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EXECUTIVE SUMMARY OF THE RISK ASSESSMENT FOR HALOSULFURON-METHYL CONTAINING PRODUCTS

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Prepared for:

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Background:
According to Regulation 8(1)(d) and 10(3)(e) respectively, the Registrar (Act 36 of 1947) may not grant or renew a registration after 1 June 2024 if a product contains substances of concern. Halosulfuron-methyl has been classified in Europe as Repr.1B (H360D) and as such would be considered a substance of concern. However, in exceptional circumstances, the Registrar may grant a registration for a product (agricultural remedy) containing a substance of concern and the Applicant can submit a derogation to achieve this. The Regulation states:

"Before commencing an application for derogation of an agricultural remedy, the applicant must conduct a risk assessment to evaluate the risks associated with the use of the remedy according to the proposed uses for which a derogation is sought and determine whether the associated risks can be sufficiently mitigated".

The Halosulfuron-methyl Derogation Group comprising of: Farm-Ag International (Pty) Ltd, ICA International Chemicals (Pty) Ltd, UPL South Africa (Pty) Ltd, Sharda International Africa (Pty) Ltd, Villa Crop Protection (Pty) Ltd, Rainbow Agrosciences (Pty) Ltd and Green Island Investments Pty Ltd, is submitting a derogation for their water dispersible granule formulations (WG/WDG) containing 750 g/kg halosulfuron-methyl that includes dietary and non-dietary human health risk assessments as well as environmental risk assessments and hereby demonstrate safe use of these products, when used according to their recommended use pattern.

Executive summary:
This derogation consists of several independent core reports, the outcome of which is presented in this executive summary. The core reports are identical for the seven members of the derogation, however for each product a separate addendum was prepared that presents confidential data and/or data that are specific to the individual products.

The core reports consist of:

- A general toxicological profile of halosulfuron-methyl where the toxicological reference values used in the risk assessments are rationalised. In that toxicological section, the relevance of the Repr.1B (H360D) concluded by the EU Authorities [ECHA-CLP classification] in the context of human health risk assessments is also discussed.
- Dietary (consumer) risk assessments.
- Non-dietary (Operator, worker, bystander and resident) risk assessments.
- Environmental assessment.

It was considered appropriate, to encompass all possible uses in the risk assessments rather than conduct a risk assessment per company to present a more realistic scenario. The supported uses are presented in Appendix 1. (Good agricultural practice – GAP)

This derogation demonstrates that the hazard represented by halosulfuron-methyl Repr.1B (H360D) classification is extremely unlikely to have any negative deleterious health effect on consumers, and users when the products are used according to their recommended GAP. The exposure to consumers can be regarded as negligible.

Indeed, despite a very conservative/precautionary approach to the risk assessments, (worst case scenarios) the consumer risk assessments demonstrate safe use to consumers for all crops with a high safety margin. The non-dietary risk assessments also demonstrate safe use without the need of PPE (personal protection equipment). It is emphasised by the derogation group that SANS

10206:2020. Ed 3: “The handling, storage and disposal of pesticides” should be strictly followed by individuals entitled to use the products.

Finally, the impact of halosulfuron-methyl on the environment is considered in another separate report and demonstrates that halosulfuron-methyl is unlikely to have any serious irreversible effects on the environment.

Toxicological assessment [Report EWC2403474.UK0-6756]
To support the derogation application and inform the human health risk assessments, a summary review of the toxicological profile of halosulfuron-methyl has been carried out, considering recent and relevant authoritative regulatory evaluations and the derivation of human health-based reference values.

In the absence of an evaluation conducted by the Joint Meeting on Pesticide Residues (JMPR), toxicological information has been sourced from evaluations by the European Union (EU) European Food Safety Authority (EFSA) and European Chemicals Agency (ECHA).

Acute toxicity:
Halosulfuron-methyl has low acute toxicity via the oral, dermal and inhalation routes, is not irritating or corrosive to the skin or the eyes and is not sensitising to the skin.
No classification is warranted.

Carcinogenicity:
In the respective 2-year dietary studies in male and female rats and in a 78-week study in male and female mice, no oncogenic effects were observed at any dose level, indicating that halosulfuron-methyl is not carcinogenic.
No classification is warranted.

Mutagenicity/ Genotoxicity:
Halosulfuron-methyl is not genotoxic based on the findings of a standard battery of *in vitro* and *in vivo* studies.
No classification is warranted.

Reproductive toxicity:
Fertility and sexual function: Halosulfuron-methyl does not affect fertility, mating or gestation.
Development toxicology:
In the consideration of the available data, the ECHA Committee on Risk Assessment (RAC) concluded that there was sufficient evidence of a substance-mediated effect on development based on experimental US EPA test guideline studies conducted in rats and in rabbits (comparable in design to OECD Test Guideline 414). The development of rat foetuses was impaired at high dose levels and rat foetal body weight was dramatically reduced. There was a biologically significant increase in early resorptions which impacted on the rat post-implantation loss and this effect was also noted in the rabbit developmental study. Several widespread developmental variations were observed and there were indications of malformations in both rats and rabbits. The RAC could not exclude a direct effect on the developing foetus, as the maternal toxicity was considered insufficient to explain the degree of severity of the effects observed in the foetuses from high dose dams.

Consequently, halosulfuron-methyl was classified as a reproductive toxicant Category 1B H360D (May damage the unborn child) in accordance with the relevant EU Regulation (EC) No 1272/2008 (CLP Regulation).

Within the EU legislative framework, the CLP Regulation serves as a hazard identification process, with direct risk management consequences, to ensure that the hazards presented by chemical substances are clearly communicated to workers and consumers in the EU, across the supply chain. As such, the CLP Regulation does not facilitate the assessment of exposures to the chemical substances, the characterisation of the hazards (i.e.: via health-based reference values) or the assessment of health risks.

Regulation (EC) No. 1107/2009, regulating pesticides in Europe has set several hazard-based "cut-off" criteria. The classification for reproductive toxicity Cat 1A or B is one of the hazard-based "cut-off" criteria. Although the RAC opinion was issued in 2017, it is noted that halosulfuron-methyl is still approved in Europe despite its classification, inferring that European Member States consider that the hazard-based classification of this active substance does not impact on the safety of the authorised halosulfuron-methyl products.

Neurotoxicity and endocrine disruption
Halosulfuron-methyl is not neurotoxic and has not been considered as having endocrine disruption potential in any regulatory jurisdiction.

Reference values:
To assess the potential risk caused using a pesticidal product, reference values are derived from experimentally determined "no-observed-adverse-effect levels "(NOAELs). The NOAEL for the most critical effect is often referred to as the "point of departure" (POD). The reference values are derived by dividing the POD by an appropriate safety factor (SF, also referred to as an uncertainty factor (UF)), which, as the name conveys, ensures that the derived reference value is sufficiently conservative and protective towards human health, based on the effects observed in the studies.

<u>Consumer risk assessments: ADI and ARfD</u>
The ADI (Acceptable Daily Intake) is commonly defined as the amount of a chemical to which a person can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect.

The potential health risk to consumers is considered to mainly result from the long-term exposure to residues of halosulfuron-methyl in food. In accordance with internationally accepted procedures, during the EU evaluation of halosulfuron-methyl as a pesticide active substance, the Acceptable Daily Intake (ADI) was derived, taking into account the critical effects and most relevant effects observed in the toxicological database, the NOAEL determined for the most sensitive species and an appropriate safety factor.

Following the peer review of the pesticide risk assessment of the active substance halosulfuron-methyl and expert consultation, the critical effect for the derivation of the ADI was determined to be offspring effects: reduced pup body weight gain in the F1, F2a and F2b generations observed in the two-generation reproduction toxicity study conducted in rats (EFSA, 2012). Based on these findings, the lowest NOAEL was determined to be 6.3 mg/kg bw/day. Applying a standard safety factor of 100 (10 to account for interspecies variability and 10 to account for intraspecies

variability) to the NOAEL of 6.3 mg/kg bw/day, the EU agreed ADI was determined to be 0.063 mg/kg bw/day.

The ARfD (Acute Reference Dose) of a chemical is an estimate of the amount a substance in food and/or drinking water, normally expressed on a body weight basis, that can be ingested in a period of 24 h or less without appreciable health risk to the consumer.

Following the peer review of the pesticide risk assessment of the active substance halosulfuron-methyl and expert consultation, the critical effect for the derivation of the ARfD was determined to be maternal toxicity observed in the rabbit pre-natal developmental toxicity study (EFSA, 2012). Based on these findings, the lowest NOAEL was determined to be 50 mg/kg bw/day. Applying a standard factor of 100 to the NOAEL of 50 mg/kg bw/day, the EU agreed ARfD was determined to be 0.5 mg/kg bw/day.

Operator/worker bystanders and residents risk assessments: AOEL and AAOEL
The AOEL (Acceptable Operator Exposure Level) is the minimum amount of active substance to which human may be exposed without adverse health effects over an extended period.
The AAOEL (Acute Acceptable Operator Exposure Level) of a chemical is an estimate of the amount a substance, normally expressed on a body weight basis, a human can be exposed to over a short time period without appreciable health risk.

Following the peer review of the pesticide risk assessment of the active substance halosulfuron-methyl and expert consultation, the critical effect for the derivation of the ADI was determined to be offspring effects: reduced pup body weight gain in the F1, F2a and F2b generations observed in the two-generation reproduction toxicity study conducted in rats (EFSA, 2012). Based on these findings, the lowest NOAEL was determined to be 6.3 mg/kg bw/day. Applying a standard safety factor of 100 to the NOAEL of 6.3 mg/kg bw/day, the EU agreed ADI was determined to be 0.063 mg/kg bw/day.

During the peer review evaluation for the active substance approval in 2012, EFSA concluded that a reference value for acute operator exposures (i.e.: an Acute Acceptable Operator Exposure Level, AAOEL value) was not required.

The following health-based reference values are considered to be relevant to inform the dietary and non-dietary risk assessments for WG products containing 750g/kg halosulfuron-methyl and are sufficiently conservatively protective in respect of human health:

Reference endpoint	**Derived value**	**Source**
ADI	**0.063 mg/kg bw/day**	EFSA (2012)
ARfD	**0.5 mg/kg bw/day**	EFSA (2012)
AOEL	**0.063 mg/kg bw/day**	EFSA (2012)
AAOEL	Not required	-

Dietary exposure assessment [Report EWC 2403474.UK0-8048]
The uses supported in South Africa by the halosulfuron derogation group, are presented in the Good Agricultural Practice (GAP) Appendix 1. The supported edible crops are Avocado, Citrus fruit, Corn/Maize grain, Mango, Sorghum grain, Sugarcane and Wheat grain.

The traces pesticides leave in treated products are called "residues". A maximum residue level (MRL) is the highest level of a pesticide residue that is legally tolerated in or on food or feed when pesticides are applied correctly (Good Agricultural Practice).

Using the Bryant Christie (BC) Global database for pesticide (Maximum residue level) MRLs, a report has been run for halosulfuron-methyl on all supported crops.

The highest Global MRLs (Maximum Residue levels) for each crop are listed in the table below. It should be noted that different methods of MRL calculation are used in different countries, and sometimes even the same dataset may result in a different MRL value. However, it is true in all countries that the MRL is a highly conservative value used to facilitate trade between countries and to monitor GAP compliant application, whereas the lower STMR (Supervised Trial Median Residue) and HR (Highest Residue) values are intended for risk assessment calculations.

Table 1: MRLs for halosulfuron-methyl around the world

Crop	**MRL (mg/kg)**					**Comments**
	Codex	**USA**	**Canada**	**Mexico**	**South Africa**	
Avocado	N.E	N.E	**0.1 (default)**	N.E	0.01	South African MRL taken from EU deferral
Citrus fruit	N.E	N.E	**0.1 (default)**	N.E	0.01	Data collated from representative commodities (Grapefruit, Lemon, Limes, Mandarin, Oranges)
Corn/Maize grain	N.E	0.05	0.05	**0.5**	0.01	South African MRL taken from EU deferral
Mango	N.E	N.E	**0.1 (default)**	N.E	0.01	South African MRL taken from EU deferral
Sorghum grain	N.E	0.05	0.05	**0.1**	0.01	South African MRL taken from EU deferral
Sugarcane	N.E	0.05	**0.1 (default)**	0.05	0.01	South African MRL taken from EU deferral
Wheat grain	N.E	N.E	**0.1 (default)**	N.E	0.01	South African MRL taken from EU deferral

Highest Global MRL for each crop presented in **bold**
Default MRL - When a specific MRL has not been set on a commodity for a pesticide, some markets defer to a set default MRL value. Policies regarding the use of default MRLs vary by country.
N.E – Not established

To present a worst-case risk assessment for consumers, the highest global MRL for each crop has been used in chronic and acute consumer risk assessment calculations (see bold values in Table X). The current Codex toxicological reference values: Acceptable Daily Intake (ADI) and Acute Reference Dose (ARfD), which were agreed by EFSA in 2012 and further elaborated on in the main body of toxicological assessment are as follows:

- ADI = 0.063 mg/kg bw/day used for chronic risk assessment
- ARfD = 0.5 mg/kg bw used for acute risk assessment

The WHO models have been used for the chronic (IEDI – International Estimated Daily Intake) and acute (IESTI – International Estimate of Short-Term Intake) calculations. The results from each assessment are presented below.

Chronic risk assessment	Acute risk assessment
Maximum IEDI (based on G12 diet):	

3.1% of ADI	Maximum IESTI = 3% of ARfD (based on consumption of maize in the Canadian Child < 6 years diet)
Maximum IEDI for South Africa (G05 diet): 1.7% of ADI	

This assessment uses the most conservative approach to dietary risk assessment (i.e. the highest worldwide MRLs have been used as the input values for each crop) and demonstrates that there is no unacceptable dietary chronic or acute risk to consumers.

Currently the registered South African GAP for halosulfuron does not trigger the need for an MRL greater than the LOQ (0.01 mg/kg). As part of this assessment, it was not possible to obtain the GAPs used in Canada and Mexico that led to the current MRLs which are the highest globally. Therefore, we cannot make a formal comparison of the GAPs. However, since the South African use does not require an MRL >0.01 mg/kg, then it can be assumed that the South African GAP is less critical than the Canadian and Mexican GAPs that underpin the high MRLs. Therefore, as mentioned above, the consumer risk assessment carried out here represents a true worse-case scenario for halosulfuron in the selected crops.

In addition to the above risk assessment, potential contamination of drinking water following the halosulfuron uses has also been explored and a drinking water assessment conducted.

The Predicted Environmental Concentration in ground water, PECgw values for halossulfuron have been determined in a separate document (2403474.UK0 – 12947 FOCUS PECgw report). All PECgw values for halosulfuron were ≤0.001 µg/L for all crops and all FOCUS scenarios modelled following applications made in accordance with each GAP. To determine the consumer exposure to halosulfuron-methyl through drinking water, the following exposure calculations have been presented below.

$$\left(\left(\frac{concentration\ in\ water\ x\ consumption}{bodyweight}\right) \div ADI\right) \times 100$$

- Exposure to infants (5kg bodyweight, consumption 0.75 L/day) = <0.001% of the ADI
- Exposure to children (10 kg bodyweight, consumption 1 L/day) = <0.001% of the ADI
- Exposure to adults (60kg bodyweight, consumption 2 L/day) = <0.001% of the ADI

The most conservative approach for consumer risk assessment was taken and an acute and chronic assessment was conducted using the highest Global MRL for each crop. This highly conservative risk assessment demonstrated that there is no unacceptable risk to consumers using the highest MRLs as input values for the assessment. This conclusion applies also to drinking water. Exposure is negligible.

Non-dietary exposure assessment [Report EWC 2403474.UK0-0380]
A risk assessment has been conducted in accordance with the newly updated EFSA (European Food Safety Agency) (2022) guidance[1] on the assessment of exposure of operators, workers, residents, and bystanders to plant protection products.

The EFSA (2022) guidance document is designed to assist risk assessors when quantifying potential non-dietary, systemic exposures as part of regulatory risk assessment for plant protection products (PPPs). To support users in performing the assessment of exposure and risk, an online calculator (reflecting the guidance content) was also developed. The underlying principles of the guidance document and the related exposure calculator are the transparency of data, the traceability of information and the reproducibility of the outcomes. In establishing the guidance document and calculator, the EFSA working group considered only databases of raw data or peer-reviewed publications that could be accessed (if requested) by third parties in accordance with the Aarhus Convention2. The EFSA guidance is based on a comprehensive, peer reviewed dataset and is continually reviewed and amended as and when new data become available.

Considering the above, the EFSA web calculator has been selected as the most appropriate model to assess non-dietary exposure to halosulfuron-methyl resulting from the application of the product water dispersible granule formulations (WG/WDG) containing 750 g/kg halosulfuron-methyl using vehicle mounted and/or handheld spraying equipment.

The EFSA web calculator is publicly available and accessible at: https://r4eu.efsa.europa.eu/

Non-dietary risk assessments have been undertaken for the product considering the endpoints listed below in Table 2 and the product uses detailed in Appendix 1 (proposed GAP).

Table 2: Product information and toxicological reference values used for exposure assessment.

Product code and name	Halosulfuron 75 WDG (and similar products)
Formulation type	Water dispersible granule (WG)
Category	Herbicide
Packaging	All products are supplied in water soluble bag
Active substance (incl. content)	Halosulfuron-methyl 750 g/kg
AOEL systemic	0.063 mg/kg bw/d
AAOEL systemic	None set
Inhalation absorption	100%
Oral absorption	100%
Dermal absorption	EFSA (2017) default dermal absorption values for an WG formulation: Concentrate: 10% Dilution: 50%
	Experimentally derived values for 750 g/kg WDG formulation Concentrate: 0.22% Dilution: 0.34% (0.075 g/kg)

[1] EFSA (2022) Guidance on the assessment of exposure of operators, workers, residents, and bystanders in risk assessment of plant protection products. EFSA Journal 2022;20(1):7032
[2] UN (1998) Convention on access to information, public participation in decision making and access to justice in environmental matters.

A summary of the risk assessment for operators, workers, residents and bystanders is presented in table 3. It should be noted that in the absence of actual studies with products to derive a dermal absorption value and conduct more realistic risk assessments, the latter relied upon default values that are in essence extremely conservative.

The default values for a WG formulation are respectively 10% (concentrate) and 50 % (dilution). It is noted that for their human health risk assessment of halosulfuron methyl, the US EPA considered the available data on dermal absorption for a range of sulfonylurea substances. Percent dermal absorption for product concentrates ranged from 0.021% to 9% across substances and for dilutions from 1% to 21%, supporting the conclusion that for sulfonylurea substances, EFSA's default dermal absorption values for WG formulations are likely to overestimate actual levels of dermal absorption.

