 0.88 x 0.84 = 2.36 + 0.7392 = 3.0992% ≈ 3.1% **Dilution** Mean absorption of the 1: 1600 spray dilution : 50.5 + 18.9 x 0.84 = 50.5 + 15.876 = 66.376 ≈ 66% Thus, the dermal penetration estimates to be used for risk assessment is 3.1% for the concentrate and 66 % for the spray dilution based on the EFSA guidance criteria.

Reference:	**KCP 7.3/01**
Report	*In vitro* percutaneous absorption of Trinexapac-ethyl, formulated as AG-T3-175EC1, through human skin. xxxxxxxxx (2018); Document no P10454; ADAMA Reference No.: 90020905
Guideline(s):	OECD 428; EU Method B.45 (Reg. No. 440/2008)
Deviations:	None
GLP:	Yes
Acceptability:	Yes
Duplication (if vertebrate study)	No

Executive Summary

The study was designed to examine the in vitro percutaneous absorption of trinexapac-ethyl, formulated as AG-T3-175EC1 (=ADM.09050.H.1.A), through human skin membranes. The test substance was tested at two target concentrations, i.e. 175 $g.L^{-1}$ (concentrate) and 0.109 $g.L^{-1}$ (field dilution). The concentrate represents the maximal concentration possible when handling the undiluted formulation, while the low concentration reflects the concentration recommended for use in the field. The objective of the study was to elucidate the extent of percutaneous absorption of the compound-related radioactivity. The contact time was 8 hours, i.e. a normal working day and the post exposure time was 16 hours. In addition to the amount of [^{14}C]Trinexapac-ethyl in the receptor fluid, the residues remaining in/on the skin membranes and in the stratum corneum (16 h post exposure) were determined. The study was performed in flow-through diffusion cells.

Table A 2.10-1: Executive Summary

Material / product tested	Trinexapac-ethyl / ADM.09050.H.1.A
Type of formulation	Emulsifiable concentrate

Nominal concentration of the active substance	Concentrate: 175 $g.L^{-1}$ Field dilution: 0.109 $g.L^{-1}$
Dilution rate	1600
Exposure time	8 h
Sampling duration	24 h
Skin sample source	Human abdominal and breast skin
Receptor fluid (RF) composition	Phosphate buffered saline (PBS) + 0.01% sodium azide, pH ca. 7.2
Solubility in RF considered adequate	Yes
Washing method used	At 8 h, using cottons swabs, a mild soap solution (3% Dove) and water

Group	(A) Concentrate	(B) Field dilution
Number of replicates	8	8
75 % absorbed in RF in first half of study	Yes	Yes
Maximal flux (µg.cm-2.h-1)	4.50 ± 1.79	0.19 ± 0.10
	Percentage of dose (%, mean +/- SD)	
Amount in RF	2.16 ± 0.84	47.8 ± 18.1
Amount in receptor compartment wash	0.0055 ± 0.0066	0.35 ± 0.93
Amount in (stripped) skin	0.19 ± 0.07	2.02 ± 0.68
Amount in tape strips 1+2	0.0041 ± 0.0020	0.21 ± 0.06
Amount in tape strips 3-last	<0.014	0.32 ± 0.18
Amount in skin wash	96.0 ± 1.4	43.2 ± 19.5
Total recovery	98.6 ± 1.0	95.2 ± 2.4
Absorbed dose[a]	2.35 ± 0.88	50.2 ± 18.9
Potentially absorbed dose[b]	2.36 ± 0.88	50.5 ± 18.9
Dermal absorption for risk assessment	**3.1 %**	**66 %**

[a] The absorbed dose is defined as the amount in the receptor fluid, the receptor compartment wash and skin membrane, excluding tape strips
[b] The potentially absorbed dose is defined as the amount in the receptor fluid, the receptor compartment wash, the skin and *stratum corneum* (*except* for the first two tape strips)

Values below LoD were considered equal to LoD. If more than 50% of the values in a group was below LoD, the mean value is presented as < calculated value>.

To address variability between replicates dermal absorption should be calculated as follows:
Absorption (mean value) + ks, where s is the sample standard deviation and k the multiplication factor correlated to the number of replicates (EFSA dermal absorption guidance 2017). There are 8 replicates leading to multiplication factor of 0.84. Thus, the relevant absorption estimates are set at 3.1% for the concentrate and 66% for the field dilution after rounding.

