FINAL REGISTRATION REPORT

Part B

Section 6

Mammalian Toxicology

Detailed summary of the risk assessment

Product code: SAE053H/01

Product name(s): KAGURA/GENKI

Chemical active substance(s):

Mesotrione, 80 g/L
Nicosulfuron, 30 g/L

Central Zone

Zonal Rapporteur Member State: Poland

CORE ASSESSMENT

Document number - SAEDoc-00017 CEU

(authorization)

Applicant: Sumi Agro Europe Limited

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When	What
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August 2020	Dossier sent for evaluation to Merit Mark (PL)
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zRMS comments:
The text highlighted in grey was provided by the evaluator.

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The intended maximal application rate to be registered is 1.2 L product/ha, which is equivalent to 96 g mesotrione/ha and 36 g nicosulfuron/ha. Nevertheless, the dossier has been prepared for a maximal application rate of 1.5 L product/ha, and thus all risk and exposure assessments presented have been performed with that exaggerated application rate, unless otherwise stated. An application rate of 1.5 L product/ha is regarded as worst case and is therefore covering the intended rate of 1.2 L product/ha.

6.1 Summary

Table 6.1-1: Information on SAE053H/01 *

Product name and code	SAE053H/01
Formulation type	oil dispersion [Code: OD]
Active substance(s) (incl. content)	mesotrione, 80 g/L nicosulfuron, 30 g/L
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 SAE053H/01 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 SAE053H/01 according to Regulation (EC) No 1272/2008

Hazard class(es), categories:	Skin Sens. 1 Repr. 2,
Hazard pictograms or Code(s) for hazard pictogram(s):	GHS07 GHS08
Signal word:	Warning
Hazard statement(s):	H317 H361d (eyes, nervous system)
Precautionary statement(s):	WARNING SECTION OF THE LABEL (first page) P201: Obtain special instructions before use. P261: Avoid breathing spray. P280: Wear protective gloves P302+P352: IF ON SKIN: Wash with plenty of soap and water. Other section of the label: P201: Do not handle until all safety precautions have been read and understood. P270: Do not eat, drink or smoke when using this product. P272: Contaminated work clothing should not be allowed out of the workplace P363: Wash contaminated clothing before reuse. P501: Dispose of contents/container to … And P280 as follows: Operator: „*Stosować rękawice ochronne oraz odzież roboczą (kombinezon) w trakcie przygotowywania cieczy roboczej oraz odzież roboczą w trakcie wykonywania zabiegu*" "Wear protective gloves and work wear (coverall) during mixing/loading and work wear during application". Worker: „*Stosować rękawice ochronne oraz odzież roboczą (długie spodnie, koszula z długim rękawem)*." "Wear protective gloves and workwear (long trousers, long-sleeve shirt)." Section First aid: P302+352: P333 + P313. ~~P362 + P364,~~
Additional labelling phrases:	~~To avoid risks to man and the environment, comply with the instructions for use.~~ To avoid risks to human health 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 SAE053H/01

	Result	PPE / Risk mitigation measures
Operators	Acceptable	Exposure: none Classification: Gloves (due to sensitising potential of SAE053H/01)
Workers	Acceptable	Exposure: none Classification: none (diluted product), gloves: recommendation (due to

	Result	PPE / Risk mitigation measures
		sensitising potential of SAE053H/01)
Bystanders	Acceptable	None
Residents	Acceptable	None

No unacceptable risk for operators, 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.

The intended maximal application rate to be registered is 1.2 L product/ha, which is equivalent to 96 g mesotrione/ha and 36 g nicosulfuron/ha. Nevertheless, the dossier has been prepared for a maximal application rate of 1.5 L product/ha, and thus all risk and exposure assessments presented have been performed with that exaggerated application rate, unless otherwise stated. An application rate of 1.5 L product/ha is regarded as worst case and is therefore covering the intended rate of 1.2 L product/ha.

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)	Max. application rate kg as/ha a) mesotrione b) nicosulfuron	Water L/ha min / max			Operator	Worker	Bystander	Residents
	Maize (BBCH 12-19)	F	Spraying, LCTM	1 ; (N/A)	a) 0.120 b) 0.045	200 - 400		EFSA-OPEX (operator, worker and residents) Martin et al. (bystander)				

* 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: No data gaps have been identified

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)

	mesotrione	**nicosulfuron**
Common Name	mesotrione	nicosulfuron
CAS-No.	104206-82-8	111991-09-4
Classification and proposed labelling		
With regard to toxicological endpoints (according to the criteria in Reg. 1272/2008, as amended)	~~Not classified~~ Repr. 2, H361d	Not classified
Agreed EU endpoints		
AOEL systemic	0.005 mg/kg bw/d (corrected for 50 % oral absorption)	0.8 mg/kg*** bw/d (corrected for 40 % oral absorption)
Reference	~~EFSA conclusion*~~ 15th ATP to Reg, 1272/2008	EFSA conclusion**
Conditions to take into account/critical areas of concern with regard to toxicology		
Review Report/EFSA Conclusion for active substance	-Potential ED activity to be clarified -metabolite AMBA genotoxic potential could not be ruled out	None

*EFSA Journal 2016;14(3):4419
**EFSA Scientific Report (2007) 120, 1-91
*** Instead, for the calculations in this dRR, the following AOEL value has been used: AOEL = 0.56 mg/kg bw / d, as proposed in the AIR supplementary dossier (document N2: List of endpoints, 2016).

Comments of zRMS:	Please note: the product SAE053H/01 (Kagura/Genki) contains the plant oil (rape seed oil) as a solvent. The rape seed oil is an approved active substance but is not relevant for the exposure assessment, since AOEL value is not applicable for this substance.

6.3 Toxicological Evaluation of Plant Protection Product

A summary of the toxicological evaluation for SAE053H/01 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 SAE053H/01

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)	> 2000 mg/kg bw	Yes	None	xxx, 2016a
LD_{50} dermal, rat (OECD 402)	> 2000 mg/kg bw	Yes	None	xxx, 2016b
LC_{50} inhalation	~~Not submitted, not necessary. Justification presented in Appendix 2~~) Not classified (acc. to additivity formula)			
Skin irritation, rabbit (OECD 404)	Non-irritant	Yes	None	xxx, 2016a
Eye irritation, in vitro BCOP, (OECD 437)	Inconclusive	Yes	None	xxx., 2016

Eye irritation, rabbit (OECD 405)	Non-irritant	Yes	None	xxx., 2016b
Skin sensitisation, mouse, LLNA, (OECD 429)	Sensitising	Yes	H317 Skin Sens. Cat 1	xxx., 2016c
Supplementary studies for combinations of plant protection products	No data			

Table 6.3-2: Additional toxicological information relevant for classification/labelling of SAE053H/01

	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 substance(s) (relevant for classification of product)	~~n.a.~~ 8%	Repr. 2, H361d	15th ATP to Reg. 1272/2008	Repr. 2, H361d
Toxicological properties of non-active substance(s) (relevant for classification of product)	n.a.			
Further toxicological information	n.a.			

* Please use concentration range or concentration limit (e.g. 1-10 % or > 1 %) as provided in MSDS.
** Material safety data sheet by the applicant
n.a. not applicable

6.4 Toxicological Evaluation of Groundwater Metabolites

Comments of zRMS:	Taking into account the toxicological data (EFSA Scientific Report (2007) 120, 1-91),, the grounwater metabolites of nicosulfuron are considered toxicologically non-relevant. The results of consumer risk calculations indicate that the use of SAE053H/01 (Kagura/Genki) according to the list of intended uses presented in GAP Table, causes no risk for health for the adults, toddlers and infants. The metabolite of mesotrione is predicted to stay in the concentrations below 0.1 µg/L.

For mesotrione, all metabolite concentrations are predicted to stay below 0.1 µg/L – no further groundwater assessment is therefore triggered.

For nicosulfuron, predicted environmental concentrations in groundwater determined according to the FOCUS guidance were below 0.6 µg/L for nicosulfuron at tier 1. At tier 2, they were below 0.1 µg/L for nicosulfuron. PEC groundwater values for the metabolites ASDM and AUSN were below 10 µg/L. For HMUD, MU-466 and UCSN they were below 0.75 µg/L. For ADMP, they stayed below 0.001 µg/L. The metabolites occurring at concentrations above 0.1 µg/L are not relevant (EFSA Conclusion 2007), not genotoxic and not toxic or highly toxic. Exposure estimations do not indicate a risk for consumers (for further information see dRR Part B10).

6.5 Dermal Absorption (KCP 7.3)

A summary of the dermal absorption rates for the active substances in SAE053H/01 are presented in the following table.

Table 6.5-1: Dermal absorption rates for active substances in SAE053H/01

	Mesotrione		Nicosulfuron	
	Value	**Reference**	**Value**	**Reference**
Concentrate	< 0.1 %	New study reported in Appendix 2	70 %	Default value at active substance < 5% (EFSA guidance on dermal absorption, 2017; SANTE/2018/10591)
Dilution (dilution factor 267)	< 0.1 %	New study reported in Appendix 2	70 %	Default value at active substance < 5% (EFSA guidance on dermal absorption, 2017; SANTE/2018/10591)

6.5.1 Justification for proposed values - mesotrione

Proposed dermal absorption rates for mesotrione are based on dermal absorption studies on formulation SAE053H/01. The study results are summarized in the following table. Full summaries of studies on the dermal absorption of active substance/formulation that have not previously been evaluated within an EU peer review process are described in detail in Appendix 2.

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

Test	**Concentrate**	**Spray dilution (dilution 1:267)**	**Formulation in study**	**Acceptability of study**	**Justification provided on representativity of study formulation for current product**	**Acceptability of justification**	**Reference***
In vitro (human)	80 g/L	0.3 g/L %	SAE053H/01	Yes	Not required	Justification accepted. Endpoint can be used for current product	Paul D., 2016

* indicates that a study was reviewed at EU level

6.5.2 Justification for proposed values - nicosulfuron

For nicosulfuron no dermal absorption study is available with the formulation. Therefore, the default values as proposed in the EFSA guidance on dermal absorption are used for the exposure calculations.

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	SAE053H/01	
Formulation type	OD	
Category	Herbicide	
Container size(s), short description	1, 5 and 10 L, PA/PE (Coex), polyethylene screw cap	
Active substance(s) (incl. content)	**Mesotrione** 80 g/L	**Nicosulfuron** 30 g/L

AOEL systemic	0.005 mg/kg bw/d	0.56 mg/kg bw/d*
Inhalation absorption	100 %	100 %
Oral absorption	50 %	40 %
Dermal absorption	Concentrate: 0.1 % Dilution: 0.1 % (Dilution rate: 1:267) (Based on product)	Concentrate: 70 % Dilution:70 % (Dilution rate: 1:267) (Default)

* as proposed in the AIR supplementary dossier (document N2: List of endpoints, 2016).

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 Zone/ EU is given in Part B, Section 0.

Justification

The critical GAP is based on the worst case condition of all GAP uses.

6.6.2 Operator exposure (KCP 7.2.1)

Comments of zRMS:	The estimations of operator exposure to mesotrione and nicosulfuron contained in SAE053H/01/Kagura, Genki (based on AOEM) performed by the Applicant are correct. Conclusions: According to the estimation based on AOEM, the use of SAE053H/01/Kagura, Genki containing mesotrione (80 g/kg) and nicosulfuron (30 g/L) **causes acceptable health risk for unprotected operator.** The potential exposure to the active substances amounts to the values lower than AOEL set for both active ingredients. Taking into account the classification of the undiluted product, protective gloves and work wear during M&L must be used by the operator. Thus, the following sentence regarding the use of PPE is recommended by the evaluator to be placed in the label: „*Stosować rękawice ochronne oraz odzież roboczą (kombinezon) w trakcie przygotowywania cieczy roboczej oraz odzież roboczą w trakcie wykonywania zabiegu*” “Wear protective gloves and work wear (coverall) during mixing/loading and work wear 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 SAE053H/01 according to the critical use(s) is presented in Table 6.6-2. Outcome of the estimation is presented in **Błąd! Nie można odnaleźć źródła odwołania.**. Detailed calculations are in Appendix 3.