Dermal absorption data are available for a 750 g/kg WDG formulation of halosulfuron-methyl, a higher (Tier 2) exposure and risk assessment was also performed using these experimentally derived dermal absorption values[3]. [0.22% (concentrate) and 0.34% (dilution)].

All supported uses (Appendix 1) are for a single application of 0.067 kg product in 200 to 400L water per ha. The products are commercialised in water soluble bags, each containing 0.067 kg of formulated product. According to the EFSA's exposure guidance (EFSA, 2022) application to amenity grassland (Kikuyu and/or Cynodon lawn) is presented as the worst case for vehicle mounted spray applications. This scenario selects the higher work rates (ha treated per day) used by the EFSA model for vehicle mounted application and includes the additional resident scenario of entry into treated areas through recreation. The exposure assessment for this crop use therefore provides a risk envelope for the other uses included in the GAP.

Table 3: Amenity grassland (covering all uses)

	Result	**PPE **/ Risk mitigation measures Dermal absorption: default values**	**PPE **/ Risk mitigation measures Dermal absorption: experimental values**
Operators	Acceptable	**Results of risk assessment:** Vehicle mounted and knapsack: None* Hand-held equipment: None*	**Results of risk assessment:** Vehicle mounted and knapsack: None* Hand-held equipment: None*
Workers	Acceptable	None*	None*
Residents	Acceptable	None	None
Bystanders	Acceptable	None	None

None* means no PPE required but standard workwear (arms, body and legs covered) are worn.
** PPE = Personal Protective Equipment

[3] EFSA-Q-2023-00183

The most conservative approach for the risk assessment was taken. The risk assessments demonstrate that no health hazard to humans is expected when the products are used according to the recommendations. The safety margin is high and even higher when actual dermal absorption data are used. Levels of exposure to halosulfuron-methyl are low and predicted to be within the AOEL for all proposed application methods and crops. No PPE are required for any application scenario.

Potential precautionary measures based on classification and labelling:

- ✓ If the product is warranted a skin sensitisation classification (Category 1) gloves, protective clothing and eye protection/face protection should be worn by the operator for mixing and loading.
- ✓ If the product is warranted a skin irritation classification (Category 2 or 3) gloves, protective clothing should be worn by the operator for mixing and loading.
- ✓ If the product is warranted an eye irritation classification (Category 1 or 2) gloves, eye protection/face protection should be worn by the operator for mixing and loading.

It is noted that all users of pesticides should in any case comply with SANS 10206 :2020. Ed 3: "The handling, storage and disposal of pesticides" and that the above-mentioned PPEs for sensitizer for mixing and loading activities are strongly recommended in all cases when handling pesticides to provide additional protection against spills and splashes.

Environmental assessment [Report EWC 2402474.UK0-0851]

The assessment of the environmental risks caused by agricultural remedies becomes increasingly important in practical environmental protection. Ecotoxicological risk assessment is used to assess the potential hazard of existing or new environmental chemicals regarding the ecosystem. The combination of exposure assessment and hazard assessment allows the assessment of hazards induced by an environmental chemical and the analysis and final evaluation of the existing risk.

<u>Exposure: what are the environmental concentrations the non target organisms are exposed to?</u>

The expected environmental concentration is assessed with the aid of computer models and Predicted Environmental Concentrations (PECs) are derived for surface water PECsw, for soil PECsoil and for groundwater PECgw.

<u>Hazard:</u>

The hazard of a substance considers various ecotoxicological effects such as acute toxicity, chronic toxicity and bioaccumulation. Tests on non-target organisms are conducted according to widely accepted OECD guidance to determine the acute (LD/LC/EC50) or chronic (NOEC/NOEL) toxicity endpoints. The LD/LC/EC50 is the "Concentration or dose where 50 % effect or mortality was observed/calculated "and the NOEC is the "No Observed Effect Concentration or Dose".

The assessment of the risks of agricultural remedies for the terrestrial environment is based on the calculation of risk indicators (e.g. TER, HQ) which compare the acute (LD/LC/EC50) or chronic (NOEC/NOEL) toxicity endpoints generated from experimental data with the formulation or the

active substance to the potential exposure in the environment. Currently TER 'Toxicity exposure ratio' values are used for the risk assessments of terrestrial vertebrates, earthworms and non-target plants when HQ 'Hazard quotients' values are used for the risk assessment of bees and non-target arthropods.

If the risk indicators (TER, HQ) are above the TER trigger or below the HQ trigger then the risk is considered acceptable.

The assessment of the risks of agricultural remedies for the aquatic environment is based on the calculation of PEC/RAC ratios. RAC is the "regulatory acceptable concentrations "which is derived by applying an assessment factor (AF) of 100 or 10 to the lowest acute or chronic toxicity value obtained from the respective tests. Both the trigger values and the assessment factors are conservative.

To assess the environmental risk to non-target organisms following the supported uses of the WG products containing 750 g/kg halosulfuron-methyl, the European model has been followed: The European model is well known for being very conservative in order to achieve the highly ambitious protection goal set out by the European commission. Furthermore, it is noted that the European guidance sets are revised regularly, in order to reflect changes of test guidelines and of scientific knowledge. in EU Guidance documents (EFSA, SANCO, EPPO, etc.).

The risk assessments conducted reflect the South African Data requirements as per Appendix A&B "Toxicological Requirements for Registration of New Pesticides RSA", in order to cover all relevant areas considered under the South African Jurisdiction.

Overview of the risk assessment outcome

An assessment has been conducted to evaluate the environmental risks associated with the uses of the water dispersible granule products containing 750g halosulfuron-methyl/kg

The comprehensive overview of the uses supported by the members of the derogation group as well as the outcome of the risk assessments for all non-target organisms in scope are presented below in Table. 4

Table 4: Outcome of the risk assessment for all non-target organisms for all supported uses

Use No.	Crop and/or situation	F, Fn, Fpn G, Gn, Gpn or I	Application				Application rate			PHI (days)	Conclusion						
			Method/Kind	Timing/Growth stage of crop & season	Max. number per crop/ season	Min. interval between applications (days)	L product/ha a) max. rate per appl. b) max. total rate per crop/season	g a.s./ha a) max. rate per appl. b) max. total rate per crop/season	Water L/ha min / max		Birds	Mammals	Aquatic organisms	Bees	Non-target arthropods	Soil organisms	Non-target plants
1	Maize	F	Knapsack sprayers or tractor mounted boom sprayers	Post emergence of the weeds (BBCH 10-14) BBCH 12-16 (2-6 leaf stage) of the crop	1	-	1	50	200 - 400	NA	A	A	R	A	A	A	R
2	Grain sorghum	F	Knapsack sprayers or tractor mounted boom sprayers	Post emergence of the weeds (BBCH 10-14) BBCH 12-16 (2-6 leaf stage) of the crop	1	-	1	50	200 - 400	NA	A	A	R	A	A	A	R
3	Wheat	F	Knapsack sprayers or tractor mounted boom sprayers	Post emergence of the weeds (BBCH 10-14) BBCH 12-21 (2 leaf stage to beginning of tillering) of the crop	1	-	1	50	200 - 400	NA	A	A	R	A	A	A	R
4	Sugarcane	F	Knapsack sprayers or tractor mounted boom sprayers	Post emergence of the weeds (BBCH 10-14) BBCH 12-16 (2-6 leaf stage) of the crop	1	-	1	50	200 - 400	NA	A	A	R	A	A	A	R

Use No.	Crop and/or situation	F, Fn, Fpn G, Gn, Gpn or I	Application				Application rate			PHI (days)	Conclusion						
			Method/Kind	Timing/Growth stage of crop & season	Max. number per crop/ season	Min. interval between applications (days)	L product/ha a) max. rate per appl. b) max. total rate per crop/season	g a.s./ha a) max. rate per appl. b) max. total rate per crop/season	Water L/ha min / max		Birds	Mammals	Aquatic organisms	Bees	Non-target arthropods	Soil organisms	Non-target plants
5	Avocado	F	Knapsack sprayers or tractor mounted boom sprayers	Post emergence of the weeds (BBCH 10-14) (BBCH 00-99 of the crop)	1	-	1	50	200 - 400	NA	A	A	R	A	A	A	R
6	Citrus	F	Knapsack sprayers or tractor mounted boom sprayers	Post emergence of the weeds (BBCH 10-14) (BBCH 00-99 of the crop)	1	-	1	50	200 - 400	NA	A	A	R	A	A	A	R
7	Mango	F	Knapsack sprayers or tractor mounted boom sprayers	Post emergence of the weeds (BBCH 10-14) (BBCH 00-99 of the crop)	1	-	1	50	200 - 400	NA	A	A	R	A	A	A	R
8	Kikuyu and/or Cynodon lawn	F	Knapsack sprayers or tractor mounted boom sprayers	Post emergence of the weeds (BBCH 10-14) (BBCH 21-65 of the crop)	1	-	1	50	200 - 400	NA	A	A	R	A	A	A	R

Explanation for column "Conclusion"

A	Acceptable, Safe use
R	Risk mitigation measures required: **Aquatics** low risk to aquatic organisms following the uses of Halosulfuron-methyl 75WG when using a 5 m buffer zone. **Non target plants**: acceptable risk at a distance of 5 m with the use of 75% drift reducing nozzles or at a distance of 10 m with the use of 50% drift reducing nozzles or at a distance of 15 m without drift reduction.

Appendix 1: All intended uses

GAP rev. 1, date: 29.09.2019

PPP (product name/code):	**WDG halosulfuron**	Formulation type:	WG [a, b]
Active substance 1:	**Halosulfuron-methyl**	Conc. of as 1:	750g/kg [c]
Safener:	**NA**	Conc. of safener:	NA
Synergist/adjuvant	Recommended with a registered surfactant	Conc. of adjuvant:	NA
Applicant:	**Halosulfuron derogation group**	Professional use:	☒
		Non professional use:	☐

Herbicide

1	2	3	4	5	6	7	8	9	10	11*	12	13	14
					Application				**Application rate**				
Use No.	**Country**	**Crop and/or situation**	**F, Fn, Fpn G, Gn, Gpn or I**	**Pests or Group of pests controlled** (additionally: developmental stages of the pest or pest group)	Method/Kind	Timing/Growth stage of crop & season	Max. number per crop/ season	Min. interval between applications (days)	Product-sachet/ha a) max. rate per appl. b) max. total rate per crop/season	g a.s./ha a) max. rate per appl. b) max. total rate per crop/season	Water L/ha min / max	**PHI** (days)	**Remarks:** product variant, other dose rate expressions dose range (min-max)
1	ZA	Maize	F	*Cyperus spp*., *Bidens pilosa, Cleome monophyla, Galinsoga spp*., *Tagetes minuta*.	Knapsack sprayers or tractor mounted boom sprayers	Post emergence of the weeds (BBCH 10-14) BBCH 12-16 (2-6 leaf stage) of the crop	1	-	1	50	200 - 400	NA	Post emergence (of the weeds). Prior to flowering of *Cyperus spp*. 3-5 weeks after planting of the crop. Sharda Villa Crop UPL Farm AG Green Island ICA Rainbow

2	ZA	Grain sorghum	F	*Cyperus spp., Bidens pilosa, Cleome monophyla, Galinsoga spp., Tagetes minuta*	Knapsack sprayers or tractor mounted boom sprayers	Post emergence of the weeds (BBCH 10-14) BBCH 12-16 (2-6 leaf stage) of the crop	1	-	1	50	200 - 400	NA	Post emergence (of the weeds). Prior to flowering of *Cyperus spp*. Sharda Villa Crop UPL Farm AG Green Island ICA Rainbow
3	ZA	Wheat	F	*Cyperus spp., Bidens pilosa, Cleome monophyla, Galinsoga spp., Tagetes minuta*	Knapsack sprayers or tractor mounted boom sprayers	Post emergence of the weeds (BBCH 10-14) BBCH 12-21 (2 leaf stage to beginning of tillering) of the crop	1	-	1	50	200 - 400	NA	Post emergence (of the weeds). Prior to flowering of *Cyperus spp*. 3 to 5 weeks after planting of the crop. Sharda Villa Crop ICA Rainbow
4	ZA	Sugarcane	F	*Cyperus spp., Bidens pilosa, Cleome monophyla, Galinsoga spp., Tagetes minuta*	Knapsack sprayers or tractor mounted boom sprayers	Post emergence of the weeds (BBCH 10-14) BBCH 12-16 (2-6 leaf stage) of the crop	1	-	1	50	200 - 400	NA	Post emergence (of the weeds). Prior to flowering of *Cyperus spp*. Villa Crop UPL Farm AG Green Islands Rainbow
5	ZA	Avocado	F	*Cyperus spp., Bidens pilosa, Cleome monophyla, Galinsoga spp., Tagetes minuta*	Knapsack sprayers or tractor mounted boom sprayers	Post emergence of the weeds (BBCH 10-14) (BBCH 00-99 of the crop)	1	-	1	50	200 - 400	NA	Post emergence (of the weeds). Prior to flowering of *Cyperus spp*. Between the rows, avoid contact with crop foliage. Villa Crop ICA Rainbow

6	ZA	Citrus	F	*Cyperus spp*., *Bidens pilosa, Cleome monophyla, Galinsoga spp., Tagetes minuta*	Knapsack sprayers or tractor mounted boom sprayers	Post emergence of the weeds (BBCH 10-14) (BBCH 00-99 of the crop)	1	-	1	50	200 - 400	NA	Post emergence (of the weeds). Prior to flowering of *Cyperus spp*. Between the rows, avoid contact with crop foliage. Villa Crop UPL Farm AG Green Island ICA Rainbow
7	ZA	Mango	F	*Cyperus spp*., *Bidens pilosa, Cleome monophyla, Galinsoga spp., Tagetes minuta*	Knapsack sprayers or tractor mounted boom sprayers	Post emergence of the weeds (BBCH 10-14) (BBCH 00-99 of the crop)	1	-	1	50	200 - 400	NA	Post emergence (of the weeds). Prior to flowering of *Cyperus spp*. Between the rows, avoid contact with crop foliage. Villa crop ICA Rainbow
8	ZA	Kikuyu and/or Cynodon lawn	F	*such as Cyperus spp., Bidens pilosa, Cleome monophyla, Galinsoga spp., Tagetes minuta*	Knapsack sprayers or tractor mounted boom sprayers	Post emergence of the weeds (BBCH 10-14) (BBCH 21-65 of the crop)	1	-	1	50	200 - 400	NA	Post emergence (of the weeds). Rainbow Villa Crop

Remarks table heading:

(a) e.g. wettable powder (WP), emulsifiable concentrate (EC), granule (GR)

(b) Catalogue of pesticide formulation types and international coding system CropLife International Technical Monograph n°2, 6th Edition Revised May 2008

(c) g/kg or g/l

(d) Select relevant

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

(f) No authorization possible for uses where the line is highlighted in grey, Use should be crossed out when the notifier no longer supports this use.

Remarks columns:

1 Numeration necessary to allow references

2 Use official codes/nomenclatures of EU Member States

3 For crops, the EU and Codex classifications (both) should be used; when relevant, the use situation should be described (e.g. fumigation of a structure)

4 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

5 Scientific names and EPPO-Codes of target pests/diseases/ weeds or, when relevant, the common names of the pest groups (e.g. biting and sucking insects, soil born insects, foliar fungi, weeds) and the developmental stages of the pests and pest groups at the moment of application must be named.

6 Method, e.g. high volume spraying, low volume spraying, spreading, dusting, drench Kind, e.g. overall, broadcast, aerial spraying, row, individual plant, between the plants - type of equipment used must be indicated.

7 Growth stage at first and last treatment (BBCH Monograph, Growth Stages of Plants, 1997, Blackwell, ISBN 3-8263-3152-4), including where relevant, information on season at time of application

8 The maximum number of application possible under practical conditions of use must be provided.

9 Minimum interval (in days) between applications of the same product

10 For specific uses other specifications might be possible, e.g.: g/m³ in case of fumigation of empty rooms. See also EPPO-Guideline PP 1/239 Dose expression for plant protection products.

11 The dimension (g, kg) must be clearly specified. (Maximum) dose of a.s. per treatment (usually g, kg or L product / ha).

12 If water volume range depends on application equipments (e.g. ULVA or LVA) it should be mentioned under “application: method/kind”.

13 PHI - minimum pre-harvest interval

14 Remarks may include: Extent of use/economic importance/restrictions

Appendix 2: Members of the halosulfuron derogation group and their product

Company	Product	Registration number
Farm-Ag International (Pty) Ltd	Brigadier 750 WG	L9218
ICA International Chemicals (Pty) Ltd	WeedO 750 WG	L11149
UPL South Africa (Pty) Ltd	Cyprex WG	L7665
Sharda International Africa (Pty) Ltd	Halosulfuron 750 WDG	L10855
Villa Crop Protection (Pty) Ltd	Halo 750 WDG	L8283
Rainbow Agrosciences (Pty) Ltd	Flagship 750 WDG	L10539
Green Island Investments Pty Ltd	Halo-Fron WG	L10152

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DIETARY RISK ASSESSMENT FOR THE PROPOSED APPLICATION OF PRODUCTS CONTAINING HALOSULFURON- METHYL

Prepared by:
Exponent International Ltd.

Prepared for the Derogation Group consisting of:

Farm-Ag International (Pty) Ltd, ICA International Chemicals (Pty)

UPL South Africa (Pty) Ltd, Sharda International Africa (Pty) Ltd

Villa Crop Protection (Pty) Ltd, Rainbow Agrosciences (Pty) Ltd

Green Island Investments (Pty) Ltd

Project number: 2403474.UK0

Document number: EWC 2403474.UK0-0848

28th November 2024

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Dietary exposure assessment

The uses supported in South Africa by the halosulfuron-methyl derogation group, are provided in the Good Agricultural Practice (GAP) table in Appendix 1. The supported crops are maize, sorghum, wheat, sugarcane, avocado, citrus and mango. Using the Bryant Christie (BC) Global database for pesticide MRLs, a report has been run for halosulfuron-methyl on these crops. The highest Global MRLs (Maximum Residue levels) for each crop are listed in the table below. It should be noted that different methods of MRL calculation are used in different countries, and sometimes even the same dataset may result in a different MRL value. However, it is true in all countries that the MRL is a highly conservative value used to facilitate trade between countries and to monitor GAP compliant application, whereas the lower STMR (Supervised Trial Median Residue) and HR (Highest Residue) values are intended for risk assessment calculations.