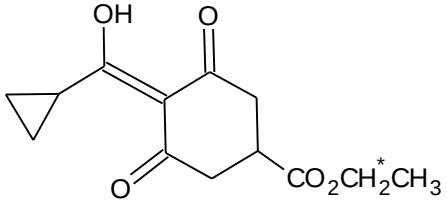
Materials and methods

Materials

Non-radiolabeled trinexapac-ethyl

IUPAC Name:	4-(cyclopropyl-hydroxymethylene)-3,5-dioxo-cyclohexanecarboxylic acid ethyl ester
CAS no	95266-40-3
Vapor pressure	2.16 x 10^{-3} Pa
log Po/w	1.5 (at pH 5), -0.29 (at pH 6.9), -2.1 (at pH 8.9)
Solubility in water	1.1 g.L^{-1} (pH 3.5 distilled water) 2.8 g.L^{-1} (pH 4.9 buffer solution), 10.2 g.L^{-1} (pH 5.5 buffer solution), 21.1 g.L^{-1} (pH 8.2 buffer solution)
Solubility in organic solvents	> 500 g.L^{-1} in acetone, methanol and dichloromethane

Radiolabeled [^{14}C] trinexapac-ethyl

Lot number	XXIV/26/A/1
Specific activity	7.561 MBq.mg^{-1}
Molar activity	1922 MBq.$mmol^{-1}$
Radiochemical purity	98.77%
Storage conditions	< –18 ºC
Structure	 *position of radiolabel

Formulation

Test material name	AG-T3-175 EC1 (trinexapac 175 EC)
Batch number	8138
Concentration trinexapac-ethyl	171.5 g.L
Density	0.999 g.mL^{-1}
Appearance	clear, orange to brown liquid
Expiry date 1	11 November 2018
Storage conditions	ambient temperature (15-25 ºC)

Blank Formulation

Test material name	Blank formulation AG-T3-175 EC1 (trinexapac 175 EC)
Batch number	BL70705
Concentration trinexapac-ethyl	0 g/L
Appearance	clear, colorless liquid
Expiry date 1	14 May 2019
Storage conditions	ambient temperature (15-25 ºC)

Radiolabelled reference compound

Test material name	[3H]H2O
Batch number	2126213
Specific activity	37 MBq.g-1
Expiry date 1	14 April 2019
Storage conditions	3-10 ºC

Study design

Preparation of skin membranes

Human skin membranes were prepared from frozen skin samples present at Triskelion. Human skin, derived from the breast and abdomen, was obtained from eight female donors after surgery.

Concentrate (group A)
Donor H-1: H17/21, born in 1967, arrival on 18 May 2017 (breast)
Donor H-2: H17/24A, born in 1978, arrival on 20 June 2017 (abdomen)
Donor H-3: H17/29, born in 1964, arrival on 18 July 2017 (breast)
Donor H-4: H17/30, born in 1953, arrival on 26 July 2017 (breast)
Donor H-5: H17/31, born in 1973, arrival on 26 July 2017 (abdomen)

Field dilution (group B)
Donor H-1: H17/41, born in 1955, arrival on 20 October 2017 (breast)
Donor H-2: H17/44, born in 1968, arrival on 3 November 2017 (breast)
Donor H-3: H17/12, born in 1981, arrival on 3 March 2017 (abdomen)
Donor H-4: H17/28, born in 1949, arrival on 14 July 2017 (breast)

Flow-through diffusion cells and receptor fluid
Approximately 20 h before the start of exposure to the test preparation, the split-thickness skin membranes were placed in 9 mm flow-through automated diffusion cells (PermeGear Inc. Riegelsville, PA, USA) to hydrate the skin.

Integrity of skin membranes
After placing the skin membranes in the diffusion cells (see section 4.3.2), membrane integrity was assessed.

Experimental design
Trinexapac-ethyl, formulated as AG-T3-175 EC1, were topically applied to the skin membranes. The exposure time was 8 h and receptor fluid samples were collected from 0-24 h. Group B consisted of two experiments; i.e. one experiment including B1-4 and one experiment including replicates B5-8. Replicates B1-4 were finally repeated and replaced due to a low total recovery. Data presented in this report are from the repeat experiment with B1-4.