Table 6.6-2: Exposure models for intended uses

Critical use(s)	Maize (max. 1.5 L product/ha), 1 application, spray dilution 200-400 water / ha
Model(s)	EFSA ~~OPEX~~ AOEM [EFSA, guidance document 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 6.6-3: Estimated operator exposure

		mesotrione		nicosulfuron	
Model data	**Level of PPE**	**Total absorbed dose (mg/kg/day)**	**% of systemic AOEL**	**Total absorbed dose (mg/kg/day)**	**% of systemic AOEL**
Outdoor downward spraying, vehicle mounted, to cereals Application rate: 0.12 kg mesotrione/ha and 0.045 kg nicosulfuron./ha					
EFSA-~~OPEX~~ AOEM	Potential exposure	0.0007	14.2	0.1870	33.4/23.4*
	Work wear – arms, body and legs covered (no gloves)	0.0005	9.83	0.1119	20.0/13.99*
	Additional gloves at mix/loading and during application	0.0002	3.18	0.0036	0.65/0.45*

*AOEL: 0.8 mg/kg bw

Operator exposure was estimated based on the AOEM (Agriculture Operator Exposure Model), as described in the EFSA-OPEX guidance (2014). For the assessment of operator exposure, the 75th percentile is used in the model.

According to the EFSA guidance, an acute risk assessment should be performed 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. However, the guidance does not define, how an acute AOEL or the RVAAS (Reference value acutely toxic active substance) shall be appropriately derived. Consequently, it was decided by the EFSA working group to remove the concept from the final version of the guidance. Therefore the acute risk assessment for operators was not performed.

Exposure to SAE053H/01 was estimated for the conditions of use defined in the GAP (Mixing/loading tank and field use by downward spraying (use on maize)). The 75th percentile model values in the chosen scenario, which served as basis for the calculations, are shown in the table below. Exposure estimation was calculated separately for mixing/loading and application, respectively. Dermal and inhalation exposures were considered.

Table 6.6-4: AOEM scenario used with respective exposure in µg (75th percentile)

Mixing/loading - tank		log exp = α·log TA + [droplets] + [formulation type] + constant
	hands	log DM(H) = 0.77·log TA + 0.57 [liquid] + 1.27 [WP] - 0.29 [glove wash] + 3.12
	protected hands	log DM(Hp) = 0.65·log TA + 0.32 [liquid] + 1.74 [WP] + 1.22
	body	log DM(B) = 0.70·log TA + 0.46 [liquid] + 1.83 [WP] + 3.09
	protected body	log DM(Bp) = 0.89·log TA + 0.11 [liquid] + 1.76 [WP] + 1.27
	head	log DM(C) = log TA + 0.90 [liquid] + 1.28 [WP] + 1.79 [no face shield] - 0.98
	inhalation	log IM = 0.30·log TA - 1.00 [liquid] + 1.76 [WP] + 1.57
Upward spraying – vehicle mounted		log exp = α·log TA + [cabin] + constant
	hands	log DA(H) = 0.89·log TA + 0.28 [no cabin] + 3.12
	protected hands	log DA(Hp) = log TA - 1.55
	body	log DA(B) = log TA + 0.48 [no cabin] + 3.47
	protected body	log DA(Bp) = log TA + 0.23 [no cabin] + 1.83
	head	log DA(C) = log TA + 1.89 [no cabin] + 1.17

	inhalation	log IA = 0.57·log TA + 0.82 [no cabin] + 0.99
Downward spraying – vehicle mounted		log exp = α·log TA + [droplets] + [equipment] + constant
	hands	log DA(H) = log TA + 0.37 [normal droplets] - 1.04 [normal equipment] + 2.84
	protected hands	log DA(Hp) = 0.54·log TA + 1.11 [normal droplets] + 0.29 [normal equipment] - 0.23
	body	protected body log DA(B) = log TA + 0.81 [normal droplets] - 1.43 [normal equipment] + 2.54
	protected body	log DA(Bp) = log TA + 0.70 [normal droplets] - 1.09 [normal equipment] + 0.74
	head	inhalation log DA(C) = log TA + 0.88 [normal droplets] - 0.53 [normal equipment] + 0.24
	inhalation	log IA = 0.50·log TA + 0.01 [normal droplets] - 0.71 [normal equipment] + 0.72
Upward spraying – hand-held		log exp = α·log TA + [culture] + constant
	hands	log DA(H) = 0.84·log TA - 0.83 [normal culture] + 4.26
	protected hands	log DA(Hp) = log TA – 0.88 [normal culture] + 2.26
	body	log DA(B) = 0.16 log TA – 1.29 [normal culture] + 6.08
	protected body	log DA(Bp) = -1.64 [normal culture] + 4.65
	head	log DA(C) = 0.32 log TA – 1.09 [normal culture] + 3.27
	inhalation	log IA = 0.83·log TA - 0.26 [normal culture] + 2.17
Downward spraying – hand-held		75th percentile (above 1.5 kg a.s. linear extrapolation)
	hands	1544
	protected hands	5
	body	88868
	protected body	8903
	head	12
	inhalation	26

SAE053H/01 is used at a range of water diluent volumes between 200 and 400 litres per hectare for the use on maize using tractor mounted boom sprayer (hydraulic nozzles). The exposure estimate has been conducted based on the respective GAP of SAE053H/01, using the respective minimum spray volume. Work rates in the AOEM model are 50 hectares per day for application to low level crops using tractor mounted boom sprayer.

Results:
The potential total systemic exposures of an operator, dressed in work wear that covers the body, arms and legs, correspond to 9.83 % AOEL for mesotrione and 20.0 % AOEL for nicosulfuron. Thus the use of SAE053H/01 has an acceptable risk for the operator, according to the EFSA-OPEX model. However, due to the sensitising potential of mesotrione gloves should be worn at mixing/loading and during application, which further reduce the exposure to 3.18 % AOEL for mesotrione and to 0.65 % AOEL for nicosulfuron.

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 necessary and was therefore not performed.

6.6.4 Worker exposure (KCP 7.2.3)

Comments of zRMS:

The estimations of worker exposure to the active substance contained in SAE053H/01/Kagura, Genki (based on AOEM) performed by the Applicant are correct. However, according to the current requirements of Polish Authorities, if a PPP is anticipated to be used only once per season EUROPOEM II should be used to estimate worker exposure towards an active substance contained in such a formulation. Therefore, the exposure data has been re-calculated based on EUROPOEM II and the results are presented:

Mesotrione:

	Exposure (mg a.s./day)	% of systemic AOEL
Cereals (TC: 0.14 m^2/h) Work duration: 2 h (inspection) b.w: 60 kg		
Work wear	0.001	**0.3**
Work wear and protective gloves	<0.001	**<0.3**

Nicosulfuron:

	Exposure (mg a.s./day)	% of systemic AOEL
Cereals (TC: 0.14 m^2/h) Work duration: 2 h (inspection) b.w: 60 kg		
Work wear	0.265	**1*/0.5****
Work wear and protective gloves	0.053	**0.2*/0.1****

AOEL:
*0.56 mg/kg b.w.
**0.8 mg/kg b.w.

Conclusions:

According to the estimation results, the use of SAE053H/01/Kagura, Genki containing mesotrione (80 g/kg) and nicosulfuron (30 g/L) **does not cause unacceptable health risk for a worker wearing work wear** during field inspection when exposure amounts to 2h.
Nevertheless, it is forbidden to re-enter area treated with SAE053H/01/Kagura, Genki until spray deposit on plant surfaces has dried.

The sensitization potential of SAE053H/01 (Skin Sens 1, H317) is confirmed for undiluted product. However, bearing in minds the risk for the most sensitive individuals and no dose-effect relationship in case of sensitization, the protective gloves and work wear is recommended for the worker.

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).”

“Wear protective gloves and workwear (long trousers, long-sleeve shirt).”

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 SAE053H/01 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. 1.5 L product/ha), 1 application, spray dilution 200-400 water / ha
Model	EFSA-OPEX [EFSA, guidance document 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

		Mesotrione		**Nicosulfuron**	
Model data	**Level of PPE**	**Total absorbed dose (mg/kg/day)**	**% of systemic AOEL**	**Total absorbed dose (mg/kg/day)**	**% of systemic AOEL**
Outdoor downward spraying, vehicle mounted, to cereals Application rate: 0.12 kg mesotrione/ha and 0.045 kg nicosulfuron/ha					
Number of applications and application rate:		0.12 kg a.s./ha		0.045 kg a.s./ha	
Inspection, irrigation (2 working hours, TC 12500 cm^2/hr (potential exposure), 1400 cm^2/hr (work wear))	Potential exposure	0.0090	3.00%	0.0394	7.03/4.93*
	Work wear – arms, body and legs covered	0.0010	0.34%	0.0044	0.79/0.55*

*AOEL: 0.8 mg/kg bw

The exposure and risk assessments for workers were performed using the EFSA OPEX model, taking in account the worst case in the GAP.

The estimation of worker exposure was performed according to the EFSA 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). The guidance states that exposure of workers must be estimated for activities that involve contact with treated crops after the application of a plant protection product, i.e. crop inspection or harvesting activities or other activities such as packaging, sorting or bundling. This means that the entry into treated crops is only relevant in the case of post-emergent application, as no exposure happens at pre-emergent application. The available study data in the EFSA-OPEX model allow calculations for re-entry only immediately after the application solution has dried, as there are no further data sets. Main routes during the post-application activities are dermal and inhalation (indoor only) and the sources of exposure are the contact with foliage, soil and possibly dust. The method for estimating exposures assume that the worker will wear no PPE (Regulation (EC) 284/2013), however where the risk assessor is confident that normal work wear will comprise long-sleeved jackets and trousers (arms, body and legs covered) or if it is considered that workers can be reliably expected to use PPE (body and hands covered), this can be allowed for in exposure estimation, by application of respective transfer coefficients (TC).

Potential dermal exposure (PDE) is calculated as the product of the application rate (AR) with the dislodgeable foliar residue (DFR), the transfer coefficient (TC) and the task duration (T):

PDE in mg a.s./day = (AR [kg a.s./ha] x DFR [µg/cm^2] × TC [cm^2/h] × T [h/day])/1 000

The default value for time of exposure is 8 hours for harvesting and maintenance type activities and 2 hours for crop inspection and irrigation-type activities. The standard DFR value in a first tier assessment is 3 µg active substance /cm2 of foliage/kg a.s. applied/ha, regarded as a highly conservative value. In case of multiple treatments, multiple application factors (MAF), assuming a default dissipation half-life of

30 days were used to consider the potential accumulation. For instance, the TC values used for the calculation are 2500 cm^2/person/hour for field vegetables (asparagus, artichoke) 1400 for cereals (including paddy rice), 4500 for oil fruits (olives), 10100 for grapes, and 4500 for stone fruits 12500 cm^2/h and 1400 cm^2/h when wearing working clothing (arms, body, and legs covered), respectively.

The worst case is defined by the maximum application rates of 0.120 kg mesotrione /ha and 0.045 kg nicosulfuron /ha. Field crops will be mechanically harvested, therefore workers may only enter treated fields for crop inspection (scouting) or irrigation activities, for which an exposure period of 2 hours is considered appropriate.

Results
The exposure to mesotrione and to nicosulfuron of the worker with work wear (arms, body and legs covered, no gloves) was estimated as 0.34 % AOEL and 0.79% AOEL, respectively. Due to the sensitizing potential of mesotrione gloves should be worn at work. This will further reduce the exposure, though it cannot be calculated with the model, due to the fact that no TC is available for work with gloves. Therefore, it is concluded that there is no unacceptable risk anticipated, when re-entering crops treated with SAE053H/01. As a standard rule, it should be mentioned on the label that treated crops should not be re-entered before spray deposits on leaf surfaces have completely dried.

6.6.4.2 Refinement of generic DFR value (KCP 7.2)

Not required.

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.

6.6.5 Bystander and resident exposure (KCP 7.2.2)

Comments of zRMS:	The results of bystander and resident exposure estimations to mesotrione and nicosulfuron contained in the formulation SAE053H/01/Kagura, Genki presented by the applicant are accepted. The reference values acutely toxic active substance (RVAAS) for active substances are not allocated. Consequently, it is assumed that the estimation of bystander exposure is covered by the calculation of resident exposure towards mesotrione and nicosulfuron. **Summary and conclusions:** The estimations performed according to AOEM indicate that the systemic exposure to mesotrione (80 g/L) and nicosulfuron (30 g/L), contained in the formulation SAE053H/01/Kagura, Genki does not exceed the values of AOEL for the active substances. The **incidental short-time exposure of bystander and resident (children and adult**) to the formulation SAE053H/01/Kagura, Genki **causes no risk** to human health if the product is used in accordance to the intended uses listed in the GAP Table.

Table 6.6-6 shows the exposure model(s) used for estimation of bystander and resident exposure to mesotrione and nicosulfuron. Outcome of the estimation is presented in Table 6.6-7 and 6.6-10. Detailed calculations are in Appendix 3.