Table 1: MRLs for halosulfuron-methyl around the world

Crop	**MRL (mg/kg)**					**Comments**
	Codex	**USA**	**Canada**	**Mexico**	**South Africa**	
Avocado	N.E	N.E	**0.1 (default)**	N.E	0.01	South African MRL taken from EU deferral
Citrus fruit	N.E	N.E	**0.1 (default)**	N.E	0.01	Data collated from representative commodities (Grapefruit, Lemon, Limes, Mandarin, Oranges)
Corn/Maize grain	N.E	0.05	0.05	**0.5**	0.01	South African MRL taken from EU deferral
Mango	N.E	N.E	**0.1 (default)**	N.E	0.01	South African MRL taken from EU deferral
Sorghum grain	N.E	0.05	0.05	**0.1**	0.01	South African MRL taken from EU deferral
Sugarcane	N.E	0.05	**0.1 (default)**	0.05	0.01	South African MRL taken from EU deferral
Wheat grain	N.E	N.E	**0.1 (default)**	N.E	0.01	South African MRL taken from EU deferral

Highest Global MRL for each crop presented in **bold**

Default MRL - When a specific MRL has not been set on a commodity for a pesticide, some markets defer to a set default MRL value. Policies regarding the use of default MRLs vary by country.

N.E – Not established

To present a worst-case risk assessment for consumers, the highest global MRL for each crop has been used in chronic and acute consumer risk assessment calculations (see bold values in Table 1). The current EU toxicological reference values: Acceptable Daily Intake (ADI) and Acute Reference Dose (ARfD), which were agreed by EFSA in 2012 and further elaborated on in the toxicological assessment are as follows:

- ADI = 0.063 mg/kg bw/day used for chronic risk assessment
- ARfD = 0.5 mg/kg bw used for acute risk assessment

The WHO models have been used for the chronic (IEDI – International Estimated Daily Intake) and acute (IESTI – International Estimate of Short-Term Intake) calculations. The results from each assessment are presented below.

Chronic risk assessment	Acute risk assessment
Maximum IEDI (based on G12 diet): 3.1% of ADI	Maximum IESTI = 3% of ARfD (based on consumption of maize in the Canadian Child < 6 years diet)
Maximum IEDI for South Africa (G05 diet): 1.7% of ADI	

This assessment uses the most conservative approach to dietary risk assessment (i.e. the highest worldwide MRLs have been used as the input values for each crop) and demonstrates that there is no unacceptable dietary chronic or acute risk to consumers.

Currently the registered South African GAP for halosulfuron does not trigger the need for an MRL greater than the LOQ (0.01 mg/kg). As part of this assessment, it was not possible to obtain the GAPs used in Canada and Mexico that led to the current MRLs which are the highest globally. Therefore, we cannot make a formal comparison of the GAPs. However, since the South African use does not require an MRL >0.01 mg/kg, then it can be assumed that the South African GAP is less critical than the Canadian and Mexican GAPs that underpin the high MRLs. Therefore, as mentioned above, the consumer risk assessment carried out here represents a true worse-case scenario for halosulfuron in the selected crops.

Drinking water assessment

Potential contamination of drinking water following the halosulfuron uses has also been explored. The ground water predicted environmental concentration values, PEC_{gw} resulting from the uses of halosulfuron have been determined in a separate document (2403474.UK0 – 2947 Halosulfuron-methyl FOCUS groundwater calculations). All PEC_{GW} values for halosulfuron were ≤0.001 µg/L for all crops and all FOCUS scenarios modelled following applications made in accordance with each GAP. To determine the consumer exposure to halosulfuron -methyl through drinking water, the exposure calculations are presented below.

$$\left(\left(\frac{concentration\ in\ water\ x\ consumption}{bodyweight}\right) \div ADI\right) \times 100$$

- Exposure to infants (5kg bodyweight, consumption 0.75 L/day) = <0.001% of the ADI
- Exposure to children (10 kg bodyweight, consumption 1 L/day) = <0.001% of the ADI
- Exposure to adults (60kg bodyweight, consumption 2 L/day) = <0.001% of the ADI

Conclusion

This assessment has considered the registered uses for halosulfuron in South Africa that were provided by the Derogation group (see Appendix 1). The GAPs that underpin the highest global MRLs in Canada and Mexico are not publicly available, therefore a formal comparison of the GAPs could not be made. However, the most conservative approach for consumer risk assessment was taken and an acute and chronic assessment was conducted using the highest Global MRL for each crop. This risk assessment demonstrated that there is no unacceptable risk to consumers using the highest MRLs as input values for the assessment. Since the South African use does not require an MRL >0.01 mg/kg, then it can be assumed that the South African GAP is less critical than the Canadian and Mexican GAPs that underpin the high MRLs.

Therefore, it is demonstrated that the uses of halosulfuron according to the South African registered labels are within the risk envelope of this assessment and the MRLs that are currently applicable worldwide. It is highly unlikely that the South African registered uses of halosulfuron on maize, sorghum, wheat, sugarcane, avocado, citrus and mango would lead to unacceptable dietary risk for consumers.

References

Bryant Christie Global Database: Regulatory Limits PESTICIDES/Pesticide MRLs (bryantchristie.com)

Members of the halosulfuron derogation group and their product

Company	Product	Registration number
Farm-Ag International (Pty) Ltd	Brigadier 750 WG	L9218
ICA International Chemicals (Pty) Ltd	WeedO 750 WG	L11149
UPL South Africa (Pty) Ltd	Cyprex WG	L7665
Sharda International Africa (Pty) Ltd	Halosulfuron 750 WDG	L10855
Villa Crop Protection (Pty) Ltd	Halo 750 WDG	L8283
Rainbow Agrosciences (Pty) Ltd	Flagship 750 WDG	L10539
Green Island Investments Pty Ltd	Halo-Fron WG	L10152

Appendix 1 – Critical GAP

The critical GAP for halosulfuron-methyl in South Africa is presented below.

GAP rev. 1, date: 29.09.2019

PPP (product name/code):	**Brigadier 750 WG, WeedO 750 WG, Cyprex WG, Halosulfuron 750WDG, etc**	Formulation type:	WG [a, b]
Active substance 1:	**Halosulfuron-methyl**	Conc. of as 1:	750 g/kg [c]
Safener:	**NA**	Conc. of safener:	NA
Synergist/adjuvant	Recommended with a registered surfactant	Conc. of adjuvant:	NA
Applicant:	**Halosulfuron derogation group**	Professional use:	☒
		Non professional use:	☐

Herbicide

1	2	3	4	5	6	7	8	9	10	11*	12	13	14
					Application				**Application rate**				
Use No.	**Country**	**Crop and/or situation**	**F, Fn, Fpn G, Gn, Gpn or I**	**Pests or Group of pests controlled** (additionally: developmental stages of the pest or pest group)	Method/Kind	Timing/Growth stage of crop & season	Max. number per crop/ season	Min. interval between applications (days)	Product-sachet/ha a) max. rate per appl. b) max. total rate per crop/season	g a.s./ha a) max. rate per appl. b) max. total rate per crop/season	Water L/ha min / max	**PHI** (days)	**Remarks:** product variant, other dose rate expressions dose range (min-max)
1	ZA	Maize	F	*Cyperus spp*., *Bidens pilosa*, *Cleome monophyla*, *Galinsoga spp*., *Tagetes minuta*.	Knapsack sprayers or tractor mounted boom sprayers	Post emergence of the weeds (BBCH 10-14) BBCH 12-16 (2-6 leaf stage) of the crop	1	-	1	50	200 - 400	NA	Post emergence (of the weeds). Prior to flowering of *Cyperus spp*. 3-5 weeks after planting of the crop. Sharda Villa Crop UPL Farm AG Green Island ICA Rainbow

1	2	3	4	5	6	7	8	9	10	11*	12	13	14
Use No.	**Country**	**Crop and/or situation**	**F, Fn, Fpn G, Gn, Gpn or I**	**Pests or Group of pests controlled** (additionally: developmental stages of the pest or pest group)	**Application**				**Application rate**			**PHI** (days)	**Remarks:** product variant, other dose rate expressions dose range (min-max)
					Method/Kind	Timing/Growth stage of crop & season	Max. number per crop/ season	Min. interval between applications (days)	Product-sachet/ha a) max. rate per appl. b) max. total rate per crop/season	g a.s./ha a) max. rate per appl. b) max. total rate per crop/season	Water L/ha min / max		
2	ZA	Grain sorghum	F	*Cyperus spp., Bidens pilosa, Cleome monophyla, Galinsoga spp., Tagetes minuta*	Knapsack sprayers or tractor mounted boom sprayers	Post emergence of the weeds (BBCH 10-14) BBCH 12-16 (2-6 leaf stage) of the crop	1	-	1	50	200 - 400	NA	Post emergence (of the weeds). Prior to flowering of *Cyperus spp*. Sharda Villa Crop UPL Farm AG Green Island ICA Rainbow
3	ZA	Wheat	F	*Cyperus spp., Bidens pilosa, Cleome monophyla, Galinsoga spp., Tagetes minuta*	Knapsack sprayers or tractor mounted boom sprayers	Post emergence of the weeds (BBCH 10-14) BBCH 12-21 (2 leaf stage to beginning of tillering) of the crop	1	-	1	50	200 - 400	NA	Post emergence (of the weeds). Prior to flowering of *Cyperus spp*. 3 to 5 weeks after planting of the crop. Sharda Villa Crop ICA Rainbow
4	ZA	Sugarcane	F	*Cyperus spp., Bidens pilosa, Cleome*	Knapsack sprayers or tractor	Post emergence of the weeds (BBCH 10-14)	1	-	1	50	200 - 400	NA	Post emergence (of the weeds). Prior to

1	2	3	4	5	6	7	8	9	10	11*	12	13	14
Use No.	**Country**	**Crop and/or situation**	**F, Fn, Fpn G, Gn, Gpn or I**	**Pests or Group of pests controlled** (additionally: developmental stages of the pest or pest group)	**Application**				**Application rate**			**PHI** (days)	**Remarks:** product variant, other dose rate expressions dose range (min-max)
					Method/Kind	Timing/Growth stage of crop & season	Max. number per crop/ season	Min. interval between applications (days)	Product-sachet/ha a) max. rate per appl. b) max. total rate per crop/season	g a.s./ha a) max. rate per appl. b) max. total rate per crop/season	Water L/ha min / max		
				monophyla, Galinsoga spp., Tagetes minuta	mounted boom sprayers	BBCH 12-16 (2-6 leaf stage) of the crop							flowering of *Cyperus spp*. Villa Crop UPL Farm AG Green Islands Rainbow
5	ZA	Avocado	F	*Cyperus spp., Bidens pilosa, Cleome monophyla, Galinsoga spp., Tagetes minuta*	Knapsack sprayers or tractor mounted boom sprayers	Post emergence of the weeds (BBCH 10-14) (BBCH 00-99 of the crop)	1	-	1	50	200 - 400	NA	Post emergence (of the weeds). Prior to flowering of *Cyperus spp*. Between the rows, avoid contact with crop foliage. Villa Crop ICA Rainbow
6	ZA	Citrus	F	*Cyperus spp., Bidens pilosa, Cleome monophyla, Galinsoga spp., Tagetes minuta*	Knapsack sprayers or tractor mounted boom sprayers	Post emergence of the weeds (BBCH 10-14) (BBCH 00-99 of the crop)	1	-	1	50	200 - 400	NA	Post emergence (of the weeds). Prior to flowering of *Cyperus spp*. Between the rows, avoid contact with crop foliage. Villa Crop UPL Farm AG Green Island ICA Rainbow

1	2	3	4	5	6	7	8	9	10	11*	12	13	14
					Application				**Application rate**				
Use No.	**Country**	**Crop and/or situation**	**F, Fn, Fpn G, Gn, Gpn or I**	**Pests or Group of pests controlled** (additionally: developmental stages of the pest or pest group)	Method/Kind	Timing/Growth stage of crop & season	Max. number per crop/ season	Min. interval between applications (days)	Product-sachet/ha a) max. rate per appl. b) max. total rate per crop/season	g a.s./ha a) max. rate per appl. b) max. total rate per crop/season	Water L/ha min / max	**PHI** (days)	**Remarks:** product variant, other dose rate expressions dose range (min-max)
7	ZA	Mango	F	*Cyperus spp*., *Bidens pilosa*, *Cleome monophyla*, *Galinsoga spp*., *Tagetes minuta*	Knapsack sprayers or tractor mounted boom sprayers	Post emergence of the weeds (BBCH 10-14) (BBCH 00-99 of the crop)	1	-	1	50	200 - 400	NA	Post emergence (of the weeds). Prior to flowering of *Cyperus spp*. Between the rows, avoid contact with crop foliage. Villa crop ICA Rainbow

Remarks table heading:

(a) e.g. wettable powder (WP), emulsifiable concentrate (EC), granule (GR)

(b) Catalogue of pesticide formulation types and international coding system CropLife International Technical Monograph n°2, 6th Edition Revised May 2008

(c) g/kg or g/l

(d) Select relevant

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

(f) No authorization possible for uses where the line is highlighted in grey, Use should be crossed out when the notifier no longer supports this use.

Remarks columns:

1 Numeration necessary to allow references

2 Use official codes/nomenclatures of EU Member States

3 For crops, the EU and Codex classifications (both) should be used; when relevant, the use situation should be described (e.g. fumigation of a structure)

4 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

5 Scientific names and EPPO-Codes of target pests/diseases/ weeds or, when relevant, the common names of the pest groups (e.g. biting and sucking insects, soil born insects, foliar fungi, weeds) and the developmental stages of the pests and pest groups at the moment of application must be named.

6 Method, e.g. high volume spraying, low volume spraying, spreading, dusting, drench
Kind, e.g. overall, broadcast, aerial spraying, row, individual plant, between the plants - type of equipment used must be indicated.

7 Growth stage at first and last treatment (BBCH Monograph, Growth Stages of Plants, 1997, Blackwell, ISBN 3-8263-3152-4), including where relevant, information on season at time of application

8 The maximum number of application possible under practical conditions of use must be provided.

9 Minimum interval (in days) between applications of the same product

10 For specific uses other specifications might be possible, e.g.: g/m³ in case of fumigation of empty rooms. See also EPPO-Guideline PP 1/239 Dose expression for plant protection products.

11 The dimension (g, kg) must be clearly specified. (Maximum) dose of a.s. per treatment (usually g, kg or L product / ha).

12 If water volume range depends on application equipments (e.g. ULVA or LVA) it should be mentioned under “application: method/kind”.

13 PHI - minimum pre-harvest interval

14 Remarks may include: Extent of use/economic importance/restrictions

Appendix 2 – BC Global MRL report

Regulatory Limits
MRL Pesticides Repor

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NON-DIETARY RISK ASSESSMENT FOR THE PROPOSED APPLICATION OF PRODUCTS CONTAINING HALOSULFURON-METHYL

Prepared by:

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Prepared for the Derogation Group consisting of:

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UPL South Africa (Pty) Ltd, Sharda International Africa (Pty) Ltd
Villa Crop Protection (Pty) Ltd, Rainbow Agrosciences (Pty) Ltd
Green Island Investments Pty Ltd

Project number: 2403474.UK0

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Date: 09/09/2024

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Executive summary

A risk assessment has been conducted in accordance with the newly updated EFSA (2022) guidance[1] on the assessment of exposure of operators, workers, residents, and bystanders to plant protection products.

The EFSA (2022) guidance document is designed to assist risk assessors when quantifying potential non-dietary, systemic exposures as part of regulatory risk assessment for plant protection products (PPPs). To support users in performing the assessment of exposure and risk, an online calculator (reflecting the guidance content) was also developed. The underlying principles of the guidance document and the related exposure calculator are the transparency of data, the traceability of information and the reproducibility of the outcomes. In establishing the guidance document and calculator, the EFSA working group considered only databases of raw data or peer-reviewed publications that could be accessed (if requested) by third parties and in accordance with the Aarhus Convention[2]. The EFSA guidance is based on a comprehensive, peer reviewed dataset and is continually reviewed and amended as and when new data become available.

Considering the above, the EFSA web calculator has been selected as the most appropriate model to assess non-dietary exposure to halosulfuron-methyl resulting from the application of the water dispersible granule products containing 750g halosulfuron-methyl/kg, using vehicle mounted and/or hand-held spraying equipment.

For field/outdoor manual application of a herbicide to a low target (weeds), also called low crops scenario, the EFSA model relies on a small dataset to model operator exposure. Given the limitations of the database no modelling factors could be identified for predicting exposure, hence it was not possible to produce a conditional model for this exposure scenario. The EFSA model therefore predicts exposure on the basis of linear extrapolation, starting from 1.5 kg a.s. applied per ha, which is the application rate used in the underlying data in the model. For application rates above 1.5 kg a.s. per ha, the 'worst case' assumption is that exposures are not expected to increase by as much as the model predicts.

The maximum application rate of halosulfuron-methyl for all products and all uses is 0.05 kg a.s./ha. This use rate is 30 times lower than the 1.5 kg a.s./ha in the EFSA model, from which exposure predictions are scaled from. Therefore, due to the small dataset conducted at such high application rates, the outdoor EFSA model for hand-held application to low crops cannot reliably be used to provide realistic exposure predictions for the recommended uses of the products.

In view of the lack of robustness of the EFSA model for predicting exposure for outdoor application to low crops at very low application rates using hand-held sprayers, the new 2021 EFSA Greenhouse model has been used to provide more representative calculations of operator exposure to halosulfuron-methyl following the manual application of the products. Even though the use to amenity grassland is only supported by Rainbow and Villa Crop, this use is a worst-case use as explained below (p6) and the exposure assessment for this crop use provides therefore a risk envelope for all other uses included in the GAP (Table 2).

[1] EFSA (2022) Guidance on the assessment of exposure of operators, workers, residents, and bystanders in risk assessment of plant protection products. EFSA Journal 2022;20(1):7032

[2] UN (1998) Convention on access to information, public participation in decision making and access to justice in environmental matters.

The EFSA Greenhouse model is based on a modern database of exposure studies with a more diverse range of studies that better reflects a predictive, generic exposure model. Whilst these data were generated from applications made to indoor crops, it is expected that levels of exposure would be similar for field applications, as comparable equipment and sprayer techniques are used, i.e., a spray gun or lance connected via a hose to a large mix tank or knapsack sprayers. The scenario for low crop, normal contact with a treated crop is deemed suitable to represent hand-held spray application of a herbicide to an outdoor low crop, as a similar level of contact to the spray is expected during the application. As the EFSA Greenhouse model does not contain the crop scenario 'amenity grassland' the use scenario 'low ornamentals' is chosen to provide the estimates of exposure from this model.