Test group	Group size	Species	Total concentration measured	Mean dose applied
A	8	human	172 $g.L^{-1}$	1739 ± 16 $\mu g.cm^{-2}$
B	8	human	0.11 $g.L^{-1}$	1.10 ± 0.03 $\mu g.cm^{-2}$

Dose formulation preparation
The dose formulations were prepared as described below. For the concentrate (group A) and replicates 1-4 of the field dilution (group B1-4), the dose formulation were prepared within two days prior to application. For replicates 5-8 of the field dilution (group B5-8), the dose formulation was applied within nine days after preparation.

Test group	Amount of [14C]Trinexapacethyl	Amount of concentrate formulation	Amount of diluted blank formulation	Total concentration measured	Radioactive concentration measured
A	63.5 µL [a] (~2.57 MBq) (~0.34 mg a.i.)	0.9924 g		171.8 $g.L^{-1}$	2.39 $MBq.mL^{-1}$
10x B1-4	212 µL [a] (~8.59 MBq) (~1.14 mg a.i.)	-	0.9635 g [b]	--	--
B1-4	0.0978 g of 10x B and 0.8762 g demineralized water			0.11 $g.L^{-1}$	0.84 $MBq.mL^{-1}$
10x B5-8	208 µL [a] (~8.42 MBq) (~1.11 mg a.i.)	-	0.8909 g [b]	--	--
B5-8	0.0978 g of 10x B and			0.11 $g.L^{-1}$	0.85 $MBq.mL^{-1}$

	0.8762 g demineralized water		

[a] Dissolved in methanol to a concentration of *ca.* 40.5 MBq.mL^{-1}, specific activity 7.561 MBq.mg^{-1}.
[b] 160 times diluted blank formulation with demineralized water

Test concentrations and homogeneity check, and application
The concentration and homogeneity of [^{14}C]Trinexapac-ethyl in the dose formulations was checked by taking random aliquots in triplicate before dosing. For homogeneity, a coefficient of variation lower than 10 % was considered sufficient. Random aliquots, in triplicate, were taken again after dose application. Prior to dose application, the skin surface was dried. The dose preparations were applied with a pipette and subsequently spread evenly on the skin surface within the donor compartment using a glass rod (dose volume ca. 10 µL.cm-2). A slightly higher volume than 6.4 µL (i.e. 6.7 µL) was applied to account for the expected loss of material during the distribution over the skin surface. Thus, a net volume of approximately 6.4 µL was applied.

Collection of mass balance samples
Twenty-four hours after application, the mass balance of the test substance was determined from the following samples: receptor fluid samples, skin wash, receptor compartment wash, donor compartment wash, tape strips, and digested skin.

Determination of radioactivity
The radioactivity in the study samples was determined by liquid scintillation counting (LSC) using a Canberra Packard Tricarb 3100TR or Tricarb 3110TR scintillation counter.

Radio-HPLC analysis of [^{14}C]Trinexapac-ethyl
The radiochemical purity of [14C]Trinexapac-ethyl, and of [14C]Trinexapac-ethyl in the dose preparations was determined by radio-HPLC analysis with UV detection.

Results

Integrity of skin membranes
Skin membranes with a Kp value below the cut-off value of 2.5 × 10-3 cm.h^{-1} were selected for the study, except for one skin membrane (i.e. replicate A-3), which showed a Kp value of 3.07 × 10-3 cm.h^{-1}.

Receptor fluid solubility
The water solubility of trinexapac-ethyl at pH 5.5 was reported to be ca. 10.2 mg.mL^{-1}.
The maximum absorption of trinexapac-ethyl into the receptor fluid in current study was 34.3 µg in ca. 40 mL over 24 h, i.e. 0.86 µg.mL^{-1}. Therefore, the solubility of the test substance in the receptor fluid was considered more than sufficient.