Table 6.6-6: Exposure models for intended uses

Critical use(s)	Maize (max. 1.5 L product/ha), 1 application, spray dilution 200-400 water / ha
Model	For residents the following model was applied: EFSA-OPEX [EFSA, guidance document on the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products (EFSA Journal 2014;12(10):3874] For bystanders the following model was applied:

	Martin S. et al. (2008) [Guidance for Exposure and Risk Evaluation for Bystanders and Residents Exposed to Plant Protection Products During and After Application; J. Verbr. Lebensm. 3 (2008): 272-281 Birkhäuser Verlag Basel] and Bundesanzeiger (BAnz), 06 January 2012, Issue No. 4, pp. 75-76.

6.6.5.1 Estimation of resident exposure

Table 6.6-7: Estimated resident exposure

	mesotrione		nicosulfuron	
Model data	**Total absorbed dose (mg/kg/day)**	**% of systemic AOEL**	**Total absorbed dose (mg/kg/day)**	**% of systemic AOEL**
Outdoor downward spraying, vehicle mounted, to cereals Application rate: 0.12 kg mesotrione/ha and 0.045 kg nicosulfuron/ha				
Residents (adult) Drift rate: 5.6 %/4.1% (2-3 m) Body weight: 60 kg	0,0002	4.85	0.0032	0.58/0.4*
Residents (children) Drift rate: 5.6 %/4.1% (2-3 m) Body weight: 10 kg	0.0011	22.8	0.0080	1.43/1.0*

*AOEL: 0.8 mg/kg bw

The estimation of resident exposure was performed according to the EFSA 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). 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. However, the guidance does not define, how an acute AOEL or the RVAAS shall be appropriately derived. Consequently, it was decided by the EFSA working group to remove the concept from the final version of the guidance. Therefore the risk assessment for bystanders was performed with the German model (Martin et al., 2008).

Estimation of resident exposure (EFSA-OPEX model)

Spray drift
The exposure from spray drift is calculated by using the following equation:

Dermal exposure × dermal absorption percentage + inhalation exposure

where the dermal absorption percentage is the value for the in-use dilution taken from the toxicological evaluation, and the dermal and inhalation exposures are those shown in the tables below. For arable crops, BREAM data are considered to be appropriate, as they provide drift data for children (using mannequins representative of 4-year-old children). For orchard crops and vines, the most appropriate dataset was considered to be the dataset for conventional nozzles (no drift reduction technologies) applying 470 L/ha from a report by Lloyd et al. (1987) for an 8-m distance downwind from the middle of the tree trunk, as this dataset gave the highest drift exposures in that report. No adjustment to the exposure values for orchard crops and vines is proposed, since the measurements in the report by Lloyd et al. (1987) relate to application across an entire orchard, and the layout of orchards and vineyards and the way equipment is operated (e.g. when at the edge of the orchard, spray is directed only into the crop) makes the values suitable for a resident located about 5 m from the edge of a field, assuming the space from the tree trunk to the edge of the field is at least 3 m; moreover, these data form a significant part of those included in EUROPOEM for this scenario, and are preferred to the others, as they were generated under more representative conditions. The dermal and inhalation exposures (75th percentile and mean values) are as shown in the following tables:

Table 6.6-8 Dermal and inhalation exposures for residents (75th percentile from data on potential dermal and inhalational exposures)

Arable crops/ground boom sprayer	**These values are the 75th percentiles for residents (assuming average breathing rates for inhalation exposures)**			
Distance from sprayer	**Dermal (mL spray dilution/person)**		**Inhalation (mL spray dilution/person)**	
	Adults	**Children**	**Adults**	**Children**
2 m	0.47	0.33	0.00010	0.00022
5 m	0.24	0.22	0.00009	0.00017
10 m	0.20	0.18	0.00009	0.00013
Orchard/broadcast air assisted applications[1]	**These values are the 75th percentiles for residents (assuming average breathing rates for inhalation exposures)**			
Distance from sprayer	**Dermal (mL spray dilution/person)**		**Inhalation (mL spray dilution/person)**	
	Adults	**Children**	**Adults**	**Children**
2 – 3 m	Not available	Not available	Not available	Not available
5 m	5.63	1.689	0.0021	0.00164
10 m	5.63	1.689	0.0021	0.00164

[1] the only available values are for the 8-m distance downwind downwind from the middle of the tree trunk, which are assumed to represent a 5-m distance from the edge of the orchard; the same value is used for 5 and 10 m

Table 6.6-9 Dermal and inhalation exposures for residents (mean data on potential dermal and inhalational exposures)

Arable crops/ground boom sprayer	**These values are the mean values (assuming average breathing rates for inhalation exposures)**			
Distance from sprayer	**Dermal (mL spray dilution/person)**		**Inhalation (mL spray dilution/person)**	
	Adults	**Children**	**Adults**	**Children**
2 m	0.22	0.18	0.00009	0.00017
5 m	0.12	0.12	0.00008	0.00014
10 m	0.11	0.10	0.00007	0.00011
Orchard/broadcast air assisted applications[1]	**These values are the mean values (assuming average breathing rates for inhalation exposures)**			
Distance from sprayer	**Dermal (mL spray dilution/person)**		**Inhalation (mL spray dilution/person)**	
	Adults	**Children**	**Adults**	**Children**
2 – 3 m	Not available	Not available	Not available	Not available
5 m	3.68	1.11	0.0017	0.0013
10 m	3.68	1.11	0.0017	0.0013

[1] the only available values are for the 8-m distance downwind downwind from the middle of the tree trunk, which are assumed to represent a 5-m distance from the edge of the orchard; the same value is used for 5 and 10 m

The BREAM calculator provides dermal and inhalation exposure estimates from arable applications for adults and children. Based on the scenario above, the 75th percentile values in Table 6.6.5.1-3 are based on the following:
-dermal exposure: adults 0.47 mg and children 0.33 mg. Note, for these examples, 1 mg a.s. = 1 mL spray solution (concentration spray solution 1 g a.s./L)

-inhalation exposure: adults, breathing 0.575 m^3/h, 0.0001 mg; and children, breathing 0.45 m^3/h, 0.00022 mg.

Lloyd et al. (1987) provides values measured for orchard applications for adults only. The values for adults in Table 6.6.5.1-3 were re-calculated for children:
- dermal exposure = 5.63 mL × 0.3 (child/adult body area) = 1.689 mL

- inhalation exposure = 0.0021 mL × 0.45 m^3/h (child breathing rate) or 0.575 m^3/h (adult breathing rate) = 0.00164 mL.

The average values from table 6.6.5.1-4 are derived from the corresponding data in the same manner.

Vapour

Exposures to vapour is estimated using the method that has been developed in the UK (CRD, 2008) and Germany (Martin et al., 2008), based on the highest time-weighted average exposure for a 24-hour period, according to the volatility of the active substance:

$SER_I = (VC \times IR \times IA)/BW$

where:

-SER_I = systemic exposure of residents via the inhalation route (mg/kg bw per day)

-VC = vapour concentration (mg/m3)

-IR = inhalation rate (m3/day)

-IA = inhalation absorption (%)

-BW = body weight (kg).

For moderately volatile compounds (vapour pressure ≥ 0.005 Pa and < 0.01 Pa), exposures should be calculated assuming a default concentration in the air of 15 µg/m3 and daily average breathing rates (0.23 for adults and 1.07 m3/day/kg for children), resulting in:

-an adult value of 15 µg/m3 × 0.23 m3/day/kg × 60 kg = 3.45 µg/day/kg × 60 kg = 207 µg/day

-a child value of 15 µg/m3 × 1.07 m3/day/kg × 10 kg = 16.05 µg/day/kg × 10 kg = 160.5 µg/day.

For compounds with low volatility (vapour pressure < 0.005 Pa), exposures should be calculated assuming a default concentration in the air of 1 µg/m3, resulting in:

-an adult value of 1 µg/m3 × 0.23 m3/day/kg × 60 kg = 0.23 µg/day/kg × 60 kg = 13.8 µg/day

-a child value of 1 µg/m3 × 1.07 m3/day/kg × 10 kg = 1.07 µg/day/kg × 10 kg = 10.7 µg/day.

Surface deposits

Dermal exposure from surface deposits based on spray drift should be based on the following equation:

$SER_D = (AR \times D \times TTR \times TC \times H \times DA)/BW$

where:

-SER_D = systemic exposure of residents via the dermal route (mg/kg bw/day)

-AR = application rate (mg/cm2) (consider MAF, if necessary)

-D = drift (%) (if multiple applications have to be taken into account, a lower percentile could be considered for risk refinement)

-TTR = turf transferable residues (%) (for products applied in liquid sprays, 5 %, and for products applied as granules, 1 % (these values come from data obtained using the Modified Californian Roller Method (Fuller et al., 2001; Rosenheck et al., 2001) and represent the upper end of the range from a number of studies with different compounds))

-TC = transfer coefficient (cm2/h) (default values of 7300 cm2/h for adults and 2600 cm2/h for children are recommended, TC values take into account minimal protection from clothes)

-H = exposure duration (hours) (a default value of two hours is recommended by US EPA, 2001)

-DA = dermal absorption (%)

-BW = body weight (kg).

Exposure from surface deposits for children aged less than three years should be calculated using the following equation:

Dermal exposure + hand to mouth transfer + object to mouth transfer

Children's hand to mouth transfer should be calculated using the following equation:

$SOEH = (AR \times D \times TTR \times SE \times SA \times Freq \times H \times OA)/BW$

where:

-SOE_H = systemic oral exposure via the hand to mouth route (mg/kg bw/day)

-AR = application rate (mg/cm2) (consider MAF, if necessary)

-D = drift (%) (if multiple applications have to be taken into account, a lower percentile could be considered for risk refinement)

-TTR = turf transferable residues (%) (for products applied in liquid sprays, 5 % is used, and, for products applied as granules, 1 % is used (these values come from data obtained using the Modified Californian Roller Method (Fuller et al., 2001; Rosenheck et al., 2001), and represent the upper end of the range from a number of studies with different compounds)

-SE = saliva extraction factor (%) (a default value of 50 % is recommended by US EPA, 2001; it refers to the fraction of pesticide extracted from a hand/object via saliva. It is a median value from a study by Camann and colleagues on the fraction of pesticide extracted by saliva from hands (Camann et al., 1995))

-SA = surface area of hands (cm2) (the assumption used here is that 20 cm2 of skin area is contacted each time a child puts a hand in his or her mouth (US EPA, 2001))

-Freq = frequency of hand to mouth (events per hour) (for short-term exposures, a value of 9.5 events per hour is recommended; this is the average of observations ranging from 0 to 70 events per hour (US EPA, 2001))

-H = exposure duration (hours) (a default value of two hours is recommended by US EPA, 2001)

-OA = oral absorption (%)

-BW = body weight (kg).

Children's object to mouth transfer should be calculated using the following equation:

SOEO = (AR × D × DRP × IgR × OA)/BW

where:

-SOE_O = systemic oral exposure via the object to mouth route (mg/kg bw/day)

-AR = application rate (mg/cm2) (consider MAF, if necessary)

-D = drift (%)

-DPR = dislodgeable residues percentage (%) (a default value of 20 % transferability for object to mouth assessments is recommended by US EPA, 2001)

-IgR = ingestion rate for mouthing of grass/day (cm2) (a default value of 25 cm2 of grass/day is recommended by US EPA, 2001)

-OA = oral absorption (%)

-BW = body weight (kg).

Values for drift percentage for field crops (from BREAM) are:

Distance	Mean (%)	75^{th} percentile (%)
2-3 m	4.1	5.6
5 m	1.8	2.3
10 m	1.0	1.3

Different risk mitigation measures for the assessment of surface deposits can be applied. For example, safety distances of > 2 or > 3 m can be used for the risk assessment. Furthermore, drift-reducing nozzles of 50 % can be considered as a risk mitigation measure in this Guidance (see for example Guidelines for the testing of plant protection products Part VII, April 2000. Federal Biological Research Centre for Agriculture and Forestry Federal Republic of Germany). Corresponding safety instructions on the label are necessary. Any further risk mitigation measures need to be supported by data (including an assessment of the conditions used to derive the proposed measures compared with the conditions used to estimate the drift values proposed in this Guidance).

Entry into treated crops

Entry into treated crops is based on exposure from activities such as walking in treated fields for adults, however is only relevant in the case of post-emergent application, as no exposure can happen at pre-emergent application.

The method used should be the same as for workers, with the same DFR and a TC based on data for inspection activities (75th percentile: 7500 cm^2/h, mean: 5980 cm^2/h), and with a 15-minute exposure. TC values are only available for adults. A factor of 0.3 has been applied to the adult TC for children re-entering treated crops.

For children, all the pathways of exposure to surface deposits are relevant. Currently, for adults, object to mouth and hand to mouth transfer of surface deposits are considered less important and are not considered in the exposure calculator.

Results
For residents, the exposure estimates to mesotrione (adults 4.85 % AOEL, children 22.8 % AOEL) and to nicosulfuron (adults 0.58 % AOEL, children 1.43 % AOEL) result in values that are distinctly lower than the respective AOEL values. It is concluded that there is no undue risk to residents by application of SAE053H/01.