The assessments confirm an acceptable risk assessment can be achieved for all uses in scope, amenity grassland, field and orchard crops with **no** Personal Protective Equipment (PPE) for vehicle mounted application, manual hand-held and knapsack equipment. A summary of the risk assessments for operators, workers, residents and bystanders is presented in the tables below. It is noted that this outcome is achieved using default values for the dermal absorption, which in essence are extremely conservative.

When experimentally derived dermal absorption values are used (more realistic scenario) an even higher safety margin is demonstrated.

It is understood that standard workwear (arms, body and legs covered) are not PPEs but that gloves are.

Amenity grassland (covering all uses)

	Result	**PPE **/ Risk mitigation measures Dermal absorption: default values**	**PPE **/ Risk mitigation measures Dermal absorption: experimental values**
Operators	Acceptable	**Results of risk assessment:** Vehicle mounted and knapsack: None* Hand-held equipment: None*	**Results of risk assessment:** Vehicle mounted and knapsack: None* Hand-held equipment: None*
Workers	Acceptable	None*	None*
Residents	Acceptable	None	None
Bystanders	Acceptable	None	None

None* means no PPE required but standard workwear (arms, body and legs covered) are worn.
** PPE = Personal Protective Equipment

Potential precautionary measures based on classification and labelling:

All products in scope contain 750 g/kg of the active substance halosulfuron-methyl but may differ in their GHS classification. Depending on the classification of the product the below PPEs would be required:

- ✓ If the product is warranted a skin sensitisation classification (Category 1) gloves, protective clothing and eye protection/face protection should be worn by the operator for mixing and loading.

- ✓ If the product is warranted a skin irritation classification (Category 2 or 3) gloves, protective clothing should be worn by the operator for mixing and loading.
- ✓ If the product is warranted an eye irritation classification (Category 1 or 2) gloves, eye protection/face protection should be worn by the operator for mixing and loading.

It is noted that all users of pesticides should in any case comply with "SANS 10206 (2010): The handling, storage and disposal of pesticides" and that the above-mentioned PPEs for skin/eye irritants and skin sensitisers for mixing and loading activities are strongly recommended in all cases when handling pesticides to provide additional protection against spills and splashes.

Non-dietary risk assessment

Non-dietary risk assessments have been undertaken for the representative product considering the endpoints listed below in Table 1 and the product uses detailed in Table 2 (proposed GAP).

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

Product code and name	Halosulfuron 75 WDG (and similar products)
Formulation type	Water dispersible granule (WG)
Category	Herbicide
Packaging	All products are supplied in water soluble bag
Active substance (incl. content)	Halosulfuron-methyl 750 g/kg
AOEL systemic	0.063 mg/kg bw/d
AAOEL systemic	None
Inhalation absorption	100%
Oral absorption	100%
Dermal absorption	EFSA (2017) default dermal absorption values for an WG formulation: Concentrate: 10% Dilution: 50%
	Experimentally derived values for 750 g/kg WDG formulation Concentrate: 0.22% Dilution: 0.34% (0.075 g/kg)

A first tier (Tier 1) exposure and risk assessment is performed using default values for dermal absorption. The assumed values for a water dispersible granule formulation are in accordance with the values recommended for this formulation type in EFSA's (2017) guidance on dermal absorption[3].

The default values for a WG are respectively 10% (concentrate) and 50 % (dilution). Default values are in essence extremely conservative. It is is noted that for their human health risk assessment of halosulfuron methyl, the US EPA[4] considered the available data on dermal

[3] EFSA (European Food Safety Authority), Buist H, Craig P, Dewhurst I, Hougaard Bennekou S, Kneuer C, Machera K, Pieper C, Court Marques D, Guillot G, Ruffo F and Chiusolo A, 2017. Guidance on dermal absorption. EFSA Journal 2017;15(6):4873, 60 pp. https://doi.org/10.2903/j.efsa. 2017.4873

[4] Halosulfuron-methyl Human Health Risk Assessment DP No. D421819 (2015)

absorption for a range of sulfonylurea substances. Percent dermal absorption for product concentrates ranged from 0.021% to 9% across substances and for dilutions from 1% to 21%, supporting the conclusion that for sulfonylurea substances, EFSA's default dermal absorption values for WG formulations are likely to overestimate actual levels of dermal absorption.

As dermal absorption data are available for a 750 g/kg WDG formulation of halosulfuron-methyl[5], a higher (Tier 2) exposure and risk assessment is also performed using these experimentally derived dermal absorption values. [0.22% (concentrate) and 0.34% (dilution)].

Table 2: Identified GAP for the product Halosulfuron 750 WDG

Use No.	**Crop and/or situation**	**F, Fn, Fpn G, Gn, Gpn or I**	**Application**				**Application rate**			**PHI** (days)
			Method/Kind	Timing/Growth stage of crop & season	Max. number per crop/ season	Min. interval between applications (days)	kg product/ha a) max. rate per appl. b) max. total rate per crop/season	g a.s./ha a) max. rate per appl. b) max. total rate per crop/season	Water L/ha min / max	
1	Maize	F	Foliar Spray (ground application) – vehicle mounted and hand-held	Post emergence of the weeds (BBCH 10-14) BBCH 12-16 (2-6 leaf stage) of the crop	1	-	0.067	0.05	200-400	NA
2	Grain sorghum	F	Foliar Spray (ground application) – vehicle mounted and hand-held	Post emergence of the weeds (BBCH 10-14) BBCH 12-16 (2-6 leaf stage) of the crop	1	-	0.067	0.05	200-400	NA
3	Wheat	F	Foliar Spray (ground application) – vehicle mounted and hand-held	Post emergence of the weeds (BBCH 10-14) BBCH 12-21 (2 leaf stage to beginning of tillering) of the crop	1	-	0.067	0.05	200-400	NA
4	Sugarcane	F	Foliar Spray (ground application) – vehicle mounted and hand-held	Post emergence of the weeds (BBCH 10-14) BBCH 12-16 (2-6 leaf stage) of the crop	1	-	0.067	0.05	200-400	NA
5	Avocado	F	Foliar Spray (ground application) – vehicle mounted and hand-held	Post emergence of the weeds (BBCH 10-14) (BBCH 00-99 of the crop)	1	-	0.067	0.05	200-400	NA

[5] EFSA-Q-2023-00183

Use No.	Crop and/or situation	F, Fn, Fpn G, Gn, Gpn or I	Application				Application rate			PHI (days)
			Method/Kind	Timing/Growth stage of crop & season	Max. number per crop/ season	Min. interval between applications (days)	kg product/ha a) max. rate per appl. b) max. total rate per crop/season	g a.s./ha a) max. rate per appl. b) max. total rate per crop/season	Water L/ha min / max	
6	Citrus	F	Foliar Spray (ground application) – vehicle mounted and hand-held	Post emergence of the weeds (BBCH 10-14) (BBCH 00-99 of the crop)	1	-	0.067	0.05	200-400	NA
7	Mango		Foliar Spray (ground application) – vehicle mounted and hand-held	Post emergence of the weeds (BBCH 10-14) (BBCH 00-99 of the crop)	1	-	0.067	0.05	200-400	NA
8	Kikuyu and/or Cynodon lawn		Foliar Spray (ground application) – vehicle mounted and hand-held	Post emergence of the weeds (BBCH 10-14) (BBCH 21-65 of the crop)	1	-	0.067	0.05	200-400	NA

All recommended uses are for a single application of 0.067 kg product in 200 to 400L water per ha. The products are commercialised in water soluble bags, each containing 0.067 kg of formulated product. According to the EFSA's exposure guidance (EFSA, 2022) application to amenity grassland (Kikuyu and/or Cynodon lawn) is presented as the worst case for vehicle mounted spray applications. This scenario selects the higher work rates (ha treated per day) used by the EFSA model for vehicle mounted application and includes the additional resident scenario of entry into treated areas through recreation. The exposure assessment for this crop use therefore provides a risk envelope for the other uses included in the GAP.

For reasons discussed above, the risk assessment for the hand-held application methods is performed using the EFSA Greenhouse model, using the scenario 'low ornamentals' as a surrogate crop for use on amenity grassland. As the EFSA greenhouse model assumes 1 ha is treated per day for all application methods, the estimates provided for application by manual hand-held equipment (hand-held lance connected to large vehicle mounted spray tank) is multiplied by 4 so as to assume the same treated area as the outdoor EFSA model assumes for this application scenario.

Detailed exposure estimates/model outputs are provided separately in the downloaded report generated by the EFSA OPEX Web calculator. A table cross-referencing the summary results is presented below and the use/model outputs detailed in the EFSA generated report is contained in Appendix 1. An input parameter zip file that may be uploaded to the online web calculator to replicate the modelling undertaken is also provided (EFSA model may be accessed at: https://r4eu.efsa.europa.eu/app/ope).

Operator exposure

A summary of the exposure models used for estimation of operator exposure to the active substance during application of the product is presented in Table 3. The outcome of the estimation is presented in Table 4 and Table 5. Detailed calculations are referenced in

Appendix 1.

At this time, no EU acute AOEL has been set for halosulfuron-methyl. Consequently, no acute risk assessment has been provided for this active substance.

Table 3: Exposure models for intended uses

Critical uses:	Amenity grassland (Kikuyu and/or Cynodon lawn): 0.067 kg product/ha equivalent to 0.05 kg/ha halosulfuron-methyl Vehicle mounted (downward) spray application outdoors Manual hand-held (downward) spray application outdoors Manual knapsack (downward) spray application outdoors
Model:	EFSA Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products. EFSA Journal 2022;20(1):7032 Web calculator version: v 1.0.2

Table 4: Estimated operator exposure (short-term or 'sub-chronic' exposure) – Tier 1 assessment using default dermal absorption values

Model data	**Level of PPE**	**Halosulfuron-methyl**	
		Total absorbed dose (mg/kg/day)	**% of systemic AOEL**
Vehicle mounted (downward) spray application outdoors to low crops			
Application rate and crop		0.05 kg a.s./ha (wheat)	
Spray application (AOEM; 75th percentile) Body weight: 60 kg	Work wear (arms, body and legs covered) M/L[a] and A[b]	0.004	6.2
	Work wear (arms, body and legs covered) and gloves M/L. Workwear (only) A	0.003[c]	5.3
Manual hand-held (downward) spray application outdoors to low crops			
Application rate and crop		0.05 kg a.s./ha	
Spray application (AOEM; 75th percentile) Body weight: 60 kg	Work wear (arms, body and legs covered) M/L and A	0.053[d]	83.6
	Work wear (arms, body and legs covered) and gloves for M/L, Work wear (only) A	0.052[c,d]	83.2
Manual knapsack (downward) spray application outdoors to low crops			
Application rate and crop		0.05 kg a.s./ha	
Spray application (AOEM; 75th percentile) Body weight: 60 kg	Work wear (arms, body and legs covered) M/L and A	0.03	46.9
	Work wear (arms, body and legs covered) and gloves for M/L, Work wear (only) A	0.014[c]	21.8

[a]M/L: Mixing and loading
[b]A: Application

[c] Systemic exposure value not provided by model. Value is back calculated from % of AOEL
[d] EFSA greenhouse model estimate is multiplied by 4 to reflect total area treated per day of 4 ha

Table 5: Estimated operator exposure (short-term or 'sub-chronic' exposure) – Tier 2 assessment using experimentally derived dermal absorption values

Model data	Level of PPE	Halosulfuron-methyl	
		Total absorbed dose (mg/kg/day)	% of systemic AOEL
Vehicle mounted (downward) spray application outdoors to low crops			
Application rate and crop		0.05 kg a.s./ha (wheat)	
Spray application (AOEM; 75th percentile) Body weight: 60 kg	Work wear (arms, body and legs covered) M/L[a] and A[b]	0.0001	0.2
	Work wear (arms, body and legs covered) and gloves M/L. Workwear (only) A	0.0001[c]	0.2
Manual hand-held (downward) spray application outdoors to low crops			
Application rate and crop		0.05 kg a.s./ha	
Spray application (AOEM; 75th percentile) Body weight: 60 kg	Work wear (arms, body and legs covered) M/L and A	0.004[d]	5.6
	Work wear (arms, body and legs covered) and gloves for M/L, Work wear (only) A	0.004[c,d]	5.6
Manual knapsack (downward) spray application outdoors to low crops			
Application rate and crop		0.05 kg a.s./ha	
Spray application (AOEM; 75th percentile) Body weight: 60 kg	Work wear (arms, body and legs covered) M/L and A	0.002	2.9
	Work wear (arms, body and legs covered) and gloves for M/L, Work wear (only) A	0.001[c]	2.3

[a]M/L: Mixing and loading
[b]A: Application
[c] Systemic exposure value not provided by model. Value is back calculated from % of AOEL
[d] EFSA greenhouse model estimate is multiplied by 4 to reflect total area treated per day of 4 ha

Conclusion

Levels of exposure to halosulfuron-methyl in operators are predicted to be within the AOEL for all proposed application methods and crops. No PPE are required for any application scenario.

Worker exposure

Table 6 shows the exposure model used for the estimation of worker exposure after entry into an area previously treated with halosulfuron-methyl according to the critical uses. For the worker risk assessment, it is assumed that the individual re-enters the treated crop immediately after the final product application has dried. Detailed calculations/model outputs are referenced in Appendix 1.

At this time, no EU acute AOEL has been set for halosulfuron-methyl and there is no guidance on acute exposure assessment for the worker. Consequently, no acute risk assessment has been provided for this active substance.

Table 6: Exposure models for intended uses

Critical uses	Amenity grassland (1 x 0.067 L product/ha equivalent to 1 x 0.05 kg/ha Halosulfuron-methyl)
Model	EFSA Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products; EFSA Journal 2022;20(1):7032 Web calculator version: v 1.0.2

Critical use: Amenity grassland (1 x 0.067 L product/ha equivalent to 1 x 0.05 kg/ha Halosulfuron-methyl)

The following assessment has considered an individual performing inspection/irrigation tasks in amenity grassland (Kikuyu and/or Cynodon lawn).

Table 7: Estimated worker exposure: Amenity grassland (Kikuyu and/or cynodon lawn) – Tier 1 assessment using default dermal absorption values

Model data	Level of PPE	Total absorbed dose (mg/kg bw/day)	% of systemic AOEL	Safe re-entry interval (days) required
Number of applications and application rate:		2 x 0.15 kg a.s./ha		
Task: Inspection, irrigation Work rate: 2 hours/day Body weight: 60 kg DT_{50}: 30 days DFR: 3 µg/cm^2/kg a.s./ha Dermal absorption: 50%	Total potential exposure TC: 12500 cm^2/person/h	0.03	49.9	0
	Work wear (arms, body and legs covered) TC: 1400 cm^2/person/h	0.004	5.6	0

Table 8: Estimated worker exposure: Amenity grassland (Kikuyu and/or Cynodon lawn) – Tier 2 assessment using experimentally derived dermal absorption values

Model data	Level of PPE	Total absorbed dose (mg/kg bw/day)	% of systemic AOEL	Safe re-entry interval (days) required
Number of applications and application rate:		2 x 0.15 kg a.s./ha		
Task: Inspection, irrigation Work rate: 2 hours/day Body weight: 60 kg DT_{50}: 30 days DFR: 3 µg/cm^2/kg a.s./ha Dermal absorption: 0.34%	Total potential exposure TC: 12500 cm^2/person/h	0.0002	0.3	0
	Work wear (arms, body and legs covered) TC: 1400 cm^2/person/h	2×10^{-5}	0.04	0

Conclusion

Levels of exposure to halosulfuron-methyl for workers are predicted to be within the AOEL when workwear (long sleeved) is worn during crop re-entry activities.

Resident / Bystander exposure

No bystander risk assessment is required for plant protection products that do not have significant acute toxicity or the potential to exert toxic effects after a single exposure. Exposure in this case will be determined by average exposure over a longer duration, and higher exposures on one day will tend to be offset by lower exposures on other days. Therefore, exposure assessment for residents also covers bystander exposure.

At this time, no EU acute AOEL has been set for halosulfuron-methyl. Consequently, no acute risk assessment has been provided for this active substance.

A summary of the exposure model used for estimation of resident exposure to the active substance according to the critical use is presented in Table 9. The outcome of the estimations is presented in Table 10 and Table 11. Detailed calculations are referenced in Appendix 1.

Table 9: Exposure model for intended uses

Critical uses	Amenity grassland (Kikuyu and/or Cynodon lawn) - 1 x 0.067 L product/ha equivalent to 1 x 0.05 kg/ha halosulfuron-methyl Minimum water volume: 200 L/ha Vehicle mounted upward spray application
Model	EFSA Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products. EFSA Journal 2022;20(1):7032 Web calculator version: v 1.0.2

Table 10: Estimated resident exposure (EFSA guidance) – Tier 1 assessment using default dermal absorption values

Model data		**Halosulfuron-methyl**	
		Total absorbed dose (mg/kg bw/day)	**% of systemic AOEL**
Vehicle mounted downward spray application outdoors Buffer: 2,3 m Drift reduction technology: no DT_{50}: 30 days DFR: 3 µg/cm^2/kg a.s./ha Dermal absorption: 50%			
Application rate:		1 x 0.05 kg a.s./ha	
Vapour pressure		1.33 x 10^{-5} Pa at 25°C	
Resident (child) Body weight: 10 kg	Drift (75th perc.)	0.003	5.4
	Vapour (75th perc.)	0.0008	1.3
	Deposits (75th perc.)	0.0004	0.6
	Re-entry (75th perc.)	0.001	1.8
	All pathways (mean)	0.004	6
	Re-entry recreational (75th perc.)	0.007	11.5
Resident (adult) Body weight:60 kg	Drift (75th perc.)	0.0008	1.3
	Vapour (75th perc.)	0.0003	0.4
	Deposits (75th perc.)	0.0002	0.3
	Re-entry (75th perc.)	0.0004	0.6
	All pathways (mean)	0.001	1.8
	Re-entry recreational (75th perc.)	0.003	4.9

Table 11: Estimated resident exposure (EFSA guidance) – Tier 2 assessment using experimentally derived dermal absorption values

Model data		Halosulfuron-methyl	
		Total absorbed dose (mg/kg bw/day)	**% of systemic AOEL**
Vehicle mounted downward spray application outdoors Buffer: 2,3 m Drift reduction technology: no DT_{50}: 30 days DFR: 3 µg/cm^2/kg a.s./ha Dermal absorption: 0.34%			
Application rate:		1 x 0.05 kg a.s./ha	
Vapour pressure		1.33 x 10^{-5} Pa at 25°C	
Resident (child) Body weight: 10 kg	Drift (75th perc.)	3 x 10^{-5}	0.04
	Vapour (75th perc.)	0.0008	1.3
	Deposits (75th perc.)	4 x 10^{-5}	0.07
	Re-entry (75th perc.)	0.0003	0.5
	All pathways (mean)	0.0009	1.4
	Re-entry recreational (75th perc.)	0.0008	1.2
Resident (adult) Body weight:60 kg	Drift (75th perc.)	6 x 10^{-6}	0.01
	Vapour (75th perc.)	0.0003	0.4
	Deposits (75th perc.)	1 x 10^{-6}	0.002
	Re-entry (75th perc.)	3 x 10^{-6}	0.004
	All pathways (mean)	0.0003	0.4
	Re-entry recreational (75th perc.)	2 x 10^{-5}	0.03

Conclusion

Levels of exposure to halosulfuron-methyl for residents are predicted to be within the AOEL without the requirement for any additional risk mitigation measures such as the use of low drift nozzles or extended non spray (buffer) zones.