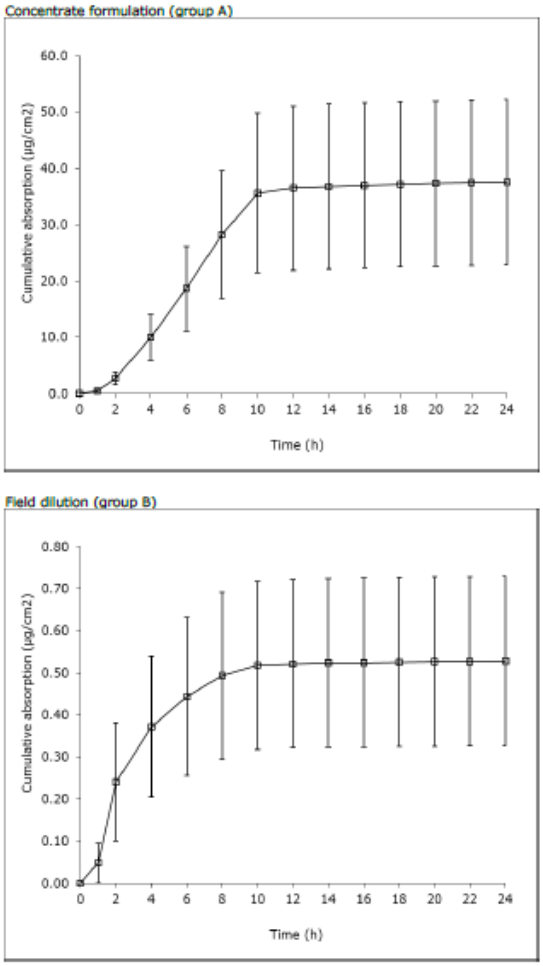
Percutaneous absorption of Trinexapac-ethyl
The homogeneity of [^{14}C]Trinexapac-ethyl in the dose preparations was checked and the coefficients of variation (CV) of the groups were 2.1 % (concentrate), 1.4 % (B1-4) and 3.7 % (B5-8) (field dilution), and therefore considered sufficient.

The reason for the low recovery of replicates B1-4 in the initial experiment is unknown. There were no abnormalities observed or recorded during the conduct of the experiment. Re-analysis and combustion of the skin wash samples did not improve the total recovery. For replicates B5-8 and the repeat experiment with replicates B1-4 the total recoveries were adequate. Therefore, the data of these experiments are presented in this report and should be used for risk assessment.

The mean absorption of trinexapac-ethyl from the concentrate formulation into the receptor fluid over the 24 h study duration was 37.5 µg.cm^{-2}, representing 2.16 % of the applied dose. The mean maximal flux for the absorption of trinexapac-ethyl through human skin was 4.50 µg.cm-2.h^{-1} and the lag time was 1.8 h. The mean absorption of trinexapac-ethyl from the field dilution into the receptor fluid was 0.53 µg.cm^{-}

^{2}, representing 47.8 % of the dose applied. The mean maximal flux through human skin was 0.19 µg.cm^{-2}.h^{-1} and the lag time was 0.8 h.

Figure A 2.10-1: Mean cumulative absorption of Trinexapac-ethyl into the receptor fluid.



The mean total absorption, defined as the compound-related radioactivity present in the receptor fluid, the receptor compartment wash and the skin membranes (excluding tape strips) was 2.35 +/- 0.88 % (concentrate formulation) and 50.2 +/- 18.9 % (field dilution) of the applied dose. The mean potentially absorbed dose, which is defined as the compound-related radioactivity present in the receptor fluid, the receptor compartment wash, the skin membranes and the stratum corneum (except for the first 2 tape strips) was 2.36 +/- 0.88 % (concentrate formulation) and 50.5 +/- 18.9 % (field dilution) of the applied dose.

The mean recovery of trinexapac-ethyl in human skin was 98.6 +/- 1.0 % and 95.2 +/- 2.4 % for the concentrate formulation and field dilution, respectively. For both the concentrate and the field dilution, more than 75 % of the absorption of trinexapac-ethyl in the receptor fluid over 24 hours occurred within half of the study duration (i.e. 12 hours).

For risk assessment, it is considered appropriate to exclude all tape strips in the calculations of the total absorption values (i.e. the absorbed dose).

Summary and Conclusion

Table A 2.10-2: Overview table of the in vitro percutaneous penetration of [^{14}C]Trinexapac-ethyl through human skin

Human skin	**(A) Concentrate**		**(B) Field dilution**	
Concentration measured [g.L^{-1}] Dose [µg.cm^{-2}]	171.8 1739 ± 16		0.11 1.10 ± 0.03	
n	8		8	
Penetration into the receptor fluid after 24 h	37.5 µg.cm^{-2}	2.16 % of dose	0.53 µg.cm^{-2}	47.8 % of dose
Maximal flux [µg.cm^{-2} h^{-1}]	4.50 ± 1.79		0.19 ± 0.10	
Lag time [h]	1.8 ± 0.2		0.8 ± 0.2	
Absorbed dose [% of dose] [a]	2.35 ± 0.88		50.2 ± 18.9	
Potentially absorbed dose [% of dose] [b]	2.36 ± 0.88		50.5 ± 18.9	
Dermal absorption considered for risk assessment	**3.1 %**		**66 %**	

[a] The absorbed dose is defined as the amount in the receptor fluid, the receptor compartment wash and skin membrane, excluding tape strips.
[b] The potentially absorbed dose is defined as the amount in the receptor fluid, the receptor compartment wash, the skin, and stratum corneum (except for the first two tape strips).