6.6.5.2 Estimation of bystander exposure

Estimation of bystander exposure (according to Martin et al., 2008)
The calculations were done for both adults and children and the assumption of exposure from the following exposure routes: Spray drift, dermal and inhalation

The presence of bystanders is incidental within or directly adjacent to an area where plant protection products are applied. A situation in which bystander exposure could occur would be a person walking alongside an area being treated at the same time. Under these conditions the bystander would never walk directly next to the outer spraying nozzle. A distance of some meters from the spraying device can always be expected. It can further be assumed that any bystander, as soon as becoming aware of an exposure will leave the spraying area. Therefore, bystander exposure is of short duration, typically a matter of minutes. Thus, exposure duration of 5 minutes is assumed.

Systemic Exposure of Bystanders (mg/kg bw/d) $\underline{SE_B}$ = Systemic Dermal Exposure of Bystanders (mg/kg bw/d) $\underline{SDE_B}$ + Systemic Inhalation Exposure of Bystanders (mg/kg bw/d) $\underline{SIE_B}$

Dermal Exposure Model (Spray Drift)
$SDE_B = (AR \times D \times BSA \times DA) / BW$

Where:
AR = Application Rate (mg/m^2)
Mesotrione 0.120 kg/ha
Nicosulfuron 0.045 kg/ha

D = Drift (%)
2.77% for low crops in 1 m distance

BSA = Exposed Body Surface Area (m^2) – 1 m^2 adults and 0.21 m^2 children

DA = Dermal Absorption (%)
Mesotrione 0.1%
Nicosulfuron 75%

BW = Body Weight (kg/person) – 60 kg adults and 16.15 kg children

Inhalation Exposure Model (Spray Drift)
$SIE_B = (I^*A \times AR \times A \times T \times IA) / BW$

Where:

I*A = Specific Inhalation Exposure (mg/kg a.s. handled per day) – 0.001 for adults and 0.00057 for children
AR = Application Rate (kg a.s./ha)
Mesotrione 0.120 kg/ha
Nicosulfuron 0.045 kg/ha

A = Area Treated (ha/day)- 20 ha for low crops, 8 ha for high crops
T = Time [Duration] (min) – 5 minutes
IA = Inhalation Absorption (%) – 100%
BW = Body Weight (kg/person) - 60 kg adults and 16.15 kg children

Table 6.6-10: Estimated bystander exposure

	mesotrione		**nicosulfuron**	
Model data	**Total absorbed dose (mg/kg/day)**	**% of systemic AOEL**	**Total absorbed dose (mg/kg/day)**	**% of systemic AOEL**
Outdoor downward spraying, vehicle mounted, to cereals Application rate: 0.12 kg mesotrione/ha and 0.045 kg nicosulfuron/ha				
Bystander (adult) Drift rate: 2.77 % (1 m) Body weight: 60 kg	0,0000006	0.12	0.0015	~~0.267~~ 0.27/0.19*
Bystander (children) Drift rate: 2.77 % (1 m) Body weight: 16 kg	0.000006	0.11	0.0011	0.20/0.14*

*AOEL: 0.8 mg/kg bw

Results
The exposure estimates to mesotrione for bystanders result in values (adults 0.12 % AOEL, children 0.11 % AOEL) that are distinctly lower than the respective AOEL values. It is concluded that there is no undue risk to bystanders by application of SAE053H/01.

The exposure estimates to nicosulfuron for bystanders result in values (adults 0.26 % AOEL, children 0.20 % AOEL) that are distinctly lower than the respective AOEL values. It is concluded that there is no undue risk to bystanders by application of SAE053H/01.

6.6.5.3 Measurement of bystander and/or resident exposure

Since the bystander and/or resident exposure estimations carried out indicated that the acceptable operator exposure level (AOEL) for mesotrione and nicosulfuron 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

Comments of zRMS:	**Summary and conclusions:** The estimations performed according to AOEM and EUROPOEM II indicate that the concurernt systemic exposure to mesotrione (80 g/L) and nicosulfuron (30 g/L) contained in the formulation SAE053H/01/Kagura, Genki does not cause unaceptable risk for the health of operators, workers, bystanders and residents (adults and children) beacause the HI values remian below 1.

6.6.6.1 Exposure Assessment of mesotrione and nicosulfuron in SAE053H/01

Note: The combined toxicological effect of these active substances has not been investigated with regard

to repeated dose toxicity.

At the first tier, combined exposure is calculated as the sum of the component exposures without regard to the mode of action or mechanism/target of toxicity. Initially, the individual Hazard Quotients (HQ) are calculated for all active substances in the PPP by assessing the exposure according to appropriate models and dividing the individual exposure levels by the respective systemic AOEL. This is equivalent to the predicted exposure as % of systemic AOEL converted to decimal. The Hazard Index (HI) is the sum of the individual HQs.

Table 6.6-11: Acute risk assessment from combined exposure

Application scenario	Active Ingredient	Estimated exposure / AOEL (HQ)
Operators – Outdoor vehicle-mounted downward spraying on cereals (worst case)	mesotrione	0.0318
	nicosulfuron	0.0065/0.0045*
	Cumulative risk Operators (HI)	**0.0383/0.0363**
Workers – inspection, irrigation	mesotrione	0.0034
	nicosulfuron	0.0079/0.0055*
	Cumulative risk Workers (HI)	**0.0113/0.0089**
Resident - Adult	mesotrione	0.0485
	nicosulfuron	0.0058/0.004*
	Cumulative risk Resident – Adult (HI)	**0.0543/0.0525**
Resident - Child	mesotrione	0.2284
	nicosulfuron	0.0143/0.01*
	Cumulative risk Resident – Child (HI)	**0.2427/0.2384**
Bystander - Adult	mesotrione	0.0012
	nicosulfuron	0.0027/0.0019*
	Cumulative risk Bystander – Adult (HI)	**0.0034/0.0031**
Bystander - Child	mesotrione	0.0011
	nicosulfuron	0.0020/0.0014*
	Cumulative risk Bystander – Child (HI)	**0.0031/0.0025**

*AOEL: 0.8 mg/kg bw

Thus, combined exposure to all active substances in AE053H/01 is not expected to present a risk for operators, workers, bystanders and residents. No further refinement of the assessment is required.

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	xxx	2016a	Acute oral toxicity study of SAE53H/01 in rats xxx, Laboratory report number: 401-1-01-15025 GLP Unpublished	Y	Sumi Agro Europe Ltd
KCP 7.1.2/01	xxx	2016b	Acute dermal toxicity study of SAE53H/01 in rats xxx, Laboratory report number: 403-1-01-15026 GLP Unpublished	Y	Sumi Agro Europe Ltd
KCP 7.1.4/01	xxx	2016a	Acute dermal irritation, xxx, Laboratory of SAE53H/01 in rabbits xxx, Laboratory report number: 406-1-01-15027 GLP Unpublished	Y	Sumi Agro Europe Ltd
KCP 7.1.5/01	xxx	2016	Bovine corneal opacity and permeability test for SAE053H/01 xxx, Laboratory report number: 530-1-01-15030 GLP Unpublished	N	Sumi Agro Europe Ltd
KCP 7.1.5/02	xxx	2016b	Acute eye irritation study of SAE53H/01 in rabbits xxx, Laboratory report number: 406-1-01-15028 GLP Unpublished	Y	Sumi Agro Europe Ltd
KCP 7.1.6/01	xxx	2016c	Skin sensitisation, xxx, Laboratory of SAE053H/01 by local lymph node assay in mice xxx, Laboratory report number: 409-1-01-15029 GLP Unpublished	Y	Sumi Agro Europe Ltd
KCP 7.3/01	Paul D.	2016	Mesotrione: Formulated as SAE053H/01 and SAE054H/01. In vitro study to investigate dermal absorption using human skin	N	Sumi Agro Europe Ltd

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
			Envigo study number NNA0003 GLP Unpublished		

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

None.

Appendix 2 Detailed evaluation of the studies relied upon

A 2.1 Statement on bridging possibilities

Comments of zRMS:	In the view of current regulations (EC Regulation 1272/2008, EC Regulation 1107/2009, EC Regulation 1907/2006), *in vivo* tests on animals should be avoided. However, the classification of the product SAE053H/01 (Kagura/Genki) was carried out based on the *in vivo* studies. This decision of the zRMS is due to the fact that presented studies had been generated in 2016 and were now available for the evaluator. The results of these tests are considered as conclusive data for the current evaluation except of the acute inhalation toxicity (lack of the experimental data, assessment based on product composition/additivity formula).

A 2.2 Acute oral toxicity (KCP 7.1.1)

Comments of zRMS:	The acute oral toxicity test by xxx, 2016a is accepted without reservation. In accordance with the provisions of the Regulation EC 1272/2008, the formulation SAE053H/01 (Kagura/Genki) does not require classification in regards to acute oral toxicity.

A 2.2.1 Study 1

Reference:	KCP 7.1.1-01
Report	Acute oral toxicity study of SA053H/01 in rats, xxx., 2016a, xxx, Laboratory report number 401-1-01-15025
Guideline(s):	OECD 420
Deviations:	None
GLP:	Yes
Acceptability:	Yes
Duplication (if vertebrate study)	No

Materials and methods

Test material (Lot/Batch No.)	SAE053H/01 (Batch No. 54606-101)
Species	Wistar rat, RccHan:WIST
No. of animals (group size)	6 females (2 in the sighting and 4 in the main experiment)
Dose(s)	300 mg/kg bw (first sighting experiment), 2000 mg/kg bw (second sighting experiment and main experiment)
Exposure	Once by gavage
Vehicle/Dilution	None
Post exposure observation period	14 days
Remarks	None

Results and discussions

Table A 1: Results of acute oral toxicity study in rats of SAE053H/01

Dose (mg/kg bw)	Toxicological results *	Duration of signs	Time of death	LD50 (mg/kg bw) (14 days)
First sighting experiment				
300	0/0/1	n.a.	n.a.	> 300
Second sighting experiment				
2000	0/0/1	n.a.	n.a.	> 2000
Main experiment				
2000	0/0/4	n.a.	n.a.	> 2000

* 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 SAE053H/01

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 LD50 of SAE053H/01 was higher than 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 acute dermal toxicity test by xxx., 2016b is accepted without reservation. In accordance with the provisions of the Regulation EC 1272/2008, the formulation SAE053H/01 (Kagura/Genki) does not require classification in regards to acute dermal toxicity.

A 2.3.1 Study 1

Reference:	KCP 7.1.2-01
Report	Acute dermal toxicity study of SA053H/01 in rats, xxx., 2016b, xxx report number 403-1-01-15026
Guideline(s):	OECD 402
Deviations:	None
GLP:	Yes
Acceptability:	Yes
Duplication (if vertebrate study)	No

Materials and methods

Test material (Lot/Batch No.)	SAE053H/01 (Batch No. 54606-101)
Species	Wistar rat, RccHan:WIST

No. of animals (group size)	5 animals / sex
Dose(s)	2000 mg/kg bw
Exposure	Dermally for 24 hours
Vehicle/Dilution	None
Post exposure observation period	14 days
Remarks	None

Results and discussions

Table A 3: Results of acute dermal toxicity study in rats of SAE053H/01

Dose (mg/kg bw)	Toxicological results *	Duration of signs	Time of death	LD50 (mg/kg bw) (14 days)
Male rats				
2000	0/0/5	n.a.	n.a.	> 2000
Female rats				
2000	0/0/5	n.a.	n.a.	> 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 SAE053H/01

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 dermal LD_{50} of SAE053H/01 was higher than 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)

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 par-ticles 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 SAE053H/01 (Kagura/Genki) can be determined based on the product composition/additivity formula. Calculations: 100/ATE mix=0.0061/1.5+2.142/1.5

	100/ATE mix=2.203/1.5 ATEmix=68.1 mg/L Taking into account the analysis of the classification of all ingredients of SAE053H/01 (Kagura/Genki) and the intended method of application (medium sprayer), the classification in regards to acute inhalation toxicity is not required.

Waiver
No acute inhalation study with SAE053H/01 has been performed. For both active substances mesotrione and nicosulfuron no mortality was noted in all reported acute inhalation studies. The LC_{50} of mesotrione was > 4.75 mg/L) and of nicosulfuron in all studies greater than the applied/achieved high dose concentration (2.04 to 5.47 mg/L air). Thus, no classification was deemed necessary for both active substances. Further, SAE053H/01
- is no gas or liquified gas;
- is no smoke generating plant protection product or fumigant;
- is not used with fogging/misting equipment;
- is not a vapour releasing plant protection product;
- is not supplied in an aerosol dispenser;
- is not a powder or a granule containing a significant proportion of particles of diameter <50 µm (> 1% on a weight basis);
- is not to be applied from aircraft in cases where inhalation exposure is relevant;
- contains no active substance with a vapour pressure > 10^{-2} Pa and is to not be used in enclosed spaces such as warehouses or glasshouses.