Human Health Risk Assessment Conclusion

The above exposure estimates confirm an acceptable risk assessment can be achieved for all halosulfuron 750 WG products (for the proposed uses on amenity grassland and other uses included in the GAP).

Operator exposure

Levels of exposure to halosulfuron-methyl for spray operators are predicted to be within the AOEL without the requirement for PPE to be worn.

If the product is warranted a skin irritation classification (Category 2 or 3) then protective gloves and protective clothing should be worn by the operator for mixing and loading.

If the product is warranted an eye irritation classification (Category 1 or 2) then eye protection/face protection should be worn by the operator for mixing and loading.

If the product is warranted a skin sensitisation classification (Category 1) then protective gloves, protective clothing and eye protection/face protection should be worn by the operator for mixing and loading.

It is noted that all users of pesticides should in any case comply with "SANS 10206 (2010): The handling, storage and disposal of pesticides" and that the above-mentioned PPEs for skin/eye irritants and skin sensitisers for mixing and loading activities are strongly recommended in all cases when handling pesticides to provide additional protection against spills and splashes.

Worker exposure

Levels of exposure to halosulfuron-methyl for re-entry workers are predicted to be within the AOEL when suitable workwear is worn during crop re-entry activities. No PPE are required.

Bystanders and residents

Levels of exposure to halosulfuron-methyl for residents (which includes bystanders) are predicted to be within the AOEL without the requirement for any additional risk mitigation measures such as the use of low drift nozzles or extended non spray (buffer) zones.

Where classification as skin sensitiser (Cat 1) applies, this has no impact on residents and bystanders or workers as these groups would only be exposed to diluted sprays. The highest content of halosulfuron-methyl in the diluted spray is 0.025% which is below the 1% generic concentration limit for skin sensitisation classification.

Appendix 1

List of EFSA modelling reports submitted by the applicant and relied on.

Exposure table reference	Risk assessment	Use number (as listed in attached generated EFSA results report)	EFSA Web Calculator input parameter file & generated results report
Table 4: Estimated operator exposure: short-term/sub-chronic	Operator exposure to halosulfuron-methyl resulting from the application of the product to amenity grassland (Kikuyu and/or Cynodon lawn) using vehicle mounted spray equipment, outdoors. Application rate: 0.67 kg product/ha Water volume: 200 L/ha Default dermal absorption values	Use 8: Amenity grassland (Kikuyu and/or Cynodon lawn)	 Halosulfuron 750 WDG_Tier 1 Assessn  **Halosulfuron 750 WDG_Tier 1 Assessn**
Table 5: Estimated operator exposure: short-term/sub-chronic	Operator exposure to halosulfuron-methyl resulting from the application of the product to amenity grassland (Kikuyu and/or Cynodon lawn) using vehicle mounted spray equipment, outdoors. Application rate: 0.67 kg product/ha Water volume: 200 L/ha Experimentally derived dermal absorption values	Use 8: Amenity grassland (Kikuyu and/or Cynodon lawn)	 Halosulfuron 750 WDG_Tier 2 Assessn  **Halosulfuron 750 WDG_Tier 2 Assessn**
Table 4: Estimated operator exposure: short-term/sub-chronic	Operator exposure to halosulfuron-methyl resulting from the application of the product to low ornamentals using manual hand-held and knapsack downward spray equipment, outdoors. Application rate: 0.67 kg product/ha Water volume: 200 L/ha Default dermal absorption values	Use 8: Amenity grassland (Kikuyu and/or Cynodon lawn)	 Halosulfuron 750 WDG_Tier 1 Assessn  **Halosulfuron 750 WDG_Tier 1 Assessn**

Table 5: Estimated operator exposure: short-term/sub-chronic	Operator exposure to halosulfuron-methyl resulting from the application of the product to low ornamentals using manual hand-held and knapsack downward spray equipment, outdoors. Application rate: 0.67 kg product/ha Water volume: 200 L/ha Experimentally derived dermal absorption values	Use 8: Amenity grassland (Kikuyu and/or Cynodon lawn)	 Halosulfuron 750 WDG_Tier 2 Assessm  **Halosulfuron 750 WDG_Tier 2 Assessm**
Table 7: Estimated worker exposure	Worker re-entry exposure to halosulfuron-methyl resulting from the application of the product to amenity grassland (Kikuyu and/or Cynodon lawn). Task: Inspection, irrigation. DT_{50}: 30 days DFR: 3 µg/cm^2/kg a.s./ha Application: 1 x 0.05 kg a.s./ha Default dermal absorption values	Use 8: Amenity grassland (Kikuyu and/or Cynodon lawn)	 Halosulfuron 750 WDG_Tier 1 Assessm  **Halosulfuron 750 WDG_Tier 1 Assessm**
Table 8: Estimated worker exposure	Worker re-entry exposure to halosulfuron-methyl resulting from the application of the product to amenity grassland (Kikuyu and/or Cynodon lawn). Task: Inspection, irrigation Task: Searching, reaching, picking DT_{50}: 30 days DFR: 3 µg/cm^2/kg a.s./ha Application: 1 x 0.05 kg a.s./ha Experimentally derived dermal absorption values	Use 8: Amenity grassland (Kikuyu and/or Cynodon lawn)	 Halosulfuron 750 WDG_Tier 2 Assessm  **Halosulfuron 750 WDG_Tier 2 Assessm**
Table 10: Estimated resident exposure	Resident exposure to Halosulfuron methyl resulting from the application of the product to amenity grassland (Kikuyu and/or Cynodon lawn) using vehicle mounted, downward spray equipment outdoors. DRT: None Buffer zone: 2,3 m Application: 1 x 0.05 kg a.s./ha Default dermal absorption values	Use 8: Amenity grassland (Kikuyu and/or Cynodon lawn)	 Halosulfuron 750 WDG_Tier 1 Assessm  **Halosulfuron 750 WDG_Tier 1 Assessm**

Table 11: Estimated resident exposure	Resident exposure to Halosulfuron methyl resulting from the application of the product to amenity grassland (Kikuyu and/or Cynodon lawn) using vehicle mounted, downward spray equipment outdoors. DRT: None Buffer zone: 2,3 m Application: 1 x 0.05 kg a.s./ha Experimentally derived dermal absorption values	Use 8: Amenity grassland (Kikuyu and/or Cynodon lawn)	 Halosulfuron 750 WDG_Tier 2 Assessm  **Halosulfuron 750 WDG_Tier 2 Assessm**

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TOXICOLOGY ASSESSMENT OF HALOSULFURON-METHYL AS AN ACTIVE SUBSTANCE IN AGRICULTURAL REMEDIES

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Green Island Investments Pty Ltd

Project No.: 2403474.UK0

Exponent Report No.: 2403474.UK0 - 6756

Date: 3rd December 2024

Table of Contents

1. Executive Summary

Halosulfuron-methyl is a sulfonylurea post-emergence herbicide used to control broad-leaved weeds and sedges in a range of crops (maize, sorghum, wheat, sugarcane etc…). It is systemic and selective, and acts as an inhibitor of acetohydroxyacid synthase restricting the biosynthesis of the essential amino acids, valine and isoleucine, thus restricting plant growth.

In the Republic of South Africa regulatory jurisdiction, according to Regulation 8(1)(d) and 10(3)(e) respectively, the Registrar (Act 36 of 1947) may not grant or renew a registration after 1 June 2024 if a plant protection product contains substances of concern. In the European Union, halosulfuron-methyl has been classified with respect to reproductive toxicity as Repr.1B H360D (May damage the unborn child) in accordance with Regulation (EC) No. 1272/2008 (also known as the CLP Regulation for Classification and Labelling), and as such would be considered a substance of concern. In exceptional circumstances, the Registrar may grant a registration for a product (i.e.: an agricultural remedy) containing a substance of concern, based on a risk assessment demonstrating the safe use of the product.

Halosulfuron-methyl is registered in South Africa and in order to maintain the registration of their product containing halosulfuron-methyl, the halosulfuron-methyl Derogation Group is submitting a derogation for their water dispersible granule (WG/WDG) formulation products containing 750 g/kg halosulfuron-methyl. This derogation includes dietary and non-dietary human health risk assessments to demonstrate the safe use of these products. To support the derogation application and inform the human health risk assessments, a summary review of the toxicological profile of halosulfuron-methyl has been carried out, considering recent and relevant authoritative regulatory evaluations and the derivation of health-based reference values. Toxicological information has been sourced from evaluations conducted primarily by the European Union (EU) European Food Safety Authority (EFSA) and the European Chemicals Agency (ECHA).

The toxicology profile of halosulfuron-methyl has been comprehensively reviewed as part of authoritative regulatory evaluations undertaken in the EU by EFSA and ECHA. Assessments conducted by EFSA have incorporated hazard identification and characterisation to inform human health risk assessments, whereas ECHA and its Committee for Risk Assessment (RAC) exclusively identified human health hazards for risk management and communication purposes in the EU.

Halosulfuron-methyl has low acute toxicity via the oral, dermal and inhalation routes, is not irritating or corrosive to the skin or the eyes and is not sensitising to the skin. Halosulfuron-methyl is not genotoxic based on the findings of a standard battery of *in vitro* and *in vivo* studies, is not neurotoxic and is not considered as having endocrine disruption potential in any regulatory jurisdiction.

The most prominent effect observed upon repeated dose testing with halosulfuron-methyl upon short-term and long-term exposure was reduction of body weight gain in dogs, rats and mice. In dogs, which were the most sensitive species, changes in clinical chemistry, haematological parameters and liver weight were also observed. The relevant short-term NOAEL was 10 mg/kg bw/day from the 90-day and 1-year studies in dogs and the long-term NOAEL was 43.8 mg/kg/day from the 2-year rat study.

In the respective 2-year dietary studies in male and female rats and in a 78-week study in male and female mice, no oncogenic effects were observed indicating that halosulfuron-methyl is not carcinogenic.

Reproductive and developmental studies showed a higher sensitivity of the offspring to halosulfuron-methyl exposure than the adult animals. The offspring's NOAEL in the multigeneration reproduction toxicity study was 6.3 mg/kg bw/day based on reduced pup body weight gain, while the parental NOAEL was 50.4 mg/kg bw/day. In this study, no effect on fertility or reproduction was observed up to the highest dose level of 223.2 mg/kg bw/day. In the developmental toxicity study in rabbits, the maternal and developmental NOAELs were 50 mg/kg bw/day based on early resorptions, decreased number of foetuses and reduced maternal body weight gain. In the rat, foetal toxicity was observed in the absence of maternal toxicity: the developmental NOAEL was 75 mg/kg bw/day based on a higher incidence of visceral and skeletal variations and the maternal NOAEL was 250 mg/kg bw/day due to reduced body weight, body weight gain and food consumption.

In the EU, halosulfuron-methyl has been classified for reproduction toxicity in Category 1B, (Repr. 1B; H360D "May damage the unborn child") in accordance with the CLP Regulation – a hazard identification process intended for the communication of risk management measures throughout the chemical supply chain. Risk assessments conducted as part of the evaluation performed within the EU regulatory jurisdiction have included the relevant developmental hazard as part of the hazard characterisation.

Based on the review of the toxicological profile of halosulfuron-methyl, the critical human health effects have been adequately identified and characterised. The following health-based reference values are considered to be relevant to inform the dietary and non-dietary risk assessments for the water dispersible granule (WG) formulation products containing 750 g/kg halosulfuron-methyl and are sufficiently conservatively protective in respect of human health:

Reference endpoint	**Derived value**	**Source**	**Based on endpoint:**
ADI	**0.063 mg/kg bw/day**	EFSA (2012)	Based on a NOAEL of 6.3 mg/kg bw/day from a rat reproductive toxicity study (offspring toxicity), UF* = 100
ARfD	**0.5 mg/kg bw/day**	EFSA (2012)	Based on the NOAEL of 50 mg/kg bw/day from a rabbit developmental toxicity study (maternal toxicity), UF = 100
AOEL	**0.063 mg/kg bw/day**	EFSA (2012)	Based on a NOAEL of 6.3 mg/kg bw/day from a rat reproductive toxicity study (offspring toxicity), UF = 100 No correction for oral absorption required
AAOEL	Not required	-	-

*UF uncertainty factor – 100 = 10 (interspecies) x 10 (intraspecies)

2. Introduction

Halosulfuron-methyl (CAS No. 100784-20-1, EC No. 600-130-3) is a sulfonylurea post-emergence herbicide used to control broad-leaved weeds and sedges in a range of crops (maize, sorghum, wheat, sugarcane etc.). It is systemic and selective, and acts as an inhibitor of acetohydroxyacid synthase restricting the biosynthesis of the essential amino acids, valine and isoleucine, thus restricting plant growth.

In the Republic of South Africa regulatory jurisdiction, according to Regulation 8(1)(d) and 10(3)(e) respectively, the Registrar (Act 36 of 1947) may not grant or renew a registration after 1 June 2024 if a plant protection product contains substances of concern. In the European Union (EU), halosulfuron-methyl has been classified with respect to reproductive toxicity as Repr.1B (H360D "May damage the unborn child") in accordance with Regulation (EC) No. 1272/2008, and as such would be considered a substance of concern. However, in exceptional circumstances, the Registrar may grant a registration for a product (i.e.: an agricultural remedy) containing a substance of concern and the Applicant can submit a derogation to achieve this. According to Section 2.1 of the *"Guideline for the Application for a Derogation for an Agricultural Remedy Identified as a Substance of Concern"* issued by the Registrar (DALLRD, 2024),

"Before commencing an application for derogation of an agricultural remedy, the applicant must conduct a risk assessment to evaluate the risks associated with the use of the remedy according to the proposed uses for which a derogation is sought and determine whether the associated risks can be sufficiently mitigated."

The Halosulfuron-methyl Derogation Group comprising of: Farm-Ag International (Pty) Ltd, ICA International Chemicals (Pty) Ltd, UPL South Africa (Pty) Ltd, Sharda International Africa (Pty) Ltd, Villa Crop Protection (Pty) Ltd, Rainbow Agrosciences (Pty) Ltd and Green Island Investments Pty Ltd, is submitting a derogation for their water dispersible granule formulations (WG/WDG) containing 750 g/kg halosulfuron-methyl.

As part of the derogation, dietary and non-dietary human health risk assessments have been carried out to demonstrate the safe use of the products containing the active substance, halosulfuron-methyl. To support the derogation application and inform the human health risk assessment, this report provides a summary review of the toxicological profile of halosulfuron-methyl, considering recent and relevant authoritative regulatory evaluations, and the derivation of health-based reference values.

3. Regulatory evaluations of halosulfuron-methyl in Europe

Sections 4 and 5 of this report provide a summary of the toxicological profile of halosulfuron-methyl and the rationale for the derived health-based reference values, respectively, sourced from recent and relevant authoritative regulatory evaluations of the toxicological data for the substance (i.e.: for its approval as a plant protection product active substance and the consideration of associated risks to human health).

Halosulfuron-methyl has not been evaluated by the Joint Meeting on Pesticide Residues (JMPR), the expert *ad hoc* body administered jointly by the United Nations (UN) Food and Agriculture Organization (FAO) and the World Health Organization (WHO). Toxicological information has therefore been sourced primarily from evaluations conducted by the European Union (EU) European Food Safety Authority (EFSA) and the European Chemicals Agency (ECHA).

These evaluations, and the regulatory context are summarised in the sections below.

3.1. European Union (EU) – EFSA evaluation of halosulfuron-methyl as a pesticide active substance

In the EU, halosulfuron-methyl was evaluated as a new pesticide active substance in the framework of Council Directive 91/414/EEC with Italy being the designated Rapporteur Member State (RMS). The RMS provided its initial evaluation of the dossier on halosulfuron-methyl in the Draft Assessment Report (DAR), which was received by the EFSA on 30 March 2008. (DAR, 2011: Public version).

EFSA published its conclusion on the peer review of the risk assessment of halosulfuron-methyl in 2012 (EFSA, 2012) and it was approved in the EU as a new plant protection active substance in September 2013. It is noted that the 2012 EFSA conclusion indicated that halosulfuron-methyl required classification for reproduction toxicity in Category 2 (Repr. 2 H361fd, "Suspected of damaging the unborn child.")

Subsequently, in 2017, RAC issued their opinion that halosulfuron-methyl should be classified as toxic for reproduction in the more severe hazard category: Repro. 1B (H360D "May damage the unborn child"), in accordance with Regulation (EC) No 1272/2008 on the Classification, Labelling and Packaging of Substances and Mixtures (referred to as the "CLP Regulation"). This conclusion was based on the same data set initially submitted for the 2013 approval and only indicates a difference of interpretation from EFSA 2012.

An application for the renewal of halosulfuron-methyl as an active substance was submitted under Regulation (EC) No 1107/2009 in 2020 and is currently under evaluation by the RMS Italy.

In summary, the current regulatory status of halosulfuron-methyl in the EU is as follows: the substance is approved as an active substance and is currently under evaluation for renewal of approval. A Draft Renewal Assessment Report was prepared by the RMS, Italy in January 2023 and an overall decision on the approval of the renewal of halosulfuron-methyl is pending. The currently approved health-based reference values in the EU are therefore those indicated in the EFSA Conclusion 2012.

3.2. European Union (EU) – ECHA hazard identification and harmonised classification

Within the EU legislative framework, Regulation (EC) No. 1272/2008 on the Classification, Labelling and Packaging of Substances and Mixtures serves as a hazard identification process, with direct risk management consequences, to ensure that the hazards presented by chemical substances are clearly communicated to workers and consumers in the European Union, across the supply chain. As such, the CLP Regulation does not facilitate the assessment of exposures to the chemical substances, the characterisation of the hazards (i.e.: via health-based reference values) or the assessment of health risks.