To address variability between replicates dermal absorption should be calculated as follows:
Absorption (mean value) + ks, where s is the sample standard deviation and k the multiplication factor correlated to the number of replicates (EFSA dermal absorption guidance 2017). There are 8 replicates leading to multiplication factor of 0.84. Thus, the relevant absorption estimates are set at 3.1% for the concentrate and 66% for the field dilution after rounding.

Assessment and conclusion by applicant:
The study is considered reliable. A summary of the study endpoints is provided in the conclusion above.

Assessment and conclusion by RMS:
Acceptability/Reliability:

The study performed on formulation AG-T3-175EC1 (ADM.09050.H.1.A) according to relevant OECD method and in GLP conditions is acceptable.

Outcome and conclusion of the study:

According to EFSA Guidance on Dermal Absorption (EFSA Journal 2017;15(6):4873) the dermal absorption in an in vitro study is equal :
mean value + ks, where k is multiplication factor and s is the sample standard deviation

The number of replicates for the concentrate was 8 and for dilution 8, thus multiplication factor is 0.84

Concentrate
Mean absorption of the concentrate: 2.36 + 0.88 x 0.84 = 2.36 + 0.7392 = 3.0992% ≈ 3.1%
Dilution
Mean absorption of the 1: 1600 spray dilution : 50.5 + 18.9 x 0.84 = 50.5 + 15.876 = 66.376 ≈ 66%

Thus, the dermal penetration estimates to be used for risk assessment is 3.1% for the concentrate and 66 % for the spray dilution based on the EFSA guidance criteria

A 2.11 Other/Special Studies

None available

Appendix 3 Exposure calculations

A 3.1 Operator exposure calculations (KCP 7.2.1.1)

A 3.1.1 Calculations for Trinexapac-ethyl

Table A 2: Input parameters considered for the estimation of operator exposure

Application rate of active substance	0.21 kg a.s./ha	*i_AppRate*	
Assumed area treated	50 ha/day	*d_AreaTreated*	
Amount of active substance applied	10.5 kg a.s./day	*i_AmoutAS*	
Dermal absorption of the product	3.10%	*i_AbsorpProduct*	
Dermal absorption of in-use dilution	66.00%	*i_AbsorInuse*	
Formulation type	Soluble concentrates, emulsifiable concentrate, etc.		
Indoor or Outdoor application	Outdoor		
Application method	Downward spraying		
Application equipment	Vehicle-mounted		
Season	not relevant		

	Exposure values	µg exposure/day mixed and loaded		Reference	Comment
		75th centile	95th centile		
Mixing and loading	Hands	29683	111041	AOEM	
	Body	18628	142613	AOEM	
	Head	545	2988	AOEM	
	Protected hands (gloves)	159	2080	AOEM	
	Protected body (workwear or protective garment and sturdy footwear)	191	1536	AOEM	
	Protected head (hood and face shield)	9	169	AOEM	
	Inhalation	7	30	AOEM	
	Protective Equipment	Select for inclusion		Penetration factor	Inhalation Protection factor
	Gloves	No			
	Clothing	Work wear - arms, body and legs covered		Incl. in AOEM model	
	Head and respiratory PPE	None		1	1
	Water soluble bag	No		1	

	Exposure values	µg exposure/day applied		Reference	Comment
		75th centile	95th centile		
Application	Hands	1557	12826	AOEM	
	Body	871	4489	AOEM	
	Head	41	124	AOEM	
	Protected hands (gloves)	152	4384	AOEM	
	Protected body (workwear or protective garment and sturdy footwear)	24	59	AOEM	
	Inhalation	3	11	AOEM	
	Protective Equipment	Select for inclusion		Penetration factor	Inhalation Protection factor
	Gloves	No			
	Clothing	Work wear - arms, body and legs covered		Incl. in AOEM model	
	Head and respiratory PPE	None		1	1
	Closed cab	No		vehicle mounted upward spraying only	

Table A 3: Estimation of operator exposure towards Trinexapac-ethyl using the EFSA model