Therefore, an acute inhalation study with SAE053H/01 is considered to be not necessary.

A 2.5 Skin irritation (KCP 7.1.4)

Comments of zRMS:	The skin irritation/corrosion test by xxx., 2016a is accepted without reservation. In accordance with the provisions of the Regulation EC 1272/2008, the formulation SAE053H/01 (Kagura/Genki) does not require classification in regards to skin irritation/corrosion.

A 2.5.1 Study 1

Reference:	KCP 7.1.4-01
Report	Acute dermal irritation study of SAE053H/01 in rabbits, xxx., 2016, xxx, Laboratory report number 406-1-01-15027
Guideline(s):	OECD 404
Deviations:	None
GLP:	Yes
Acceptability:	Yes
Duplication (if vertebrate study)	No

Materials and methods

Test material (Lot/Batch No.)	SAE053H/01 (Batch No. 54606-101)
Species	Rabbit, New Zealand White
No. of animals (group size)	3 males
Initial test using one animal	Yes
Exposure	0.5 mL (4 hours, semi-occlusive)

Vehicle/Dilution	None
Post exposure observation period	14 days
Remarks	None

Results and discussions

Table A 5: Skin irritation of SAE053H/01

Animal No.		Scores after treatment *				Mean scores (24-72 h)	Reversible (day)
		1 h	24 h	48 h	72 h		
1	Erythema Oedema	1 1	1 1	0 0	0 0	0.33 0.33	n.a. n.a.
2	Erythema Oedema	1 1	1 0	0 0	0 0	0.33 0.00	n.a. n.a.
3	Erythema Oedema	1 1	1 1	0 0	0 0	0.33 0.33	n.a. n.a.

* scores in the range of 0 to 4

Clinical signs:	No clinical signs of toxicity were observed.
Skin reactions, mean dermal irritation scores	The mean scores of erythema (0.33) and oedema (0.00 to 0.33) observed for 24, 48, and 72 hours observation time-points indicated that SAE053H/01 is a non-irritant.

Conclusion
Under the experimental conditions, SAE053H/01 was not a skin irritant. No classification is required according to Regulation (EC) No. 1272/2008.

A 2.6 Eye irritation (KCP 7.1.5)

Comments of zRMS:	The study presented by the applicant (xxx., 2016) is accepted without reservation. Based on the results of the study and in accordance with OECD Guideline No 43~~8~~7, no prediction can be made. Therefore, **further *in vivo* eye irritation test on SAE053H/01 (Kagura/Genki) is justified.** The *in vivo* study by xxx., 2016b is accepted without reservation. The most advanced alteration caused by SAE053H/01 (Kagura/Genki) was conjunctiva redness (mean score 24-72h amounted to 0.33-0.67) without corneal epithelium damage. Thus, formulation SAE053H/01 (Kagura/Genki) is not irritating to the rabbit eye. According to Regulation EC 1272/2008, the formulation SAE053H/01 (Kagura/Genki) **does not warrant classification in regards to eye irritation.**

A 2.6.1 Study 1

Reference:	KCP 7.1.5-01
Report	Bovine corneal opacity and permeability test for SAE053H/01, xxx., 2016, xxx, Laboratory report number 530-1-01-15030
Guideline(s):	OECD 437
Deviations:	None
GLP:	Yes
Acceptability:	Yes
Duplication (if vertebrate study)	n.a.

n.a. not applicable

Materials and methods

Test material (Lot/Batch No.)	SAE053H/01 (Batch No. 54606-101)

Test system	Isolated cornea from the eyes of freshly slaughtered cattles
No. of replicates	3 corneas per test group (test item, positive control, negative control)
Exposure	0.75 mL, applied undiluted
Vehicle/Dilution	None
Positive control	N,N-Dimethylformamide (CAS No 68-12-2)
Negative control	Normal saline, 0.9% (w/v) NaCl
Remarks	None

Results and discussions

Corneal opacity: the opacity values for the SAE053H/01 treated eyes did not show any observable increase in comparison to the control group.

Corneal permeability: the mean final corneal permeability values for the SAE053H/01 treated eyes did not show any observable increase in comparison to the control group.

In vitro Irritancy Score (IVIS): The mean *In-Vitro* Irritancy Score (IVIS) for the corneas treated with SAE053H/01 was 3.67. The IVIS scores of the vehicle control (normal saline) and the positive control (Dimethylformamide) treated corneas were 0.41 and 145.45, respectively, which confirmed the reliability of the test system.

Table A 6: Bovine corneal opacity and permeability test of SAE053H/01, *in vitro* irritation score

Group : 1 [Normal Saline, 0.75 mL]

Cornea Holder N°	Io (LUX)	I (Initial) (LUX)	Initial Opacity Value	I (Post Treatment) (LUX)	Post Treatment Opacity Value	Corr. Opacity Value	OD_{490} Value	Corr. OD_{490} Value	IVIS
1	1138	1082	2.48	1071	2.91	0.43	0.071	0.024	0.79
2	1126	988	5.99	979	6.40	0.41	0.061	0.014	0.62
3	1106	1009	4.25	1018	3.87	-0.38	0.06	0.013	-0.19
Mean						**0.15**	-	**0.017**	**0.41**
SD						**0.46**	-	**0.006**	**0.52**

Group : 2 [SAE053H/01, 0.75 mL]

Cornea holder N°	Io (LUX)	I (Initial) (LUX)	Initial Opacity Value	I (Post Treatment) (LUX)	Post Treatment Opacity Value	Corr. Opacity Value	Final Opacity Value	OD_{490} Value	Corr. OD_{490} Value	Final OD_{490} Value	IVIS
4	1081	988	4.17	966	5.17	1.00	0.85	0.184	0.137	0.120	2.65
5	1117	1010	4.64	939	7.97	3.33	3.18	0.182	0.135	0.118	4.95
6	1102	956	6.51	922	8.20	1.69	1.54	0.188	0.141	0.124	3.40
Mean							**1.86**	-	**0.138**	**0.121**	**3.67**
SD							**1.20**	-	**0.003**	**0.003**	**1.17**

Group : 3 [Dimethylformamide, 0.75 mL]

Cornea holder N°	Io (LUX)	I (Initial) (LUX)	Initial Opacity Value	I (Post Treatment) (LUX)	Post Treatment Opacity	Corr. Opacity	Final Opacity	OD_{490}	Corr. OD_{490}	Final OD_{490}	IVIS Score
7	1101	1028	3.25	314	100.28	97.03	96.88	2.214	2.167	2.150	129.13
8	1103	966	6.07	276	119.80	113.73	113.58	1.964	1.917	1.900	142.08
10	1088	957	5.88	274	118.78	112.90	112.75	3.559	3.512	3.495	165.18
Mean							**107.74**	-	**2.532**	**2.515**	**145.46**
SD							**9.41**	-	**0.858**	**0.858**	**18.26**

Keys: IVIS = In Vitro Irritation Score, Io = Baseline Reading (With medium but without cornea), I = LUX Reading with Medium and Cornea, OD_{490} = Optical Density at 490 Wave Length, - = Not Applicable, Corr. = Corrected. Blank OD_{490} value = 0.047.

Classification, according OECD GD 437

IVIS	UN GHS
≤ 3	No Category
> 3; ≤ 55	No prediction can be made
> 55	Category 1

The IVIS score for the corneas treated with SAE053H/01 was found to be 3.67. Therefore , the indication

of the classification for SAE053H/01 is: No prediction can be made.

Conclusion

Under the experimental conditions, the prediction was not possible for SAE053H/01.

A 2.6.2 Study 2

Reference:	KCP 7.1.5-02
Report	Acute eye irritation study of SAE053H/01 in rabbits, xxx., 2016b, xxx
Guideline(s):	OECD 405
Deviations:	None
GLP:	Yes
Acceptability:	Yes
Duplication (if vertebrate study)	No

Materials and methods

Test material (Lot/Batch No.)	SAE053H/01 (Batch No. 54606-101)
Species	Rabbit, New Zealand White
No. of animals (group size)	3 males
Initial test using one animal	Yes
Exposure	0.1 mL (single instillation in conjunctival sac)
Irrigation (time point)	Yes (at 24 hours post test item application)
Vehicle/Dilution	None
Post exposure observation period	14 days
Remarks	None

Results and discussions

Table A 7: Eye irritation of SAE053H/01

Animal No.		Scores after treatment *				Mean scores (24-72 h)	Reversible (day)
		1 h	24 h	48 h	72 h		
1	Corneal opacity	0	0	0	0	0.00	n.a.
	Iritis	0	0	0	0	0.00	n.a.
	Redness conjunctivae	1	1	0	0	0.33	n.a.
	Chemosis conjunctivae	1	0	0	0	0.00	n.a.
2	Corneal opacity	0	0	0	0	0.00	n.a.
	Iritis	0	0	0	0	0.00	n.a.
	Redness conjunctivae	1	1	1	0	0.67	n.a.
	Chemosis conjunctivae	1	0	0	0	0.00	n.a.
3	Corneal opacity	0	0	0	0	0.00	n.a.
	Iritis	0	0	0	0	0.00	n.a.
	Redness conjunctivae	1	1	1	0	0.67	n.a.
	Chemosis conjunctivae	1	0	0	0	0.00	n.a.

* 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.
Eye reactions, mean eye irritation scores	The mean eye irritation scores of 0.00 for opacity, of 0.33, 0.67, 0.67 for conjunctival redness and of 0.00 for conjunctival chemosis indicate that SAE053H/01 is not an eye irritant Further, examination with fluorescein dye and cobalt blue filter at 24 hours post test item application did not reveal any corneal damage in all animals.

Conclusion

Under the experimental conditions, SAE053H/01 was not an eye irritant. No classification is required according to Regulation (EC) No. 1272/2008.

A 2.7 Skin sensitisation (KCP 7.1.6)

Comments of zRMS:	The skin sensitisation test by xxx., 2016c is accepted without reservation. The results of the study show that the EC3 value is greater than 2%. In accordance with the provisions of the Regulation EC 1272/2008, the formulation SAE053H/01 (Kagura/Genki) requires classification in regards to skin sensitisation (Skin Sens.1B, H317).

A 2.7.1 Study 1

Reference:	KCP 7.1.6-01
Report	Skin sensitisation study of SAE053H/01 by local lymph node assay in mice, xxx., 2016c, xxx report number 409-1-01-15029
Guideline(s):	OECD 429
Deviations:	None
GLP:	Yes
Acceptability:	Yes
Duplication (if vertebrate study)	No

Materials and methods

Test material (Lot/Batch No.)	SAE053H/01 (Batch No. 54606-101)
Species	Mouse, CBA/J strain
No. of animals (group size)	8 females in the preliminary test (2 / test group) 25 females in the main test (5 / test group)
Pre-screen range finding:	Yes, solubility test was performed to define the vehicle, and the maximum concentration which is technically applicable to the animals was determined.
Exposure (concentration(s), no. of applications)	Preliminary test: Treatment with 25 µL SAE053H/01 at 1%, 10%, 50% (v/v) in 1% vehicle and 100% (undiluted) for 3 consecutive days on the dorsum of both ears. Main test: Treatment with 25 µL SAE053H/01 at 10%, 25%, 50% (v/v) for 3 consecutive days on the dorsum of both ears.
Vehicle*	1% Pluronic L92 Surfactant: this vehicle was chosen based on strong schientific rationale and therefore compliant with the test guideline requirements. SAE053H/01 was found to be soluble in the chosen vehicle up to 75% v/v
Positive control	α-Hexylcinnamaldehyde (HCA)
Test regime	Topical application: Each mouse was treated with 25µL of the dose solution to the dorsal surface of each ear. Topical applications were performed once daily over three consecutive days.