With respect to human health hazards, at the time of the classification review, there were no existing harmonised classifications for halosulfuron-methyl. Following the public consultation and the assessment of the available evidence against the classification criteria, RAC included a new classification for reproductive toxicity: Repro. 1B, with the hazard statement H360D: *"May damage the unborn child"* in their Opinion, that was adopted in September 2017. This conclusion was based on the same data set initially submitted for the 2013 approval and only indicates a difference of interpretation between EFSA 2012 and ECHA 2017.

4. Halosulfuron-methyl: Summary of mammalian toxicity data

This section presents a summary of the mammalian toxicological profile of halosulfuron-methyl based on the conclusions of authoritative regulatory evaluations conducted by EFSA and ECHA respectively, as part of evaluations in the EU.

As the renewal of the approval of halosulfuron-methyl is still on-going in the EU, there is currently no EFSA conclusion pertaining to this evaluation. The Applicants dossier (redacted version 1, December 2020: available from OpenEFSA (https://open-efsa.europa.eu) indicates that the toxicological data package submitted for the renewal is in the main part comparable to that submitted during the first active substance approval. While some additional studies were submitted in line with the changes in the data requirements since the new active substance approval in Europe, the findings from these studies do not impact overall on the toxicological profile of the substance.

It is noted that during the renewal evaluation, the RMS has made some changes in the interpretation in the findings of some studies in the dataset (i.e.: different No-Observed-Adverse-Effect-Levels, NOAEL have been derived in some cases) and while these changes do not impact overall on the critical effects identified as the points of departure for setting reference values, these interpretations are currently tentative subject to agreement at the level. Hence, in the sections below, relevant toxicological data has been sourced primarily from the RMS Assessment Report (DAR) prepared during the new active substance evaluation (EU, 2011: Public version DAR) as the conclusions drawn from interpretation of this dataset have informed the currently agreed EU health-based reference values.

4.1. Absorption, distribution, metabolism and excretion.

EU – EFSA evaluation and conclusions, 2012.

EFSA concluded that based on toxicokinetic studies, halosulfuron-methyl is rapidly absorbed (with the highest concentrations reached 0.5 hours post-dosing) and has high bioavailability (>80% of dose, based on urinary and biliary excretion and residues in the carcass). There was no evidence for absorption saturation.

In toxicokinetic studies, halosulfuron-methyl was widely distributed to different organs and had a very low potential for accumulation (<1% of residues were detected 168 hours after dosing, independently of the treatment regime).

Halosulfuron-methyl was found to be rapidly and extensively excreted with >70% excreted via the urine within 12 hours or via the faeces within 48 hours. Overall, between 79-102% of the administered dose was found to be excreted within 7 days. Between 32-55% of the administered dose was excreted via the urine within 7 days and 29-40% of the administered dose was excreted via the bile within 38 hours.

Halosulfuron-methyl is extensively metabolised in animals: no parent compound was detected in urine and low amounts (0.6-7%) only were detected in the faeces. The major metabolic pathway involved the demethylation and hydroxylation of the pyrimidine moiety with a minor pathway (<3%) involving the cleavage between the pyrimidine and pyrazole moieties. The major metabolites were determined to be: demethyl halosulfuron-methyl (urine: 13.3-37.7%; faeces: 6.6-22.6%) and 5-hydroxy demethyl halosulfuron-methyl (urine: not detected-39.9%; faeces: 1.6-24.5%).

EFSA concluded that the toxicologically relevant compound in animals, plants and the environment was determined to be halosulfuron-methyl.

4.2. Acute toxicity

EU – EFSA evaluation and conclusions, 2012

The acute toxicity studies conducted using halosulfuron-methyl evaluated as part of the EU toxicological assessment included: respective acute oral toxicity studies in rats and in mice, an acute dermal toxicity study in rats, an acute, whole body inhalation exposure study, respective skin and eye irritation and corrosion studies in rabbits and a skin sensitisation study conducted using the guinea pig maximisation test. These studies are detailed in the 2011 DAR (EC, 2011) and are summarised in the table below.

Based on the evaluation of the acute toxicity dataset, EFSA concluded that halosulfuron-methyl has low acute toxicity when administered via the oral, dermal or inhalation routes. Halosulfuron-methyl was not irritating to the skin or the eyes and did not have potential for skin sensitisation based on a Magnusson and Klingman test. The critical endpoints for the acute toxicity of halosulfuron-methyl included in Appendix A of the 2012 EFSA conclusion are indicated in bold in the table below (EFSA, 2012).

At renewal, an additional phototoxicity study was submitted indicating that halosulfuron-methyl does not have any phototoxic potential (EC, 2022).

Table 4.1: Summary of acute toxicity studies using halosulfuron-methyl

STUDY	SPECIES/STRAIN AND DOSES	LD_{50}/LC_{50}	TARGET ORGAN/SIGNIFICANT EFFECTS/COMMENTS	REFERENCE/ STUDY NUMBER
Acute oral US EPA 81-1 (1984); JMAFF 59 NohSan no. 4200 (1985), GLP	Rat (Sprague Dawley; 10/sex/group) Dose levels: 4000, 5000, 7500,10000 mg/kg bw 14-day observation period	LD_{50} = 10,435 mg/kg bw (males); 7758 mg/kg bw (females) **Overall LD_{50} = 7758 mg/kg bw**	Low toxicity	EC, 2011, Anon. 1990a (IIA, 5.2.1.1) **EFSA Conclusion, 2012 (LoE)**
Acute oral US EPA 81-1 (1984); JMAFF 59 NohSan no. 4200 (1985), GLP	Mouse (CD-1; 10/sex/group) Dose levels: 4000, 5000, 7500,10000 mg/kg bw 14-day observation period	LD_{50} = 16, 156 mg/kg bw (males); 9295 mg/kg bw (females) **Overall LD_{50} = 9295 mg/kg bw**	Low toxicity	EC, 2011, Anon. 1990b (IIA, 5.2.1.2) **EFSA Conclusion, 2012 (LoE)**
Acute dermal US EPA 81-1 (1984); JMAFF 59 NohSan no. 4200 (1985), GLP	Rat (Sprague-Dawley; 10/sex/group) Dose: 2000 mg/kg bw (Limit dose) 14-day observation period	**LD_{50} = > 2000 mg/kg bw**	Low toxicity	EC 2011, Anon. 1990c (IIA, 5.2.2) **EFSA Conclusion, 2012 (LoE)**
Acute inhalation US EPA 81-3 (1984);	Rat (Sprague-Dawley; 5/sex/group)	**LC_{50} > 6.0 mg/L air/4 h (whole body)**	Low toxicity	EC, 2011, Anon. 1991 (IIA, 5.2.3)

STUDY	SPECIES/STRAIN AND DOSES	LD_{50}/LC_{50}	TARGET ORGAN/SIGNIFICANT EFFECTS/COMMENTS	REFERENCE/ STUDY NUMBER
JMAFF 59 NohSan no. 4200 (1985); EU 92/69/EEC, B.2 (1992); (OECD 403 (1981); GLP	4h whole body exposure to 6 mg/L MMAD approx.4.3 µm 14-day observation period			**EFSA Conclusion, 2012 (LoE)**
Skin irritation OECD 404 (1981), GLP	Rabbit (NZW, 6 males) 0.5g for 4 hours (semi-occlusive)	-	**Non-irritant**	EC 2011, Anon. 1990a (IIA, 5.2.4) **EFSA Conclusion, 2012 (LoE)**
Eye irritation OECD 405 (1987) GLP	Rabbit (NZW, 3 males) 0.1 mL	-	Mild, transient ocular irritation **Non-irritant**	EC 2011, Anon. 1991 (IIA, 5.2.5) **EFSA Conclusion, 2012 (LoE)**
Skin sensitisation (Magnusson and Klingman maximisation Test) OECD 406 (1981)	Guinea pigs (Dunkin-Harley, 10/sex/group)	-	**Non-sensitiser (Magnusson and Klingman test)**	EC, 2011, Anon 1990b (IIA, 5.2.6) **EFSA Conclusion, 2012 (LoE)**

Key: LoE – List of Endpoints, NZW – New Zealand White

4.3. Short-term toxicity

EU – EFSA evaluation and conclusions, 2012

The short-term oral toxicity studies conducted using halosulfuron-methyl evaluated as part of the EU toxicological assessment included: 28-day and 90-day repeated dose dietary toxicity studies in rats, a 90-day repeated dose and a 12-month capsule study in dogs and a 21-day repeated dermal study in rats. These studies are detailed in the 2011 DAR (EC, 2011) and are summarised in the table below.

Based on the evaluation of the available short-term, repeated dose toxicity studies conducted using halosulfuron-methyl, EFSA concluded that the prominent effect observed was the reduction of body weight gain in dogs, rats and mice. In dogs, considered to be the most sensitive species, changes in clinical chemistry, haematological parameters and liver weight were also observed. The relevant short-term NOAEL was determined to be 10 mg/kg bw/day from the 90-day and 1-year studies in dogs (EFSA, 2012).

Summary of studies from the 2011 DAR:

In a 28-day repeated dose, dietary study, Sprague-Dawley (10/sex/group) were administered halosulfuron-methyl at 0, 300, 1000, 3000 or 10000 ppm (corresponding to 0, 23, 78, 231 and 777 mg/kg bw/day in males and 0, 25, 85, 241 and 888 mg/kg bw/day in females).

In the study, body weight gain was reduced in both sexes treated at 10000 ppm and in females treated at 3000 ppm, with a corresponding significant reduction in food consumption. Some changes in clinical chemistry parameters (lower protein, albumin, globulin and glucose and higher chloride ion) were also recorded in females treated at and above 300 ppm. The main finding observed in the study was an increased incidence of individual cell degeneration/necrosis of pancreatic acinar cells at 3000 ppm and above. However, this effect was not found in any other repeated oral toxicity rat studies even at higher dose levels. A NOEL was not determined in the study as slight effects in clinical chemistry parameters were observed in females treated at the lowest dose of 300 ppm. The NOAEL for the study was determined to be 300 ppm (corresponding to 23 mg/kg bw/day in males and 25 mg/kg bw/day in females), based on the absence of any histopathological lesions at this dose level.

In a 90-day repeated dose, dietary study, Sprague-Dawley (20/sex/group) were administered halosulfuron-methyl at 0, 100, 400, 1600, or 6400 ppm (corresponding to 0, 7.4, 28.8, 116 and 497 mg/kg bw/day in males and 0, 8.9, 37.3, 147and 640 mg/kg bw/day in females). In the study, body weight gain was reduced at 6400 ppm of halosulfuron-methyl, the highest dose level. Reductions in cholesterol (37% in males and 29% in females) and in total bilirubin (46% in males and 26% in females) as well as increased pigmentation of the renal tubular epithelium due to haemosiderin deposition and mild vacuolation in the liver were also seen at this dose level. Increased haemosiderin pigmentation of the kidney tubules was observed also at 1600 ppm. Since the increased haemosiderin pigmentation of kidney tubules was the only effect seen at 1600 ppm, was not statistically significant and not associated with any other toxic effect, the NOAEL for the study was determined to be 1600 ppm (corresponding to 116 and 147 mg/kg bw/day of halosulfuron-methyl in males and females, respectively). The NOEL was determined to be 400 ppm (28.8 mg/kg bw/day in males and 37.3 mg/kg bw/day in females).

In a 90-day capsular study, Beagle dogs (4/sex/group) were administered halosulfuron-methyl at 0, 2.5, 10, 40 or 160 mg/kg bw/day. In the study, halosulfuron-methyl administered at 40 or 160 mg/kg bw/day reduced body weight gain and increased liver weight. The highest dose level, 160 mg/kg bw/day, induced a variety of haematological and clinical chemistry changes including: a decrease in red cell parameters (erythrocyte and packed cell volume) for females, a decrease in total white cell counts and a shift towards myeloid cells in the bone marrow of males, and a reduction in cholesterol levels. The NOAEL for the study was determined to be 10 mg/kg bw/day.

In a 12-month capsule study, Beagle dogs (4/sex/group) were administered halosulfuron-methyl at 0, 0.25, 1, 10 or 40 mg/kg/day. In the study, doses at and above 40 mg/kg bw/day reduced haematological parameters. The mean body weight gain of males given 10 and 40 mg/kg/day was reduced for the first 16 weeks of treatment although statistical significance was not attained and body weight was unaffected at study termination. Based on haematological changes observed in both sexes at 40 mg/kg/day, the NOAEL for the study was determined to be 10 mg/kg/day; the NOEL was 1 mg/kg bw/day.

In a 21-day dermal study, Sprague-Dawley (5/sex/group) were treated with halosulfuron-methyl at 0, 10, 100 or 1000 mg/kg bw/day. In the study, there was no evidence of irritation at the treated skin sites; at the highest dose a reduction in body weight gain was observed and a statistically significant increase in haemoglobin and haematocrit values in males treated with

100 or 1000 mg/kg bw/day was observed. The NOEL for the study was determined to be 10 mg/kg bw/day.

EFSA Conclusion, 2012: Appendix 2, List of Endpoints

The critical effects associated with the short-term toxicity of halosulfuron-methyl were considered to be: reduced body weight gain, liver effects and haematological changes in the dog and in the rat and increased haemosiderin pigmentation in the renal tubular epithelium in the rat. The following NOAELs were agreed for the short-term toxicity of halosulfuron-methyl:

Relevant oral NOAEL (Short-term toxicity): 90-day and 1-year, dog: 10 mg/kg bw/day; 90-day, rat: 116 mg/kg bw/day.

Relevant dermal NOAEL (Short-term toxicity): 21-day, rat: 100 mg/kg bw/day.

Relevant inhalation NOAEL (Short-term toxicity): Not required.

Table 4.2: Summary of short-term toxicity studies using halosulfuron-methyl

STUDY	SPECIES/STRAIN AND DOSES	NOAEL	TARGET ORGAN/SIGNIFICANT EFFECTS/COMMENTS	REFERENCE/ STUDY NUMBER
Rat 28-day oral (dietary) US EPA 40 CFR 158.135; JMAFF 59 NohSan no. 4200 (1985), GLP	Sprague-Dawley (10/sex/group) 0, 300, 1000, 3000, 10000 ppm (Males: 0, 23, 78, 231 and 777 mg/kg/day; Females: 0, 25, 85, 241 and 888 mg/kg/day) (purity: 98.5%)	NOAEL: 300 ppm (Males: 23 mg/kg/day Females: 25 mg/kg/day)	LOEL: 1000 ppm (Males 78 mg/kg/day Females: 85 mg/kg/day) Reduced body weight gain and overall food consumption, some clinical chemistry changes. At higher doses degeneration/necrosis of pancreatic acinar cells	EC 2011, Anon. 1988 (IIA, 5.3.1)
Rat 90-day oral (dietary) US EPA FIFRA 82-1 (1984); JMAFF 59 NohSan no. 4200 (1985). GLP	Sprague-Dawley (20/sex/group) 0, 100, 400, 1600, 6400 ppm (Males: 0, 7.4, 28.8, 116 and 497 mg/kg/day; Females: 0, 8.9, 37.3, 147 and 640 mg/kg/day) (purity: 98.6%)	NOAEL: 1600 ppm (Males: 116 mg/kg bw/day; Females: 147 mg/kg bw/day) NOEL: 400 ppm (Males: 28.8 mg/kg/day; Females: 37.3 mg/kg bw/day	LOEL: 6400 ppm Males: 497 mg/kg bw/day Females: 640 mg/kg bw/day) Reductions in: body weight gain, cholesterol, total bilirubin; increased (haemosiderin) pigmentation of renal tubular epithelium; mild vacuolation in the liver	EC 2011, Anon. 1990 (IIA, 5.3.2)
Dog 90-day oral (capsule) Similar to OECD 409, GLP	Beagle (4/sex/group) 0, 2.5, 10, 40 and 160 mg/kg/day (purity: 98.5%)	NOEL: 10 mg/kg/day	LOEL: 40 mg/kg/day Reduced body weight gain; increased liver weight and clinical chemistry alterations	EC 2011, Anon. 1991 (IIA, 5.3.3)
Dog 12-month oral (capsule) US EPA FIFRA 83-1 (1984); JMAFF	Beagle (6/sex/group) 0, 0.25, 1, 10 and 40 mg/kg/day (purity: 98.7%)	NOAEL: 10 mg/kg bw/day NOEL: 1 mg/kg/day	LOEL: 40 mg/kg/day Haematological changes (increased mean haemoglobin and haematocrit)	EC 2011, Anon 1991 (IIA, 5.3.4)

STUDY	SPECIES/STRAIN AND DOSES	NOAEL	TARGET ORGAN/SIGNIFICANT EFFECTS/COMMENTS	REFERENCE/ STUDY NUMBER
NohSan no. 4200 (1985). GLP				
Rat 21-day Dermal US EPA FIFRA 82-2 (1984). GLP	Sprague-Dawley (5/sex/group) 0, 10, 100, 1000 mg/kg/day (purity: 99.1%)	NOEL: 10 mg/kg/day	LOEL: 100 mg/kg/day Haematological changes (reduced body weight gain at higher doses)	EC 2011, Anon. 1991 (IIA, 5.3.7)

4.4. Genotoxicity

EU – EFSA evaluation and conclusions, 2012

As part of the EU toxicological assessment, the mutagenic potential of halosulfuron-methyl was evaluated in a regulatory battery of genotoxicity tests comprising: *in vitro* tests for bacterial and mammalian cell gene mutation, and chromosome aberrations and for unscheduled DNA, and an *in vivo* mouse micronucleus test for chromosome damage. These studies are detailed in the 2011 DAR (EC, 2011) and are summarised in the table below.

All the available *in vitro* and *in vivo* genotoxicity studies gave negative results, where applicable, in the presence and in the absence of a metabolic activation system, therefore, during the EU evaluation, EFSA concluded that halosulfuron-methyl did not have any genotoxic potential.