1. Total

	Without RPE/PPE	With RPE/PPE	
Longer term			
Total systemic exposure from mixing, loading and application (mg a.s./day)	**3.1550857**	**2.0245979**	
Total systemic exposure from mixing, loading and application per kg body weight (mg/kg bw/day)	**0.0525848**	**0.0337433**	
% of RVNAS	**15.47%**	**9.92%**	
Acute			
Total systemic exposure from mixing, loading and application (mg a.s./day)	**19.5072013**	**12.2097910**	
Total systemic exposure from mixing, loading and application per kg body weight (mg/kg bw/day)	**0.3251200**	**0.2034965**	
% of RVAAS	**#WERT!**	**#WERT!**	

2. Longer term exposure

2.1 Mixing and loading

	Systemic exposure [µg a.s. /day]	Systemic exposure [µg a.s./kg bw/day]	Formula
Without RPE/PPE			
Hands	**920.1610629**	**15.3360177**	*D15*i_AbsorpProduct*
Body	**577.4525292**	**9.6242088**	*D16*i_AbsorpProduct*
Head	**16.8881078**	**0.2814685**	*D17*i_AbsorpProduct*
Inhalation	**7.4525678**	**0.1242095**	*D21*i_AbsorpInhalation*
Sum	**1521.9542677**	**25.3659045**	
With RPE/PPE (as selected above)			
Hands	**920.1610629**	**15.3360177**	*D18*i_AbsorpProduct*
Body	**5.9224752**	**0.0987079**	*D19*i_AbsorpProduct or D15*i_AbsorpProduct*F24*
Head	**16.8881078**	**0.2814685**	*D20*i_AbsorpProduct or D17*i_AbsorpProduct*F25*
Inhalation	**7.4525678**	**0.1242095**	*D21*i_AbsorpInhalation*G25*
Sum	**950.4242138**	**15.8404036**	
Water soluble	**950.4242138**	**15.8404036**	*C70*F26*

2.2 Application

	Systemic exposure [µg a.s. /day]	Systemic exposure [µg a.s./kg bw/day]	Formula
Without RPE/PPE			
Hands	**1027.8810227**	**17.1313504**	*D30*i_AbsorpInuse*
Body	**574.7234127**	**9.5787235**	*D31*i_AbsorpInuse*
Head	**27.1633975**	**0.4527233**	*D32*i_AbsorpInuse*
Inhalation	**3.3636223**	**0.0560604**	*D35*i_AbsorpInhalation*
Sum	**1633.1314551**	**27.2188576**	
With RPE/PPE (as selected above)			
Hands	**1027.8810227**	**17.1313504**	*D33*i_AbsorpInuse*
Body	**15.7656330**	**0.2627606**	*D34*i_AbsorpInuse or D31*i_AbsorpInuse*F38*
Head	**27.1633975**	**0.4527233**	*D32*i_AbsorpInuse*F39*
Inhalation	**3.3636223**	**0.0560604**	*D35*i_AbsorpInuse*G39*
Sum	**1074.1736754**	**17.9028946**	

A 3.2 Worker exposure calculations (KCP 7.2.3.1)

A 3.2.1 Calculations for Trinexapac-ethyl

Table A 4: Input parameters considered for the estimation of worker exposure

Worker exposure from residues on foliage for STEMPER (ADM.09050.H.1.A)			
Crop type	Cereals		
Indoor or outdoor	Outdoor		
Application method	Downward spraying		
Application equipment	Vehicle-mounted		
Worker's task	Inspection, irrigation		
Main body parts in contact with foliage	Hand and body		
Application rate of active substance	0.21	kg a.s./ha	*i_AppRate*
Number of applications	1		*i_AppNo*
Interval between multiple applications	365	days	*i_AppInt*
Half-life of active substance	30	days	*d_HalflifeAS*
Multiple application factor	1.0		*d_MAF*
Dermal absorption of the product	3.10%		*i_AbsorpProduct*
Dermal absorption of the in-use dilution	66.00%		*i_AbsorpInuse*
Dislodgeable foliar residue (i_AppRate*i_DFR)	0.63	µg a.s./cm^2	*d_DFR*
Working hours	2	hr	*d_WorkHr*
Dermal transfer coefficient - Total potential exposure	12500	cm^2/hr	*d_DermTcUCV*
Dermal transfer coefficient - arms, body and legs covered	1400	cm^2/hr	*d_DermTcCV1*
Dermal transfer coefficient - hands, arms, body and legs covered	no TC available for this assessment	cm^2/hr	*d_DermTcCV2*