	Administration of ^{3}H-methyl thymidine: 5 days after the first topical application all mice were dosed with 250 µL 20 µCi 3H-methylthymidine by intravenous injection via the tail vein. Preparation of cell suspension: 5 hours after ^{3}H-thymidine injection animals were sacrificed. The draining auricular lymph nodes were excised, individually pooled for each animal (2 lymph nodes per mouse). Single cell suspension was prepared, several times washed and finally re-collected in 1 mL 5% TCA. Each precipitate was transferred to a scintillation vial with 10mL scintillation fluid, thoroughly mixed. After a minimum of 30 minutes, incorporated ^{3}H-methyl thymidine was measured.
Clinical observations / mortality	Prior to application and once a day thereafter observation for any clinical signs of systemic toxicity or local irritation at the application site.
Body weights	Performed on the first day of dosing (day 0) and prior to to the administration with 3HTdR (day 5).
Ear thickness and local reactions	Ear thickness measurements were performed on day 0, day 2 and on day 5.
Stimulation index and determination of EC 3 value	The proliferative response of lymph nodes from each mouse was expressed as the number of radioactive disintegrations per minute (DPM) per mouse, calculated by subtracting out background DPM. The DPM per mouse were calculated for each test group and vehicle and positive control groups. Final results were expressed as the Stimulation Index (SI) which is calculated as a ratio of the mean DPM of test group divided by mean DPM of vehicle control group. EC3 values were determined by linear interpolation between 2 points of the stimulation indices axis one above and one below the SI of 3. If all measured points are above or below the SI of 3, no EC3 value can be stated.
Evaluation	A substance is regarded as a sensitiser in the LLNA if at least one concentraion of the test item results in a 3-fold or greater increase in 3H-methyl thymidine incorporation into lymph node cells of the test group animals, relative to that recorded for the lymph nodes of control group animals (SI equal to or greater than 3.0). On the basis of the test results, the test substance is classified.
Reliability check	Yes, with the concurrent running positive control.
Remarks	None

*Test item was unsoluble in acetone/olive oil, dimethylformamide, methyl ethyl ketone, propylene glycol and DMSO.

Results and discussions

Table A 9: Results of skin sensitisation study of SAE053H/01

	No. of ani-mals	**Concentration (%)**	**Mean DPM / group**	**Stimulation index (SI)****
SAE053H/01	5	1	9635.80 ± 7666.80	2.27
	5	10	12214.80 ± 3330.15*	2.88
	5	50	31773.40 ± 9351.80*	7.48

Test Vehicle Control Group	5	1% Pluronic L92	4247 ± 1058.45	1
Positive control	5	25% HCA	19999.40 ± 6909.39*±	4.71

* Significantly higher than control ($p \leq 0.01$)
** Stimulation Index = Mean DPM of test group divided by mean DPM of vehicle group

Clinical signs:	No clinical signs of toxicity were observed in any group. No erythema was observed in any treated mice at 1% and 10% (v/v) SAE053H/01 on day 0 to day 5. Very slight oedema was observed at 50% (v/v) SAE053H/01 (during days 3 to 5) in all mice and in the group treated with 25% HCA (during days 1 to 5) in all mice.
Body weights	The mean body weight of positive control as well as SAE053H/01 treated mice was comparable to that of the control group.
Ear test	
Group mean DPM	A statistically significant increase in DPM was observed at 10% and 50% (v/v)SAE053H/01 and 25% (v/v) HCA when compared to control group values.
Stimulation index and EC3 value	Stimulation index (SI) values calculated for groups treated with SAE053H/01 were found to be 2.27, 2.88, and 7.48 at the dose concentrations of 1%, 10% and 50% (v/v), respectively and 4.71% for the 25% HCA treated positive control group.. The SI obtained for SAE053H/01 at 50% (v/v) showed greater than three-fold increase over the control value and EC3 value was found to be 11.04.

Conclusion

The SI obtained for SAE053H/01 at 50% concentration showed a greater than 3-fold increase over the control value with an EC3 value of 11.04%. Therefore, SAE053H/01 demonstrates weak sensitisation potential under the experimental conditions. Classification with Skin Sens. 1, H317, is required according to Regulation (EC) No. 1272/2008.

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

No studies available, not needed.

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 dermal absorption study of mesotrione contained in the product SAE053H/01 and SAE054H/01 performed by Paul D., 2016 is accepted without reservation. The summary of results provided by the Applicant relates to the preparation SAE053H/01. The value of dermal absorption of this active substance amounts to 0.1% for concentrate and product dilution. According to the Guidance on Dermal Absorption (2017;15(6):4873) Chapter 6.1.) the default value of dermal absorption for nicosulforon is accepted and amounts to 70 % for both concentrated and product dilution.

Reference: KCP 7.3

Report	Mesotrione: Formulated as SAE053H/01 and SAE054H/01. In vitro study to investigate dermal absorption using human skin, Paul D., 2016, Envigo study number NNA0003
Guideline(s):	OECD 428, EC 440/2008 method B.45
Deviations:	None
GLP:	Yes
Acceptability:	Yes
Duplication (if vertebrate study)	n.a.

Executive Summary

The rate and extent of absorption of radioactivity were investigated following topical application of Mesotrione, labelled with carbon-14, to excised human skin in an Oil Dispersion (OD) formulation at two dose concentrations for two different formulations (SAE053H/01 and SAE054H/01).

Here only the data gained for formulation SAE053H/01 are summarized. The high dose level (80 g a.s./L) was equivalent to the commercially supplied concentrate. The low dose level was selected as 0.3 g a.s./L, corresponding to one in-use application rate of the product.

The group mean distributions of radioactivity are summarised for the formulation SAE053H/01in the following table: results are expressed as mean % applied radioactivity.

Formulation SAE053H/01

Dose level	High	Low
Total non-absorbed	99.1	102.0
Total absorbed	<0.1	<0.1
Total in stratum corneum	0.4	1.1
Absorption rate (µg/cm²/hr)	nc	nc

nc Not calculated

For formulation SAE053H/01, data show that the total amounts of applied material directly absorbed after 24 hours were <0.1% for both high and low dose levels, respectively.

It was considered that the material recovered in the stratum corneum after 24 hours was not available for absorption. Therefore the total amounts of radioactivity absorbable by 24 hours were <0.1% at the high and low dose levels, respectively. According to the EFSA guidance where there is variability between replicates i.e. the standard deviation is > 25% of the mean value, the value of the standard deviation should be added to the overall absorbable value. Therefore the amount considered as absorbable for formulation SAE053H/01 is <0.1% at the high level and <0.1% at the low dose level.

Materials and methods

Test material	
Name	mesotrione
Chemical name	2-{4-methylsulfonyl)-2-nitrobenzoyl]-1,3-cyclohexanedione
CAS number	104206-82-8
Radiolabelled test substance	

Position of radiolabel	Mesotrione, [1,3-cyclohexanedione-1(3)-14C]
Specific activity	6.03 MBq/mg
Batch number	XXII/20/A/3
Radiochemical purity	100%
Non-radiolabelled test substance	
Name	Mesotrione technical
Batch number	MST1401004
Purity	98.33%
Formulated product	
Name	SAE053H/01
Formulation type	OD (oil dispersion)
Batch number	002
Concentration of a.i.	80g/L (mesotrione) + 30g/L (nicosulfuron)
Blank formulation	
Name	SAE053H/01 BLANK
Batch number	54171-112

Skin samples	
Source	Skin samples from abdominal or back region were obtained from 5 female human donors (age 37 to 57 years), following surgery, supplied by the Tissue Solutions, and were stored at < -15°C, until preparation for use.
Preparation	Prior to use, skin samples were thawed to room temperature. Each full thickness skin membrane was then swabbed with 70% v/v ethanol/water to remove residual fat and blood, wiped dry and re-hydrated with distilled water prior to dermatoming. The full thickness skin sample was pinned out on a dermatome board (cork board with raised rubber cutting surface) and a mini-dermatome was used to cut slices of skin which contained epidermis and some dermis (dermatomed skin was 200 - 400 µm thick).

Doses, solubility in the receptor fluid, study conduct	
Solubility of test substance in the receptor fluid	The solubility of mesotrione in the chosen receptor fluid (physiological phosphate-buffered saline, supplemented with 5% bovine serum albumin, adjusted to pH 7.4) was demonstrated to be sufficient for the study and not to be rate limiting for the absorption process.
Doses	Concentrate: 80g/L Dilution: 0.3g/L
Group size/ number of wells	Twelve Scott-Dick flow-through diffusion cells were prepared at each dose level for SAE053H/01.
Assay: application rate, exposure time swabbing, sampling duration, tape stripping, processing of samples	Dermatomed skin membranes were maintained in the cells at approximately 32°C. The integrity of the skin membranes was first assessed using tritiated water (^3H_2O). After removal of the residual ^3H_2O, the [^{14}C]-Mesotrione formulations

	were applied to the unoccluded skin samples at a rate of 10 µL/cm^2. The skin samples were exposed to the test material for 6 hours, after which time the remaining dose was washed off the skin with a mild detergent solution. Receptor fluid samples were collected at hourly intervals for the duration of the experiment (24 hours). At the end of the experiment, the skin samples were tape stripped using 3M Scotch "magic" tap to remove residual surface dose and stratum corneum. The initial tape strips (1-2) were collected separately into a glass vial and represented material that was associated with surface residues. Subsequent tape strips containing the stratum corneum were analysed individually. The remaining skin was retained and analysed separately. The receptor fluid remaining in the cell and outlet tubing at the end of the experiment was retained and analysed for mass balance purposes. The diffusion cell components were also retained, washed and the washings analysed for mass balance purposes.
Measurement of radioactivity	Radioactivity was measured by liquid scintillation counting (LSC). Generally radioactivity in gross amounts of less than twice background (4 minute counts) was considered to be below the limit of detection. Aliquots of liquid samples were mixed with Ultima Gold scintillator (PerkinElmer Life and Analytical Sciences, Boston, USA) for measurement of radioactivity. Solid samples were combusted in oxygen using a Packard sample oxidiser. The efficiency of the oxidiser was determined using aliquots of Spec-Chec-14C check source for sample oxidisers (Packard BioScience) and was greater than 95%. Measurements of radioactivity were corrected for oxidiser efficiency
Calculation of absorption rate	The absorption rate was determined by plotting the amount absorbed per unit area of skin (µg/cm^2) versus time (hr). The linear (steepest) portion of the resulting curve is regarded as the steady-state region. For each cell the portion of the curve at its steepest part, over a data range of at least three data points (if possible), was used to calculate the absorption rate of test substance (µg/cm^2/hr). The mean steady-state absorption rate for test substances in human skin were not calculated due to the low absorption profiles observed for each formulation.

Results and discussion

The material recovered in the skin swabs, surface tape strips and that remaining on the donor chamber was considered to be non-absorbed accounting for 99.1% at the high dose level and 102.0% at the low dose level. In total, <0.1% of the radioactivity applied at the high and low dose level, respectively had penetrated through the skin within the 24 -hour exposure period. There was little affinity of [^{14}C]-Mesotrione for the stratum corneum, with means of 0.4% and 1.1% of the applied dose located in this compartment at the high and low dose levels, respectively.

Table A 10: Results of dermal absorption study of SAE053H/01: distribution of radioactivity (concentrate 80 g/L))

Skin source	Cell number	Dose in receptor (0 - 24 hr) (%)	Dose in receptor at termination (%)	Dose remaining in skin (%)	Dose remaining on receptor chamber (%)	Total absorbable (%)	Dose on tape (s.corneum) (%)	Dose in skin swab (6 hr) (%)	Dose on tape (surface) (%)	Dose remaining on donor chamber (%)	Total non-absorbed (%)	Total recovery (%)
H1	1	<0.1	nd	<0.1	0.1	0.1	0.6	91.6	2.8	2.5	96.9	97.6
H1	2	<0.1	nd	0.1	nd	0.1	1.1	90.5	1.6	2.3	94.4	95.6
H2	3	<0.1	nd	nd	nd	<0.1	0.1	97.3	0.5	0.1	97.9	98.0
H2	4	<0.1	nd	nd	nd	<0.1	0.2	101.8	0.4	0.2	102.4	102.6
H2	5	<0.1	nd	<0.1	nd	<0.1	0.5	93.7	2.7	2.1	98.5	99.0
H3	6	<0.1	nd	<0.1	nd	<0.1	0.4	96.0	0.3	0.1	96.4	96.8
H3	7	<0.1	nd	<0.1	nd	<0.1	0.2	92.3	3.5	0.6	96.4	96.6
H4	9	<0.1	nd	nd	nd	<0.1	0.1	97.4	0.2	nd	97.6	97.7
H4	10	<0.1	nd	<0.1	nd	<0.1	0.1	96.2	0.9	0.2	97.3	97.4
H5	11	<0.1	nd	nd	nd	<0.1	0.2	107.6	0.3	0.1	108.0	108.2
H5	12	<0.1	nd	<0.1	0.1	0.1	0.4	101.7	1.3	1.5	104.5	105.0
	Mean	<0.1	nd	<0.1	<0.1	<0.1	0.4	96.9	1.3	0.9	99.1	99.5
	sd	-	-	-	-	-	0.3	5.1	1.2	1.0	4.1	4.0
	cv	-	-	-	-	-	75	5.3	92.3	111.1	4.1	4.0

Results expressed as percent applied radiochemical dose
nd Not detected
sd Standard deviation
cv Coefficient of variance
- Not calculable