Table 4.3: Summary of genotoxicity studies using halosulfuron-methyl

STUDY	SPECIES/STRAIN AND DOSES	RESULTS	REFERENCE/STUDY NUMBER
***In vitro* studies**			
Bacterial reverse mutation US EPA FIFRA 84-2 (1984), GLP	*Salmonella typhimurium:* (TA1535, TA1537, TA1538, TA98 and TA100) *Escherichia coli:* WP2 uvrA First test: -/+ S9 mix: 1, 10, 100, 500, 100, 2500, 5001 and 10002 µg/plate (S. typhimurium) 333, 667, 1000, 3330, 6670 and 10000 µg/plate (E. coli) Second test: -/+ S9 mix: 1, 10, 100, 500, 1000, 2500, 5000, and 9999 µg/plate (S. typhimurium) 333, 667, 1000, 3330, 6670 and 10000 µg/plate (E. coli)	Negative +/- S9 mix	EC 2011, Jagannath and Lawlor, 1988 (IIA, 5.4.1)
Chromosome aberrations (clastogenicity) US EPA FIFRA 84-2 (1984), GLP	Chinese hamster ovary cells -S9 mix: 451, 903, 1020, 1050 and 1810 µg/ml +S9 mix: 449, 899, 1350 and 1800 µg/ml	Negative +/- S9 mix	EC 2011, Muri, 1988 (IIA, 5.4.2)
Mammalian cell gene mutation	Chinese hamster ovary cells (HGPRT assay)	Negative +/- S9 mix	EC 2011, Stegeman *et al.*, 1993 (IIA, 5.4.3)

STUDY	SPECIES/STRAIN AND DOSES	RESULTS	REFERENCE/STUDY NUMBER
***In vitro* studies**			
US EPA FIFRA 84-2 (1984), GLP	First test: -/+ S9 mix: 100, 200, 500, 700 and 900 µg/ml *Second test:* -/+ S9 mix: 50, 100, 200, 500 and 700 µg/ml		
Unscheduled DNA Synthesis US EPA FIFRA 84-2 (1984), GLP	Rat primary hepatocytes Trial 1: 25, 50, 100, 250, 500 and 1000 µg/ml Trial 3: 5.06, 10.1, 25.3, 50.6, 101 and 253 µg/ml	Negative	EC, 2011, Cifone, 1988 (IIA, 5.4.7)
***In vivo* studies**			
Micronucleus test US EPA FIFRA 84-2 (1984), GLP	Male and female ICR mice (5/sex/group) Bone marrow erythrocytes Doses: 0, 500, 1667 and 5000 mg/kg	Negative (no clastogenic or aneugenic potential	EC, 2011, Anon. 1989 (IIA, 5.4.4)

4.5. Chronic toxicity and oncogenicity

EU – EFSA and conclusions, 2012

The long-term toxicity and carcinogenicity studies conducted using halosulfuron-methyl evaluated as part of the EU toxicological assessment included: a 2-year combined chronic toxicity and carcinogenicity dietary feeding study in male and female Sprague-Dawley rats and a 78-week dietary feeding oncogenicity study in male and female CD-1 mice. These studies are detailed in the 2011 DAR (EC, 2011) and are summarised in the table below.

Based on the evaluation of long-term, repeated dose toxicity studies conducted using halosulfuron-methyl, EFSA concluded that the prominent effect observed was the reduction of body weight gain in rats and mice. The relevant long-term NOAEL was determined to be 43.8 mg/kg bw/day from the 2-year rat study.

No carcinogenic potential was observed in either rats or mice.

Summary of studies from the 2011 DAR

In a 104-week dietary combined chronic toxicity and oncogenicity study, Sprague-Dawley rats (85/sex/group) were administered halosulfuron-methyl at 0, 10, 100, 1000, 2500 or 5000 ppm in the male groups (corresponding to 0, 0.44, 4.4, 43.8, 108.3 or 225.2 mg/kg bw/day) and 0, 10, 100, 1000 or 2500 ppm in the female groups (corresponding to 0, 0.56, 5.6, 56.3 or 138.6 mg/kg bw/day). The critical effects in the study were reduced mean body weights observed throughout the study in males treated at 5000 ppm and between weeks 13 and 52 in females treated at 2500 ppm. The NOAEL for chronic toxicity (i.e.: non neoplastic end-points) was determined to be 1000 ppm, based on body weight reduction seen in females, corresponding to 56.3 mg/kg bw/day halosulfuron-methyl.

There was no evidence of oncogenic activity at any dose level. The respective NOAELs for oncogenicity was therefore determined to be: 5000 ppm in males and 2500 ppm in females, corresponding to 225.2 and 138.6 mg/kg bw/day of halosulfuron-methyl respectively.

In a 78-week dietary feeding oncogenicity study, CD-1 mice (75/sex/group) were administered halosulfuron-methyl at 0, 30, 300, 3000 or 7000 ppm (corresponding to 0, 4, 41.1, 410.0 or 971.9 mg/kg bw/day in males and 0, 5.2, 51.0, 509.1 or 1214.6 mg/kg bw/day in females).

In male mice treated at 7000 ppm, body weight gain was significantly reduced over weeks 0 to 13, whilst mean body weight was significantly reduced at weeks 4, 13 and 24. Furthermore, there were increased incidences of microconcentrations/mineralisation within the lumen of both the epididymal and testis tubules (epididymis: 5/44 compared with 0/40 in controls; testis 12/63 compared with 5/70 in controls). On the basis of these results observed in males treated at the highest dose, the NOAEL for the chronic toxicity (i.e.: non neoplastic end-points) of halosulfuron-methyl was determined to be 3000 ppm, corresponding to a mean achieved daily intake of 410.0 mg/kg bw/day.

No carcinogenic effects were observed in the study. The NOEL for oncogenicity was therefore determined to be 7000 ppm, corresponding to mean achieved daily intakes of 971.9 and 1214.6 mg/kg bw/day of halosulfuron-methyl in males and females, respectively i.e.: the highest dose tested.

EFSA Conclusion, 2012: Appendix A, List of Endpoints

The critical effects associated with the long-term toxicity of halosulfuron-methyl were considered to be: reduced body weight gain in rats and in mice, and increased microconcretions/mineralisation in the testis and epididymal tubules in mice. The following NOAELs were concluded for the long-term toxicity of halosulfuron-methyl:

Relevant NOAEL (Long-term toxicity): 43.8 mg/kg bw/day; 2-year, rat; 410 mg/kg bw/day; 18-month, mouse.

It was concluded that halosulfuron-methyl did not have carcinogenic potential.

Table 4.4: Summary of chronic toxicity and oncogenicity studies using halosulfuron-methyl

STUDY	SPECIES/ STRAIN AND DOSES	NOAEL	TARGET ORGAN/SIGNIFICANT EFFECTS/COMMENTS	REFERENCE/ STUDY NUMBER
Rat 2-year combined chronic toxicity and carcinogenicity study (dietary) US EPA 83-5 (1984); JMAFF 59 NohSan No. 4200 (1985), GLP	Sprague-Dawley (85/sex/group) **Males**: 0, 10, 100, 1000, 2500 and 5000 ppm (0, 0.44, 4.4, 43.8, 108.3, 225.2 mg/kg/day) **Females**: 0, 10, 100, 1000 and 2500 ppm (0, 0.56, 5.6, 56.3, 138.6 mg/kg/day) (Purity: 98.7%)	**Chronic toxicity:** NOEL: 1000 ppm = 56.3 mg/kg/day (Females:) **Carcinogenicity:** NOEL: Males: 5000 ppm Females: 2500 ppm (Males: 225.2 mg/kg/day Females: 138.6 mg/kg/day)	**Chronic toxicity:** LOEL: 2500 ppm=138.6 mg/kg/day (Females) Critical effect: reduced body weight gain **Carcinogenicity:** LOEL: Males: 5000 ppm Females: 2500 ppm (Males: 225.2 mg/kg/day Females: 138.6 mg/kg/day	EC 2011, Anon. 1992a (IIA, 5.5.1-5.5.2)

STUDY	SPECIES/ STRAIN AND DOSES	NOAEL	TARGET ORGAN/SIGNIFICANT EFFECTS/COMMENTS	REFERENCE/ STUDY NUMBER
			No carcinogenic potential at any dose level	
Mouse dietary 78-week oncogenicity study US EPA 83-5 (1984); JMAFF 59 NohSan No. 4200 (1985), GLP	CD-1 (75/sex/group) 0, 30, 300, 3000 and 7000 ppm (Males: 0, 4, 41.1, 410.0 and 971.9 mg/kg/day; Females: 0, 5.2, 51.0, 509.1 and 1214.6 mg/kg/day) (Purity: 98.7%)	**Chronic toxicity** NOAEL: 3000 ppm=410.0 mg/kg/day (Males) **Carcinogenicity:** NOEL: 7000 ppm (Males: 971.9 mg/kg/day Females: 1214.6 mg/kg/day)	**Chronic toxicity** LOAEL: 7000 ppm=971.9 mg/kg/day (Males) Critical effect: Reduced male body weight gain, increased microconcretions/ mineralisation in testis and epididymal tubules. **Carcinogenicity:** LOEL: 7000 ppm (Males: 971.9 mg/kg/day Females: 1214.6 mg/kg/day) No carcinogenic potential at any dose level	EC 2011, Anon. 1992b (IIA, 5.5.3)

4.6. Reproduction toxicity – Effects on fertility and sexual function

EU – EFSA and conclusions, 2012

The reproduction toxicity studies conducted using halosulfuron-methyl evaluated as part of the EU toxicological assessment included: a dietary two-generation reproduction toxicity study conducted in rats (with one litter in the first generation and two litters in the second generation. This study is detailed in the 2011 DAR (EC, 2011) and is summarised in the table below.

Summary of studies from the DAR, 2011

In a two-generation reproduction toxicity study, Sprague-Dawley rats (26/sex/group) were administered halosulfuron-methyl via the diet at 0, 100, 800 or 3600 ppm in two successive generations (corresponding to: 0, 6.3, 50.4, 223.2 mg/kg bw/day in F0 males and 0, 7.4, 61.0 or 274.2 mg/kg bw/day in F1 males; 0, 7.4, 58.7 or 261.4 mg/kg bw/day in F0 females and 0, 8.9, 69.7 or 319.9 mg/kg bw/day in F1 females.

In the study, reduced parental and pup body weights and/or body weight gains and parental food consumption were observed in both generations treated with halosulfuron-methyl at 3600 ppm. Overall, body weight gain was generally unaffected. There were no effects on fertility, reproductive performance or pup survival at any dose level. The NOAEL for general toxicity was determined to be 800 ppm, corresponding to mean achieved intakes of 50.4 mg/kg bw/day in males and 58.7 mg/kg bw/day in females. The NOAEL for effects on reproduction and fertility was 223.3 mg/kg bw/day i.e. the highest dose tested. The NOAEL for developmental

effects was determined to be 6.3 mg/kg bw/day based on decreased pup bodyweight gain at 800 ppm.

EFSA Conclusion, 2012: Appendix A, List of Endpoints

The critical effects for the reproduction toxicity of halosulfuron-methyl were concluded to be: reduced parental body weight and body weight gain and reduced pup body weight gain in the F1, F2a and F2b generation offspring. No adverse effects on reproduction or on fertility were observed. The following NOAELs were concluded for the reproductive and the developmental toxicity of halosulfuron-methyl:

Relevant parental NOAEL: 50.4 mg/kg bw/day

Relevant reproduction NOAEL: 223.2 mg/kg bw/day (the highest dose tested)

Relevant offspring NOAEL: 6.3 mg/kg bw/day

RAC Evaluation of reproductive toxicity – Effects on fertility and sexual function, 2017

The findings from the two-generation reproductive toxicity study were additionally evaluated in the consideration of the harmonised classification and labelling for halosulfuron-methyl in accordance with the CLP Regulation. On the basis that there were no treatment-related adverse effects on fertility or on reproductive performance in the study, including pre-coital interval at doses up to 3600 ppm in the study, the Dossier Submitter (DS), Italy concluded that no classification for adverse effects on sexual function and fertility was warranted.

In their assessment of the study, the RAC noted some inconsistencies associated with reduced pregnancy rates and numbers of dams with litters but did not consider these effects to be treatment-related. Both F1 matings showed reduced pregnancy rates without a clear dose response. The pregnancy rates increased with the dose in F0 matings (65%, 81%, 92% and 92% at 0, 100, 800 and 3600 ppm), but the very low control in the F0 mating was considered to reduce the confidence in this effect. Overall, the evidence of reduced pregnancy rates was not considered by the RAC to be sufficiently robust to propose classification for fertility. In addition, the RAC noted that there was no evidence of a reduction in the number of pregnant females or in the mean number of offspring born per litter.

Based on the available data and its interpretation, the RAC agreed with the DS's assessment that no classification for adverse effects on sexual function and fertility was warranted (ECHA, 2017).

Regarding effects on or via lactation, in the rat 2-generation study, pup weights were not affected by treatment on day 0 of lactation following continual gestational exposure and there was no developmental delay on growth rate. However, F1 pup weights on subsequent days of lactation (days 7-21) were significantly different to controls at dam dose levels of 88.1 (800 ppm) and 429 mg/kg bw/day (3600 ppm). The effects observed in F2a and F2b pups were considered not to be consistent or biologically significant. Overall, the RAC agreed with the DS that the evidence for these effects were equivocal and classification for effects on or via lactation was not warranted.

Table 4.5: Summary of reproduction toxicity studies (effects on fertility and sexual function) using halosulfuron-methyl

STUDY	SPECIES/ STRAIN AND DOSES	NOAEL	TARGET ORGAN/SIGNIFICANT EFFECTS/COMMENTS	REFERENCE/ STUDY NUMBER
Two-generation (dietary) US EPA Guideline 83-4 (1984) JMAFF 59 NohSan No. 3850 (1984)	Rat (Sprague-Dawley Crl:CD BR; 26/sex/group) 0, 100, 800 and 3600 ppm (F0 males: 0, 6.3, 50.4, 223.2 mg/kg/day; F1 males: 0, 7.4, 61.0, 274.2 mg/kg/day; F0 females: 0, 7.4, 58.7, 261.4 mg/kg/day; F1 females: 0, 8.9, 69.7, 319.9 mg/kg/day)	NOAEL: General toxicity: 800 ppm (Males: 50.4 mg/kg/day Females: 58.7 mg/kg/day) Reproductive toxicity: 100 ppm (Males: 6.3 mg/kg/day; Females: 7.4-11.8 mg/kg/day) **EFSA Conclusion, 2012: NOAEL: Offspring: 100 ppm (males 6.3 mg/kg bw/day)**	LOAEL: General toxicity: 3600 ppm Reproductive toxicity: marginal LOAEL of 100 ppm (corresponding to 6.3 mg/kg/day for males and 7.4-11.8 mg/kg/day for females)	EC 2011, Anon. 1991 (IIA, 5.6.1)

4.7. Reproduction toxicity - Developmental effects

EU – EFSA evaluation and conclusions (2012)

The developmental toxicity studies conducted using halosulfuron-methyl evaluated as part of the EU toxicological assessment included: respective pre-natal, embryofoetal toxicity studies conducted in rats and in rabbits. These studies are detailed in the 2011 DAR (EC, 2011) and are summarised in the table below.

Summary of studies from the 2011 DAR

In a pre-natal developmental toxicity study, CD Crl:CD BR rats (25 females/group) were administered halosulfuron-methyl via oral gavage at 0, 75, 250 or 750 mg/kg bw/day from gestation day (GD) 6 to 15. In the study, the administration of halosulfuron-methyl at 750 mg/kg bw/day was maternally toxic causing clinical signs (alopecia and stained fur), reduced body weight and body weight gain. Developmental toxicity at this dose level was evidenced as a slight increase in early embryonic resorptions, reduced foetal weight, dilatation of the brain ventricles and reduced ossification. There was no indication of teratogenicity. The NOEL for maternal effects was determined to be 250 mg/kg bw/day. The NOEL for developmental toxicity was determined to be 75 mg/kg bw/day based on an increased number of foetuses and litters with soft tissue variations and less than 4 caudal vertebrae ossified observed in rats treated at 250 and at 750 mg/kg bw/day.

In the corresponding rabbit pre-natal developmental toxicity study, New Zealand White rabbits (17 females/group) were administered halosulfuron-methyl via oral gavage at 0, 15, 50 or 150 mg/kg bw/day from GD 7 to 19. In the study, maternal body weight was reduced at the highest dose level, 150 mg/kg bw/day. Embryofoetal toxicity was evidenced as an increased incidence of early resorptions. No indication of teratogenicity was found.

The NOEL for maternal toxicity was determined to be 50 mg/kg bw/day. The NOEL for developmental toxicity was not defined due to the increased mean early resorptions (15.3%, 10.0%, 24.4% vs 9.7% in controls) and decreased number of foetuses (21.3%, 16.0%, 19.2% less than controls) observed at the 15, 50 and 150 mg/kg/day dose levels respectively. A marginal developmental LOEL of 15 mg/kg bw/day was defined.

EFSA Conclusion, 2012: Appendix A, List of Endpoints.

The critical effects for the developmental toxicity of halosulfuron methyl in rats were concluded to be: decreased maternal body weight/body weight gain and reduced food consumption and an increased number of foetuses and litters with visceral and skeletal variations. The following NOAELs were agreed during the EU evaluation:

Relevant maternal NOAEL (rat): 250 mg/kg bw/day

Relevant developmental NOAEL (rat): 75 mg/kg bw/day

The critical effects for the developmental toxicity of halosulfuron methyl in rabbits were concluded to be decreased maternal body weight/body weight gain and the increased in mean early resorptions and decreased number of foetuses. The following NOAELs were agreed during the EU evaluation:

Relevant maternal NOAEL (rabbit): 50 mg/kg bw/day

Relevant developmental NOAEL (rabbit): 50 mg/kg bw/day

Based on the findings of the developmental toxicity studies in rats and in rabbits, EFSA concluded that halosulfuron methyl meets the criteria for classification as reproduction toxicity in Category 2 (Repro. 2 H361fd). It was considered that the findings warranted consideration in respect of hazard classification for reproductive toxicity: the harmonised classification of halosulfuron-methyl was subsequently discussed by the ECHA RAC in the context of the human health hazard criteria indicated in the CLP Regulation (as discussed below).

EU - RAC Evaluation of developmental toxicity, 2017

The RAC evaluated the findings of the 2-generation reproduction study and the respective rat and rabbit developmental toxicity studies against the criteria indicated in the CLP Regulation:

"Categories 1B and 2 are reserved for presumed and suspected human reproductive toxicants, respectively, and shall be based on the presence of clear (Category 1B) or some (Category 2) evidence of an adverse effect on sexual function and fertility and/or on development. In addition, the evidence for both hazard categories shall be present in the absence of other toxic effects or if occurring together with other toxic effects, the adverse effect on reproduction is considered not to be a secondary non-specific consequence of the other concurrent toxic effects." (ECHA, 2017).