Table A 5: Estimation of worker exposure towards Trinexapac-ethyl using the EFSA re-entry model

1. Total

	Potential exposure	Work wear - arms, body and legs covered	Working wear and gloves	Comments
Total systemic exposure (mg a.s./day)	10.3950000	1.1642400	no TC available for this assessment	
Total systemic exposure per kg body weight (mg/kg bw/day)	0.1732500	0.0194040		
% of RVNAS	50.96%	5.71%		

2. Details

	Systemic exposure [mg a.s. /day]	Systemic exposure [mg a.s./kg bw/day]	Formula	Comments
Dermal - Potential	10.3950000	0.1732500	*d_DermTcUCV*d_WorkHr*i_DFR*i_MAF/1000*i_AbsorpInuse*	
Dermal - Work wear - arms, body and legs covered	1.1642400	0.0194040	*d_DermTcCV1*d_WorkHr*d_DFR*d_MAF/1000*i_AbsorpInuse*	
Dermal - Working wear and gloves	no TC available for this assessment		*d_DermTcCV2*d_WorkHr*d_DFR*d_MAF/1000*i_AbsorpInuse*	
Inhalation				Na for outdoor activities

A 3.3 Bystander and resident exposure calculations (KCP 7.2.2.1)

A 3.3.1 Calculations for Trinexapac-ethyl – residents

Table A 6: Input parameters considered for the estimation of resident exposure

Croptype	Cereals		
Application method	Downward spraying		
Application equipment	Vehicle-mounted		*i_AppEquip*
Formulation type	Soluble concentrates, emulsifiable concentrate, etc.		*i_FormVal*
Buffer strip	2-3	m	*i_Buffer*
Application rate of the product	0.21	kg a.s./ha	*i_AppRate*
Concentration of active substance (in-use dilution for liquid applications)	1.05	g a.s./l	*d_ConcAS*
Dermal absorption of product	3.10%		*i_AbsorpProduct*
Dermal absorption of in-use dilution	66.00%		*i_AbsorpInuse*
Oral absorption	100.00%		*i_AbsorpOralInuse*
Dislodgeable foliar residue (i_AppRate*i_DFR)	0.63	µg a.s./cm^2	*d_DFR*
Vapour pressure of in-use dilution	low volatile substances having a vapour pressure of <5*10-3Pa	Pa	*i_Volat*
Concentration in air	0.001	mg/m^3	*d_AirCon*
Resident dermal spray drift exposure 75th percentile - adult	0.47	ml spray dilution/person	
Resident dermal spray drift exposure 75th percentile - child	0.327	ml spray dilution/person	
Resident inhal. spray drift exposure 75th percentile - adult	0.00010	ml spray dilution/person	
Resident inhal. spray drift exposure 75th percentile - child	0.00022	ml spray dilution/person	
Resident dermal spray drift exposure mean - adult	0.22318	ml spray dilution/person	
Resident dermal spray drift exposure mean - child	0.18	ml spray dilution/person	
Resident inhal. spray drift exposure mean - adult	0.00009	ml spray dilution/person	
Resident inhal. spray drift exposure mean - child	0.00017	ml spray dilution/person	
Exposure duration dermal	2	hours	*d_ReExpDur*
Exposure duration inhalation	24	hours	*d_ReExpDurInhal*
Exposure duration entry into treated crops	0.25	hours	*d_ExpDurTreatCrop*
Light clothing adjustment factor	18.0%		*d_ClothAF*
Breathing rate adult	0.23	m^3/day/kg	*d_BreathRAd*
Breathing rate child (1-3 year old)	1.07	m^3/day/kg	*d_BreathRCh*
Drift percentage on surface (75th percentile)	5.60%		
Drift percentage on surface (mean)	4.10%		
Turf transferable residues percentage	5.00%		*d_Turf*
Transfer coeff. of surface deposits-adult	7300	cm^2/hour	*d_ReTCAd*
Transfer coeff. of surface deposits-child (1-3 year old)	2600	cm^2/hour	*d_ReTCCh*
Saliva extraction percentage	50.00%		*d_SalExt*
Surface area of hands mouthed	20	cm^2	*d_AreaHM*
Frequency of hand to mouth activity	9.5	events/hour	*d_ReFreqHM*
Ingestion rate for mouthing of grass per day	25	cm^2	*d_MouthGrass*
Dislodgeable residues percentage transferability for object to mouth	20.00%		*d_DRP*
Transfer coefficient for entry into treated crops (75th percentile) - adı	7500	cm^2/h	*d_TcEntryAd*
Transfer coefficient for entry into treated crops (75th percentile) - chi	2250	cm^2/h	*d_TcEntryCh*
Transfer coefficient for entry into treated crops (mean) - adult	5980	cm^2/h	*d_TcEntryAd*
Transfer coefficient for entry into treated crops (mean) - child	1794	cm^2/h	*d_TcEntryCh*