Table A 11: Results of dermal absorption study of SAE053H/01 distribution of radioactivity (dilution 0.3 g/L)

Skin source	Cell number	Dose in receptor (0 - 24 hr) (%)	Dose in receptor at termination (%)	Dose remaining in skin (%)	Dose remaining on receptor chamber (%)	Total absorbable (%)	Dose on tape (s.corneum) (%)	Dose in skin swab (6 hr) (%)	Dose on tape (surface) (%)	Dose remaining on donor chamber (%)	Total non-absorbed (%)	Total recovery (%)
H1	13	<0.1	nd	nd	nd	<0.1	0.6	99.9	2.8	<0.1	102.7	103.3
H1	14	<0.1	nd	nd	nd	<0.1	1.6	98.9	3.7	0.1	102.7	104.3
H1	15	<0.1	nd	nd	nd	<0.1	1.0	101.7	2.1	0.1	103.9	104.9
H2	16	0.1	nd	nd	nd	0.1	0.8	96.3	4.6	0.8	101.7	102.6
H2	17	0.1	nd	nd	nd	0.1	0.7	98.5	3.4	0.1	102.0	102.8
H3	18	<0.1	nd	nd	nd	<0.1	1.6	96.8	5.2	0.1	102.1	103.7
H3	19	<0.1	nd	0.1	nd	0.1	1.5	100.2	2.4	0.1	102.7	104.3
H4	20	<0.1	nd	nd	nd	<0.1	0.9	96.9	3.4	0.1	100.4	101.3
H4	21	<0.1	nd	nd	nd	<0.1	1.9	95.6	4.9	0.2	100.7	102.6
H4	22	<0.1	nd	nd	nd	<0.1	1.5	98.6	3.4	0.3	102.3	103.8
H5	23	<0.1	nd	nd	nd	<0.1	0.8	99.5	2.4	0.2	102.1	102.9
H5	24	<0.1	nd	nd	nd	<0.1	0.7	98.9	1.7	0.3	100.9	101.6
	Mean	<0.1	nd	<0.1	nd	<0.1	1.1	98.5	3.3	0.2	102.0	103.2
	sd	-	-	-	-	-	0.5	1.8	1.1	0.2	1.0	1.1
	cv	-	-	-	-	-	45.5	1.8	33.3	100	1.0	1.1

Results expressed as percent applied radiochemical dose
nd Not detected
sd Standard deviation
cv Coefficient of variance
- Not applicable

Table A 12: Results of dermal absorption study of SAE053H/01: distribution of radioactivity in the tape strips (concentrate 80 g/L))

Cell number		1	2	3	4	5	6	7	9	10	11	12	Mean	sd
Skin source		H1	H1	H2	H2	H2	H3	H3	H4	H4	H5	H5		
Tape strip	1 - 2	2.8	1.6	0.5	0.4	2.7	0.3	3.5	0.2	0.9	0.3	1.3	1.3	1.2
TOTAL IN TAPE SURFACE		2.8	1.6	0.5	0.4	2.7	0.3	3.5	0.2	0.9	0.3	1.3	1.3	1.2
Tape strip	3	0.28	0.3	0.05	0.08	0.12	0.08	0.11	0.02	0.03	0.05	0.16	0.1	0.1
	4	0.16	0.22	0.03	0.03	0.08	0.07	0.07	0.02	0.02	0.04	0.07	0.1	0.1
	5	0.07	0.12	0.02	0.03	0.11	0.07	0.04	0.02	0.01	0.02	0.05	0.1	<0.1
	6	0.03	0.28	0.01	0.03	0.06	0.06	0.02	0.02	ns	0.03	0.1	0.1	0.1
	7	0.02	0.07	0.03	0.03	0.13	0.1	nd	nd	ns	0.02	0.03	<0.1	<0.1
	8	ns	0.06	nd	nd	0.02	ns	nd	ns	ns	nd	ns	<0.1	<0.1
	9	ns	0.09	ns	nd	ns	ns	ns	ns	ns	0.01	ns	<0.1	<0.1
	10	ns	ns	ns	nd	ns	ns	ns	ns	ns	ns	ns	<0.1	-
	11	ns	ns	ns	nd	ns	ns	ns	ns	ns	ns	ns	<0.1	-
	12	ns	ns	ns	nd	ns	ns	ns	ns	ns	ns	ns	<0.1	-
	13	ns	ns	ns	nd	ns	ns	ns	ns	ns	ns	ns	<0.1	-
	14	ns	ns	ns	nd	ns	ns	ns	ns	ns	ns	ns	<0.1	-
	15	ns	ns	ns	0.03	ns	ns	ns	ns	ns	ns	ns	<0.1	-
	16	ns	ns	ns		ns	ns	ns	ns	ns	ns	ns	<0.1	-
TOTAL IN STRATUM CORNEUM		0.56	1.14	0.14	0.23	0.52	0.38	0.24	0.08	0.06	0.17	0.41	0.3	0.3

Results are expressed as percent applied radiochemical dose
nd Not detected
sd Standard deviation
ns No sample (stratum corneum removed)
- Not applicable

Table A 13: Results of dermal absorption study of SAE053H/01: distribution of radioactivity in the tape strips (dilution 0.3 g/L))

Cell number		13	14	15	16	17	18	19	20	21	22	23	24	Mean	sd
Skin source		H1	H1	H2	H2	H2	H3	H3	H4	H4	H4	H5	H5		
Tape strip	1 - 2	2.8	3.7	2.1	4.6	3.4	5.2	2.4	3.4	4.9	3.4	2.4	1.7	3.3	1.1
TOTAL IN TAPE SURFACE		2.8	3.7	2.1	4.6	3.4	5.2	2.4	3.4	4.9	3.4	2.4	1.7	3.3	1.1
Tape strip	3	0.19	0.32	0.5	0.31	0.19	0.81	0.52	0.39	0.98	0.81	0.33	0.4	0.5	0.3
	4	0.23	0.38	0.17	0.28	0.17	0.34	0.38	0.51	0.43	0.64	0.15	0.14	0.3	0.2
	5	0.05	0.19	0.14	0.19	0.19	0.15	0.24	nd	0.49	ns	0.09	0.15	0.2	0.1
	6	0.1	0.63	0.05	0.03	0.06	0.2	0.14	ns	nd	ns	0.15	0.05	0.1	0.2
	7	nd	0.1	0.05	ns	0.11	0.05	0.2	ns	ns	ns	0.11	nd	0.1	0.1
	8	ns	ns	0.09	ns	nd	ns	0.05	ns	ns	ns	nd	nd	<0.1	<0.1
	9	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	nd	ns	<0.1	-
	10	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	-	-
	11	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	-	-
TOTAL IN STRATUM CORNEUM		0.57	1.62	1.0	0.81	0.72	1.55	1.53	0.9	1.9	1.45	0.83	0.74	1.1	0.4

Results are expressed as percent applied radiochemical dose
nd Not detected
sd Standard deviation
ns No sample (stratum corneum removed)
- Not applicable

The data show that the absorption of [14C]-Mesotrione was essentially complete at the midpoint of the study (>75% absorption had occurred by this point). It is therefore considered that the material remaining in the stratum corneum would not be available for absorption and should be excluded from the absorption calculation. Therefore the material recovered in the skin, receptor fluid and on the receptor chamber should be considered as absorbable and accounts for <0.1% at the high dose level and low dose level, and corresponding standard deviation values of zero.

Conclusion

Therefore the amount considered as absorbed is <0.1% at both the high dose level and the low dose level.

A 2.11 Other/Special Studies

None.

Appendix 3 Exposure calculations

A 3.1 Operator exposure calculations (KCP 7.2.1.1)

A 3.1.1 Calculations for mesotrione

Table A 5: Input parameters considered for the estimation of operator exposure

Substance name	mesotrione	
Product name	SAE053H/01	
Reference value non acutely toxic active substance (RVNAS)	0.005	mg/kg bw/day
Reference value acutely toxic active substance (RVAAS)		mg/kg bw/day
Crop type	Cereals	
Substance properties		
Formulation type	Soluble concentrates, emulsifiable concentrate, etc.	
Miniumum volume water for application (liquids)	200	L/ha
Maximum application rate of active substance	0.12	kg a.s. /ha
50% Dissipation Time DT50	30	days
Initial Dislodgeable Foliar Residue	3	µg/cm2 of foliage/kg a.s. applied/ha
Dermal absorption of product	0.10%	
Dermal absorption of in-use dilution	0.10%	
Oral absorption of active substance	50.00%	
Inhalation absorption of active substance	100.00%	
Vapour pressure of active substance	low volatile substances having a vapour pressure of <5*10-3Pa	
Scenario		
Indoor or Outdoor application	Outdoor	
Application method	Downward spraying	
Application equipment	Vehicle-mounted	
Buffer strip	2-3	m
Number of applications	1	
Interval between multiple applications	365	days
Season (upward spraying orchards only)	not relevant	

Table A 15: Estimation of operator exposure towards mesotrione using the EFSA-OPEX model

Operator exposure for SAE053H/01 outdoor spray applications

Application rate of active substance	0.12	kg a.s./ha	*i_AppRate*
Assumed area treated	50	ha/day	*d_AreaTreated*
Amount of active substance applied	6	kg a.s./day	*i_AmoutAS*
Dermal absorption of the product	0.10%		*i_AbsorpProduct*
Dermal absorption of in-use dilution	0.10%		*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		

OutdoorSoluble concentrates, emulsifiable concentrate, etc.Downward sprayingVehicle-mounted

	Exposure values	µg exposure/day mixed and loaded 75th centile	95th centile	Reference	Comment
Mixing and loading	Hands	19293	71819	AOEM	
	Body	12569	121213	AOEM	
	Head	311	1707	AOEM	
	Protected hands (gloves)	111	1188	AOEM	
	Protected body (workwear or protective garment and sturdy footwear)	116	878	AOEM	
	Protected head (hood and face shield)	5	97	AOEM	
	Inhalation	6	30	AOEM	
	Protective Equipment	Select for inclusion		Penetration factor	Inhalation Protection factor
	Gloves	Yes		Incl. in AOEM model	
	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 75th centile	95th centile	Reference	Comment
Application	Hands	890	8513	AOEM	
	Body	498	2565	AOEM	
	Head	24	71	AOEM	
	Protected hands (gloves)	112	4107	AOEM	
	Protected body (workwear or protective garment and sturdy footwear)	14	33	AOEM	
	Inhalation	3	8	AOEM	
	Protective Equipment	Select for inclusion		Penetration factor	Inhalation Protection factor
	Gloves	Yes		Incl. in AOEM model	
	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	

1. Total

	Without RPE/PPE	With RPE/PPE	
Longer term			
Total systemic exposure from mixing, loading and application (mg a.s./day)	0.0424355	0.0095379	
Total systemic exposure from mixing, loading and application per kg body weight (mg/kg bw/day)	0.0007073	0.0001590	
% of RVNAS	14.15%	3.18%	

A 3.1.2 Calculations for nicosulfuron

Table A 16: Input parameters considered for the estimation of operator exposure

Substance name	nicosulfuron	
Product name	SAE053H/01	
Reference value non acutely toxic active substance (RVNAS)	0.56	mg/kg bw/day
Reference value acutely toxic active substance (RVAAS)		mg/kg bw/day
Crop type	Cereals	
Substance properties		
Formulation type	Soluble concentrates, emulsifiable concentrate, etc.	
Miniumum volume water for application (liquids)	200	L/ha
Maximum application rate of active substance	0.045	kg a.s. /ha
50% Dissipation Time DT50	30	days
Initial Dislodgeable Foliar Residue	3	µg/cm2 of foliage/kg a.s. applied/ha
Dermal absorption of product	70.00%	
Dermal absorption of in-use dilution	70.00%	
Oral absorption of active substance	40.00%	
Inhalation absorption of active substance	100.00%	
Vapour pressure of active substance	low volatile substances having a vapour pressure of <5*10-3Pa	
Scenario		
Indoor or Outdoor application	Outdoor	
Application method	Downward spraying	
Application equipment	Vehicle-mounted	
Buffer strip	2-3	m
Number of applications	1	
Interval between multiple applications	365	days
Season (upward spraying orchards only)	not relevant	

Table A 17: Estimation of operator exposure towards nicosulfuron using the EFSA-OPEX model

Operator exposure for SAE053H/01 outdoor spray applications

Application rate of active substance	0.045 kg a.s./ha		*i_AppRate*
Assumed area treated	50 ha/day		*d_AreaTreated*
Amount of active substance applied	2.25 kg a.s./day		*i_AmoutAS*
Dermal absorption of the product	70.00%		*i_AbsorpProduct*
Dermal absorption of in-use dilution	70.00%		*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		

OutdoorSoluble concentrates, emulsifiable concentrate, etc.Downward sprayingVehicle-mounted

	Exposure values	µg exposure/day mixed and loaded 75th centile	95th centile	Reference	Comment
Mixing and loading	Hands	9067	33462	AOEM	
	Body	6308	91158	AOEM	
	Head	117	640	AOEM	
	Protected hands (gloves)	58	446	AOEM	
	Protected body (workwear or protective garment and sturdy footwear)	49	329	AOEM	
	Protected head (hood and face shield)	2	36	AOEM	
	Inhalation	5	29	AOEM	
	Protective Equipment	Select for inclusion		Penetration factor	Inhalation Protection factor
	Gloves	Yes		Incl. in AOEM model	
	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 75th centile	95th centile	Reference	Comment
Application	Hands	334	4150	AOEM	
	Body	187	962	AOEM	
	Head	9	27	AOEM	
	Protected hands (gloves)	66	3664	AOEM	
	Protected body (workwear or protective garment and sturdy footwear)	5	13	AOEM	
	Inhalation	2	5	AOEM	
	Protective Equipment	Select for inclusion		Penetration factor	Inhalation Protection factor
	Gloves	Yes		Incl. in AOEM model	
	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	

1. Total

	Without RPE/PPE	With RPE/PPE	
Longer term			
Total systemic exposure from mixing, loading and application (mg a.s./day)	11.2211137	0.2188121	
Total systemic exposure from mixing, loading and application per kg body weight (mg/kg bw/day)	0.1870186	0.0036469	
% of RVNAS	33.40%	0.65%	

A 3.2 Worker exposure calculations (KCP 7.2.3.1)

A 3.2.1 Calculations for mesotrione

Table A 18: Estimation of worker exposure towards mesotrione using the EFSA-OPEX model

Worker exposure from residues on foliage for SAE053H/01			
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	0.12	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	0.10%		*i_AbsorpProduct*
Dermal absorption of the in-use dilution	0.10%		*i_AbsorpInuse*
Dislodgeable foliar residue (i_AppRate*i_DFR)	0.36	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*
Inhalation transfer coefficient for automated applications	NA	ha/hr*10^(-3)	*d_InhalTcAut*
Inhalation transfer coefficient for cutting ornamentals	NA	ha/hr*10^(-3)	*d_InhalTcCut*
Inhalation transfer coefficient for sorting / bundling ornamentals	NA	ha/hr*10^(-3)	*d_InhalTcSort*

1. Total

	Potential exposure	Work wear - arms, body and legs covered	Working wear and gloves	Comments
Total systemic exposure (mg a.s./day)	0.0090000	0.0010080	no TC available for this assessment	
Total systemic exposure per kg body weight (mg/kg bw/day)	0.0001500	0.0000168		
% of RVNAS	3.00%	0.34%		

A 3.2.2 Calculations for nicosulfuron

Table A 19: Estimation of worker exposure towards nicosulfuron using the EFSA-OPEX model

Worker exposure from residues on foliage for SAE053H/01			
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	0.045	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	70.00%		*i_AbsorpProduct*
Dermal absorption of the in-use dilution	70.00%		*i_AbsorpInuse*
Dislodgeable foliar residue (i_AppRate*i_DFR)	0.135	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*
Inhalation transfer coefficient for automated applications	NA	ha/hr*10^(-3)	*d_InhalTcAut*
Inhalation transfer coefficient for cutting ornamentals	NA	ha/hr*10^(-3)	*d_InhalTcCut*
Inhalation transfer coefficient for sorting / bundling ornamentals	NA	ha/hr*10^(-3)	*d_InhalTcSort*

1. Total

	Potential exposure	Work wear - arms, body and legs covered	Working wear and gloves	Comments
Total systemic exposure (mg a.s./day)	2.3625000	0.2646000	no TC available for this assessment	
Total systemic exposure per kg body weight (mg/kg bw/day)	0.0393750	0.0044100		
% of RVNAS	7.03%	0.79%		

A 3.3 Bystander and resident exposure calculations (KCP 7.2.2.1)

A 3.3.1 Calculations for mesotrione

Table A 21: Estimation of resident exposure towards mesotrione with EFSA-OPEX model

Resident exposure for SAE053H/01				
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	0.12	kg a.s./ha		*i_AppRate*
Concentration of active substance (in-use dilution for liquid applications)	0.6	g a.s./l		*d_ConcAS*
Dermal absorption of product	0.10%			*i_AbsorpProduct*
Dermal absorption of in-use dilution	0.10%			*i_AbsorpInuse*
Oral absorption	50.00%			*i_AbsorpOralInuse*
Dislodgeable foliar residue (i_AppRate*i_DFR)	0.36	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*

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)	0.0002929	0.0107000	0.0005047	0.0002025	0.0114215
Total systemic exposure per kg body weight	0.0000293	0.0010700	0.0000505	0.0000203	0.0011422
% of RVNAS	0.59%	21.40%	1.01%	0.41%	22.84%

1.2 Adult

	Spray drift	Vapour	Surface deposits	Entry into treated crops	All pathways (mean)
Total systemic exposure (mg a.s./day)	0.0002912	0.0138000	0.0000491	0.0006750	0.0145379
Total systemic exposure per kg body weight	0.0000049	0.0002300	0.0000008	0.0000113	0.0002423
% of RVNAS	0.10%	4.60%	0.02%	0.23%	4.85%

Table A 22: Estimation of bystander exposure towards mesotrione with the German model (Martin et al., 2008)

Estimation of bystander and resident exposure (adults and children)

Active substance (a.s.)	**mesotrione**	
Product	**SAE053H/01**	
Intended uses	**Field Crops, Tractor Mounted (FCTM)**	
Treated area per day (A)	**20**	**ha/d**
Application rate (AR)	**0.12**	kg a.s./ha
Number of applications (NA)	**1**	1)

1) Consideration of more than two applications are not necessary if degradation of the active substance on foliage of at least 50 % can be assumed between two applications (otherwise use multiple application factor).

Dermal absorption (DA)	**0.1**	% (worst case, e.g. during application)
Inhalation absorption (IA)	**100**	%
Oral absorption (OA)	**100**	%
Systemic AOEL	**0.005**	mg/kg bw/d
Body weight (BW)	**60**	kg/person (adults)
	16.15	kg/person (children)

Distance between application and bystander or resident:

FCTM:	**1**	m
High crops not selected		
		m
Home & garden not selected		
		m

Drift deposit (D) for 1 appl. based on appl. technique and distance: 2.77 % (FCTM, 1 m)

Airborne vapour concentration (ACv) mg/m^3 2)

2) 1 µg/m^3 for semivolatile substances, i.e. vapour pressure (20 °C): ≥ 1x10^{-5} - < 5x10^{-3} Pa; 15 µg/m^3 for volatile substances, i.e. vapour pressure (20 °C): ≥ 5x10^{-3} Pa

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

Input parameters considered for the estimation of bystander exposure:

Intended use(s):			**Drift (D):**	2.77	% (FCTM, 1 m)
Application rate (AR):	0.12	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):	0.10	% ('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		
(12 x 2.77% x 1 x 0.1%) / 60			(12 x 2.77% x 0.21 x 0.1%) / 16.15		
External exposure	0.3324	mg/person	External exposure	0.069804	mg/person
External exposure	0.00554	mg/kg bw/d	External exposure	0.00432223	mg/kg bw/d
Absorbed dose:	**0.0000055**	**mg/kg bw/d**	**Absorbed dose:**	**0.0000043**	**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 0.12 x 20 x 5 x 100%) / 60			(0,000 / 360 x 0.12 x 20 x 5 x 100%) / 16.15		
External exposure	3.3333E-05	mg/person	External exposure	1.9157E-05	mg/person
External exposure	5.5556E-07	mg/kg bw/d	External exposure	1.1862E-06	mg/kg bw/d
Absorbed dose:	**0.0000006**	**mg/kg bw/d**	**Absorbed dose:**	**0.0000012**	**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)	0.00036573	mg/person	Total systemic exposure (absorbed dose)	8.8961E-05	mg/person
Total systemic exposure (absorbed dose)	**0.0000061**	**mg/kg bw/d**	**Total systemic exposure** (absorbed dose)	**0.0000055**	**mg/kg bw/d**
% of AOEL:	**0.12**	**%**	**% of AOEL:**	**0.11**	**%**

A 3.3.2 Calculations for nicosulfuron

Table A 23: Estimation of resident exposure towards nicosulfuron with EFSA-OPEX model

Resident exposure for SAE053H/01			
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	0.045	kg a.s./ha	i_AppRate
Concentration of active substance (in-use dilution for liquid applications)	0.225	g a.s./l	d_ConcAS
Dermal absorption of product	70.00%		i_AbsorpProduct
Dermal absorption of in-use dilution	70.00%		i_AbsorpInuse
Oral absorption	40.00%		i_AbsorpOralInuse
Dislodgeable foliar residue (i_AppRate*i_DFR)	0.135	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) - ad	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

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)	0.0422816	0.0107000	0.0047326	0.0531563	0.0798334
Total systemic exposure per kg body weight	0.0042282	0.0010700	0.0004733	0.0053156	0.0079833
% of RVNAS	0.76%	0.19%	0.08%	0.95%	1.43%

1.2 Adult

	Spray drift	Vapour	Surface deposits	Entry into treated crops	All pathways (mean)
Total systemic exposure (mg a.s./day)	0.0607230	0.0138000	0.0128772	0.1771875	0.1933494
Total systemic exposure per kg body weight	0.0010121	0.0002300	0.0002146	0.0029531	0.0032225
% of RVNAS	0.18%	0.04%	0.04%	0.53%	0.58%

Table A 24: Estimation of bystander exposure towards nicosulfuron with the German model (Martin et al., 2008)

Estimation of bystander and resident exposure (adults and children)

Active substance (a.s.)	**nicosulfuron**	
Product	**SAE053H/01**	
Intended uses	**Field Crops, Tractor Mounted (FCTM)**	
Treated area per day (A)	**20**	**ha/d**
Application rate (AR)	**0.045**	kg a.s./ha
Number of applications (NA)	**1**	1)

1) Consideration of more than two applications are not necessary if degradation of the active substance on foliage of at least 50 % can be assumed between two applications (otherwise use multiple application factor).

Dermal absorption (DA)	**70**	% (worst case, e.g. during application)
Inhalation absorption (IA)	**100**	%
Oral absorption (OA)	**100**	%
Systemic AOEL	**0.56**	mg/kg bw/d
Body weight (BW)	**60**	kg/person (adults)
	16.15	kg/person (children)

Distance between application and bystander or resident:

FCTM:	**1**	m
High crops not selected		
		m
Home & garden not selected		
		m

Drift deposit (D) for 1 appl. based on appl. technique and distance: 2.77 % (FCTM, 1 m)

Airborne vapour concentration (ACv) mg/m^3 2)

2) 1 µg/m^3 for semivolatile substances, i.e. vapour pressure (20 °C): ≥ 1x10^{-5} - < 5x10^{-3} Pa; 15 µg/m^3 for volatile substances, i.e. vapour pressure (20 °C): ≥ 5x10^{-3} Pa

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

Input parameters considered for the estimation of bystander exposure:

Intended use(s):			**Drift (D):**	2.77	% (FCTM, 1 m)
Application rate (AR):	0.045	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):	70.00	% ('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:	0.56	mg/kg bw/d			

Bystander exposure towards nicosulfuron					
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		
(4.5 x 2.77% x 1 x 70%) / 60			(4.5 x 2.77% x 0.21 x 70%) / 16.15		
External exposure	0.12465	mg/person	External exposure	0.0261765	mg/person
External exposure	0.0020775	mg/kg bw/d	External exposure	0.00162084	mg/kg bw/d
Absorbed dose:	**0.0014543**	**mg/kg bw/d**	**Absorbed dose:**	**0.0011346**	**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 0.045 x 20 x 5 x 100%) / 60			(0,000 / 360 x 0.045 x 20 x 5 x 100%) / 16.15		
External exposure	0.0000125	mg/person	External exposure	7.1839E-06	mg/person
External exposure	2.0833E-07	mg/kg bw/d	External exposure	4.4482E-07	mg/kg bw/d
Absorbed dose:	**0.0000002**	**mg/kg bw/d**	**Absorbed dose:**	**0.0000004**	**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)	0.0872675	mg/person	Total systemic exposure (absorbed dose)	0.01833073	mg/person
Total systemic exposure (absorbed dose)	**0.0014545**	**mg/kg bw/d**	**Total systemic exposure** (absorbed dose)	**0.0011350**	**mg/kg bw/d**
% of AOEL:	**0.26**	**%**	**% of AOEL:**	**0.20**	**%**

A 3.4 Combined exposure calculations for mesotrione and nicosulfuron

See chapter 6.6.6