Table A 7: Estimation of resident exposure towards trinexpac-ethyl

1. Total

1.1 1-3 year old child

	Spray drift (75th percentile)	Vapour (75th percentile)	Surface deposits (75th percentile)	Entry into treated crops (75th percentile)	All pathways (mean)
Total systemic exposure (mg a.s./day)	0.1860520	0.0107000	0.0218172	0.2338875	0.3156249
Total systemic exposure per kg body weight (mg/kg bw/day)	0.0186052	0.0010700	0.0021817	0.0233888	0.0315625
% of RVNAS	5.47%	0.31%	0.64%	6.88%	9.28%

1.2 Adult

	Spray drift	Vapour	Surface deposits	Entry into treated crops	All pathways (mean)
Total systemic exposure (mg a.s./day)	0.2671872	0.0138000	0.0566597	0.7796250	0.8038227
Total systemic exposure per kg body weight (mg/kg bw/day)	0.0044531	0.0002300	0.0009443	0.0129938	0.0133970
% of RVNAS	1.31%	0.07%	0.28%	3.82%	3.94%

2. Resident exposure 75th Percentile

	Systemic exposure [mg a.s. /day]	Systemic exposure [mg a.s./kg bw/day]	Formula	Comments
1-3 year old child				
Spray drift	0.1860520	0.0186052	*((C16*i_AbsorpInuse*(1-d_ClothAF))+C18)*d_ConcAS*	
Vapour	0.0107000	0.0010700	*d_AirCon*d_BreathRCh*d_BwChild*	
Surface deposits				
Dermal	0.0201802	0.0020180	*(i_AppRate/100)*C29*d_Turf*d_ReTCCh*d_ReExpDur*MAX(i_AbsorpProduct,i_AbsorpInuse)*d_MAF*IF(i_AppEquip = "Vehicle-mounted-Drift Reduction",0.5,1))*	
Hand to mouth	0.0010725	0.0001073	*(i_AppRate/100)*C29*d_Turf*d_SalExt*d_AreaHM*d_ReFreqHM*d_ReExpDur*i_AbsorpOralInuse*d_MAF*	
Object to mouth	0.0005645	0.0000564	*(i_AppRate/100)*C29*d_DRP*d_MouthGrass*i_AbsorpOralInuse*d_MAF*	
Entry into treated crops				
Dermal	0.2338875	0.0233888	*(d_TcEntryCh*0.25*d_DFR*d_MAF)/1000*MAX(i_AbsorpProduct,i_AbsorpInuse)*	
Hand to mouth			*(i_AppRate/100)*d_Turf*d_MAF*d_SalExt*d_AreaHM*d_ReFreqHM*d_ReExpDur*i_AbsorpOralInuse*	Considered only for application on grassland and lawns and for application on golf course, turf or other sports lawns.
Object to mouth			*(i_AppRate/100)*d_DRP*d_MouthGrass*i_AbsorpOralInuse*d_MAF*	Considered only for application on grassland and lawns and for application on golf course, turf or other sports lawns.
Adult				
Spray drift	0.2671872	0.0044531	*(C15*i_AbsorpInuse*(1-d_ClothAF))+C17)*d_ConcAS*	
Vapour	0.0138000	0.0002300	*d_AirCon*d_BreathRAd*d_BwAdult*	
Surface deposits (dermal)	0.0566597	0.0009443	*(i_AppRate/100)*C30*d_Turf*d_ReTCAd*d_ReExpDur*i_AbsorpInuse*	
Entry into treated crops (dermal)	0.7796250	0.0129938	*(d_TcEntryAd*0.25*d_DFR*d_MAF)/1000*MAX(i_AbsorpProduct,i_AbsorpInuse)*	

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)

no data available