In their consideration of the findings in the rat 2-generation study (EC 2011, Anon. 1991 (IIA, 5.6.1), the RAC concluded there were no treatment-related adverse effects on development at doses up to 3600 ppm: the pup live birth index, litter size, pup viability (survival) and sex ratio were unaffected by treatment. There were no treatment-related clinical signs in the pups, and necropsy and histopathology did not show any treatment-related effects.

The RAC considered the following evidence for developmental effects associated with halosulfuron-methyl observed in the respective rat (Morseth, 1990a; EC 2011, Anon. 1990a (IIA, 5.6.10)) and rabbit (Morseth, 1990b; EC 2007, Anon. 1990b (IIA, 5.6.11)) developmental studies (ECHA, 2017):

1. Delayed development: there was a dramatic and statistically significant reduction in rat foetal body weight in both sexes:

i. Males: 3.4 ± 0.3 vs 2.6 ± 0.3 g, controls vs. high dose (-24%)

ii. Females: 3.2 ± 0.4 vs 2.5 ± 0.3 g, controls vs. high dose (-22%)

2. Delayed development: there was an extensive and widespread increase in rat skeletal variations:

i. (skeletal - total variations: 105/23 – 115/25 – 114/23 – 146/22)

3. Malformations: there was evidence for increased rat external, skeletal and visceral malformations (foetuses/litters)

i. External – tail: 0/0 – 0/0 – 0/0 – 4/3

ii. Skeletal – forked / fused ribs: 0/0 – 0/0 – 0/0 – 2/2

iii. Visceral – heart / great vessel: 0/0 – 0/0 – 0/0 – 2/2

4. There was an increase in mean rat early resorptions and post-implantation loss

i. resorptions: 1.0 vs. 1.5 (controls vs. high dose) [HCD: 0.3–1.5]

ii. post-implantation loss: 6.9% vs. 10.1% (controls vs. high dose) [HCD: 2.9–13.6%]

5. There was a reduction in rabbit mean live litter size at the high dose:

i. foetuses per litter: 7.2 – 7.4 – 7.2 – 5.8

6. There was a substantial increase in rabbit early resorptions and post-implantation loss:

i. resorptions: 0.8 vs. 2.0 (controls vs. high dose) [HCD: 0.1–1.0]

ii. post-implantation loss: 12.2% vs. 31.5% (controls vs. high dose) [HCD: 2.4–23%]

7. There was evidence of increased rabbit skeletal malformations:

i. skeletal – forked / fused ribs: 1/1 – 0/0 – 0/0 – 4/4

While the developmental toxicity was limited in both rats and rabbits to a single (high) dose group only in each study with no dose response observed at lower doses, the RAC concluded that potency, considered in isolation, was not a factor that should be considered in categorisation for reproductive toxicity. Although the reductions in foetal body weight were seen in only one study and species (i.e.: the rat), the RAC noted that the changes were statistically significant, outside the historical control data (HCD) range and associated with skeletal variations. The increase in rat external, skeletal and visceral variations and a very extensive and biologically significant delayed development of the skeletal system was observed at the top dose level of 750 mg/kg bw/day and in a few cases at 250 mg/kg bw/day (in this case maturation delay without any effect from maternal toxicity or foetal body weight reductions). There was also a high incidence of lateral ventricle dilatation at the high dose.

The RAC did not consider the adverse effects on development observed in the respective rat and rabbit studies to be secondary non-specific consequences of maternal toxicity. In the rabbit developmental study, the increase in post-implantation loss at high dose was accompanied by a marked retardation of uncorrected maternal body weight gain during the dosing period, but the body weight data was highly variable and the weight change differed significantly depending on the gestational interval under the study. According to the CLP criteria, the body weight gain in rabbits was not considered be a useful indicator of maternal toxicity because of normal fluctuations in body weight during pregnancy. In addition, there were no clinical signs

of toxicity during the dosing period. Overall, the RAC concluded that the maternal body weight data was equivocal in rabbits and there was insufficient maternal toxicity to explain the degree of severity of the effects at the high dose. In addition, halosulfuron-methyl induced early resorptions impacting the post-implantation losses were also observed in rats in the presence of only minimal maternal toxicity. Although these effects were not statistically significant in either species, the incidences were above the concurrent control values and HCD in rabbits and above the concurrent control values in rats. Based on these considerations, the effects were considered biologically significant by the RAC.

Although the incidences of malformations at the high dose group of the rat study were considered to be low, the RAC considered that the increased rat external, skeletal and visceral malformations were severe effects and toxicologically significant and relevant since the incidences were higher than in concurrent controls and above the very low HCD. The HCD showed that tail malformations in rats were rare malformations with a range of 0 to 1 foetus in any single study and only 1 foetus affected out of 3787 from 12 studies, equivalent to a 0.03% foetal incidence. In the study by Morseth (1990a), 4 rat foetuses (1.4% foetal incidence) had tail malformations in the high dose group only. In addition, the increased rabbit skeletal malformations at the top dose level of 150 mg/kg bw/day were not considered to be common findings as the HCD showed forked/fused rib malformations with a range of 0 to 3 foetuses in any single study and only 8 foetuses affected out of 947 from 9 studies, equivalent to a 0.8% foetal incidence. In the study by Morseth (1990b), 4 rabbit foetuses (1.4% foetal incidence) from 4 litters had forked/fused ribs in the high dose compared to 1 rabbit foetus in the control group. These findings were considered to support similar effects observed in rats.

In the assessment of developmental toxicity, the RAC also evaluated the results of a single low dose (5 mg/kg bw/day) oral gavage autoradiography study with pregnant rats, which was not considered to provide a convincing argument against the trans-placental transfer of the active substance (McCarthy, 1991b - The autoradiography, disposition in tissues and biliary excretion of NC-319 in male and female rats). Without data of concomitant plasma levels of substance in both maternal and foetal blood, it was not possible for RAC to determine the relationship between the observed findings. Consequently, the toxicokinetics of the substance in the foetus and the amount actually present in the foetal blood stream were considered to be unknown, although it was assumed there would be very little restriction to the movement of the substance across the placenta for higher dosed pregnant females.

In the consideration of the available data, the RAC concluded that there was sufficient evidence of a substance-mediated effect. The development of rat foetuses was impaired at high dose levels and rat foetal body weight was dramatically reduced. There was a biologically significant increase in early resorptions which impacted on the rat post-implantation loss and this effect was also noted in the rabbit developmental study. Several widespread developmental variations were observed and there were indications of malformations in both rats and rabbits. The RAC could not exclude a direct effect on the developing foetus, as the maternal toxicity was considered insufficient to explain the degree of severity of the effects observed in the foetuses from high dose dams.

Overall, the RAC concluded that there was clear evidence for adverse effects on development in the absence of excessive maternal toxicity, observed in both rats and rabbits with significant severity of findings in the offspring to warrant classification for development. The RAC adopted the opinion that classification with Repr. 1B – H360D “May damage the unborn child” was the most appropriate classification.

Table 4.6: Summary of reproduction toxicity studies (effects on development) using halosulfuron-methyl

STUDY	SPECIES/ STRAIN AND DOSES	NOAEL	TARGET ORGAN/SIGNIFICANT EFFECTS/COMMENTS	REFERENCE/ STUDY NUMBER
Developmental toxicity (oral gavage) US EPA FIFRA 83-3 (1984), GLP	Rat (CD Crl:CD BR; 25 females/group 0, 75, 250 and 750 mg/kg/day (GD 6 to 15)	NOEL: Maternal toxicity: 250 mg/kg/day Developmental toxicity: 75 mg/kg/day	LOEL: Maternal: 750 mg/kg/day Based on clinical signs, reduced maternal and foetal body weight, slight increase in early embryonic resorptions, dilated brain ventricles and reduced ossification Developmental: Increased number of foetuses and litters with soft tissue variations and less than 4 caudal vertebrae ossified at 250 and 750 mg/kg	EC 2011, Anon. 1990a (IIA, 5.6.10)
Developmental toxicity (oral gavage) US EPA 83-3 (1984), GLP	Rabbit (NZW, 17 females/group) 0, 15, 50 and 150 mg/kg/day (GD 7 to 19)	NOEL: Maternal toxicity: 50 mg/kg/day Developmental toxicity: not defined due to the increased mean early resorptions (15.3%, 10.0%, 24.4% vs 9.7% in controls) and decreased number of foetuses (21.3%, 16.0%, 19.2% less than controls) at 15, 50 and 150 mg/kg/day.	LOEL: Maternal: 150 mg/kg/day Based on reduced maternal body weight gain and increased early embryonic deaths	EC 2007, Anon. 1990b (IIA, 5.6.11)

4.8. Neurotoxicity

EU – EFSA evaluation and conclusions (2012)

The neurotoxicity studies conducted using halosulfuron-methyl evaluated as part of the EU toxicological assessment included: an acute oral neurotoxicity study and a 13-week subchronic dietary neurotoxicity study conducted in rats.

Summary of studies from the 2011 DAR (EC, 2011)

In an acute neurotoxicity study, rats received a single oral dose of halosulfuron-methyl at 0, 200, 600 or 2000 mg/kg bw/day. In the study, the highest dose level, 2000 mg/kg bw of halosulfuron-methyl, caused treatment-related transient increases in uncoordinated righting

reflex in both sexes at seven hours post-dosing. In addition, reduced body weight gain was seen in males during the first week post dosing. There were no microscopic neuropathological lesions. The NOAEL for acute neurotoxicity was 600 mg/kg bw/day.

In a subchronic dietary neurotoxicity study, male rats were dosed with halosulfuron-methyl at 0, 100, 1000 and 10000 ppm (0, 6.3, 62.8 and 706.0 mg/kg bw/day) whereas females were dosed at 0, 100, 1000 and 4000 ppm (0, 8.1, 82.5, 315.9 mg/kg bw/day) for 90 days. In the study, subchronic dietary treatment with up to 10000 ppm of halosulfuron-methyl in males and up to 4000 ppm in females did not induce any evidence of neurotoxicity, including any microscopic lesions of central and peripheral nervous systems. Overall body weight gain was reduced in males at 10000 ppm and a non-significant reduction was seen in females at 4000 ppm. Centrilobular hepatocyte hypertrophy in high dose males was associated with increased body weight and relative liver weight. The NOELs for neurotoxicity were 10000 ppm and 4000 ppm corresponding to 706.0 and 315.9 mg/kg bw/day of halosulfuron-methyl in males and females, respectively. The NOEL for general systemic toxicity was 1000 ppm in both sexes, corresponding to 62.8 and 82.5 mg/kg bw/day of halosulfuron-methyl in males and females, respectively.

Taking into account that the neurotoxicity study investigated a limited number of parameters compared with the repeated oral 90-day toxicity study in rats, there were no discrepancies in the data from the two respective studies.

Table 4.7: Summary of neurotoxicity studies using halosufuron-methyl

STUDY	SPECIES/ STRAIN AND DOSES	NOAEL	TARGET ORGAN/ SIGNIFICANT EFFECTS/ COMMENTS	REFERENCE/ STUDY NUMBER
Acute neurotoxicity (OECD 424, GLP)	Sprague-Dawley Single oral dose 0, 200, 600 and 2000 mg/kg	Neurotoxicity: 600 mg/kg	Decreased body weight gain and transient uncoordinated aerial righting reflexes in both sexes 7 hours post dosing, evidence of systemic toxicity. No progressive long term or irreversible neurotoxic changes were associated with treatment	Anon, 1994
90-Day neurotoxicity (OECD 424, GLP)	Sprague-Dawley Dietary Dose levels: Males 0, 100, 1000 and 10,000 ppm (0, 6.3, 62.8 and 706.0 mg/kg bw/day) Females 0, 100, 1000 and 4000 ppm (0, 8.1, 82.5, 315.9 mg/kg bw/day)	Neurotoxicity: Males 10,000 ppm, (706.0 mg/kg/day) Females 4000 ppm, (315.9 mg/kg/day) General systemic toxicity: 1000 ppm for both males and females, (62.8 and 82.5 mg/kg/day, respectively).	No evidence of neurotoxicity. Systemic toxicity: Body weight gain was reduced and, in males, centrilobular hepatocyte hypertrophy was increased at 10,000 ppm	Anon, 1992

4.9. Endocrine disrupting properties

At the current time, halosulfuron-methyl is not considered as having any endocrine disruption potential in any regulatory jurisdiction.

4.10. Summary of the toxicology profile of halosulfuron-methyl

The toxicology profile of halosulfuron-methyl has been comprehensively reviewed as part of authoritative regulatory evaluations undertaken in the EU by EFSA and ECHA. Assessments conducted by EFSA have incorporated hazard identification and characterisation to inform human health risk assessments, whereas ECHA and the RAC exclusively identified human health hazards for risk management and communication purposes in the EU.

Halosulfuron-methyl has low acute toxicity via the oral, dermal and inhalation routes, is not irritating or corrosive to the skin or the eyes and is not sensitising to the skin. Halosulfuron-methyl is not genotoxic based on the findings of a standard battery of *in vitro* and *in vivo* studies, is not neurotoxic and is not considered as having endocrine disruption potential in any regulatory jurisdiction.

The most prominent effect observed upon repeated dose testing with halosulfuron-methyl upon short-term and long-term exposure was reduction of body weight gain in dogs, rats and mice. In dogs, which were the most sensitive species, changes in clinical chemistry, haematological parameters and liver weight were also observed. The relevant short-term NOAEL was 10 mg/kg bw/day from the 90-day and 1-year studies in dogs and the long-term NOAEL was 43.8 mg/kg bw/day from the 2-year rat study.

In the respective 2-year dietary studies in male and female rats and in a 78-week study in male and female mice, no oncogenic effects were observed indicating that halosulfuron-methyl is not carcinogenic.

Reproductive and developmental studies showed a higher sensitivity of the offspring to halosulfuron-methyl exposure than the adult animals. The offspring's NOAEL in the multigeneration reproduction toxicity study was 6.3 mg/kg bw/day based on reduced pup body weight gain, while the parental NOAEL was 50.4 mg/kg bw/day regarding the same endpoint. In this study no effect on fertility or reproduction was observed up to the highest dose level of 223.2 mg/kg bw/day. In the developmental toxicity study in rabbits, the maternal and developmental NOAELs were 50 mg/kg bw/day based on early resorptions, decreased number of foetuses and reduced maternal body weight gain. In the rat, foetal toxicity was observed in the absence of maternal toxicity: the developmental NOAEL was 75 mg/kg bw/day based on a higher incidence of visceral and skeletal variations and the maternal NOAEL was 250 mg/kg bw/day due to reduced body weight, body weight gain and food consumption.

In the EU, halosulfuron-methyl has been classified for reproduction toxicity in Category 1B, (Repr. 1B; H360D *"May damage the unborn child")* in accordance with the CLP Regulation – a hazard identification process intended for the communication of risk management measures throughout the chemical supply chain. Risk assessments conducted as part of the evaluation performed within the EU regulatory jurisdiction have included the relevant developmental hazard as part of the hazard characterisation, as indicated in the derivation of human health reference values discussed in Section 5.

5. Derivation of human health reference values

Following the evaluation of the mammalian toxicology and hazard profile of halosulfuron-methyl, the currently agreed health-based reference values adopted in the EU for use in regulatory risk assessments are summarised in Table 5.1 and discussed further in the sections below. The EU agreed reference values have been established based on the robust and critical evaluation of a comprehensive toxicological dataset for halosulfuron-methyl where the points of departure have taken into account the relevant critical effects and are considered to be adequately protective in the context of a health-based risk assessment. These reference values are therefore appropriate for informing the human health risk assessments submitted as part of the derogation application to support the safe use of the 750 WG products:

Table 5.1: Summary of health-based reference values derived for human health risk assessment (Source: EFSA Conclusion, 2012)

Reference endpoint	Derived value	Source	Based on endpoint:
ADI	**0.063 mg/kg bw/day**	EFSA (2012)	Based on a NOAEL of 6.3 mg/kg bw/day from a rat reproductive toxicity study (offspring toxicity), UF = 100
ARfD	**0.5 mg/kg bw/day**	EFSA (2012)	Based on the NOAEL of 50 mg/kg bw/day from a rabbit developmental toxicity study (maternal toxicity), UF = 100
AOEL	**0.063 mg/kg bw/day**	EFSA (2012)	Based on a NOAEL of 6.3 mg/kg bw/day from a rat reproductive toxicity study (offspring toxicity), UF = 100 No correction for oral absorption required
AAOEL	Not required	-	-

5.1. Reference values for dietary risk assessments

Derivation of the ADI

The potential health risk to consumers is considered to mainly result from the long-term exposure to residues of halosulfuron-methyl in food. In accordance with internationally accepted procedures, during the EU evaluation of halosulfuron-methyl as a pesticide active substance, the Acceptable Daily Intake (ADI) was derived, taking into account the critical effects and most relevant effects observed in the toxicological database, the NOAEL determined for the most sensitive species and an appropriate safety factor.

Following the peer review of the pesticide risk assessment of the active substance halosulfuron-methyl and expert consultation, the critical effect for the derivation of the ADI was determined to be offspring effects: reduced pup body weight gain in the F1, F2a and F2b generations observed in the two-generation reproduction toxicity study conducted in rats (EFSA, 2012). Based on these findings, the lowest NOAEL was determined to be 6.3 mg/kg bw/day. Applying a standard safety factor of 100 (i.e.: 10 for interspecies variability and 10 for intraspecies variability) to the NOAEL of 6.3 mg/kg bw/day, **the EU agreed ADI was determined to be 0.063 mg/kg bw/day.**

Derivation of an ARfD

The Acute Reference Dose (ARfD) is defined as an estimate of a substance in food or drinking water, that can be ingested over a short period, usually one day, without appreciable health risks to the consumer.

Following the peer review of the pesticide risk assessment of the active substance halosulfuron-methyl and expert consultation, the critical effect for the derivation of the ARfD was determined to be maternal toxicity observed in the rabbit pre-natal developmental toxicity study (EFSA, 2012). Based on these findings, the lowest NOAEL was determined to be 50 mg/kg bw/day. Applying a standard factor of 100 to the NOAEL of 50 mg/kg bw/day, **the EU agreed ARfD was determined to be 0.5 mg/kg bw/day.**

It is noted that as part of the on-going EU renewal evaluation of halosulfuron-methyl, the RMS has proposed the same reference values for the dietary risk assessment as are currently agreed at the EU level.

5.2. Reference values for non-dietary risk assessments

Derivation of the AOEL

The Acceptable Operator Exposure Level (AOEL) is the maximum amount of active substance to which an operator may be exposed without any adverse health effects.

Following the peer review of the pesticide risk assessment of the active substance halosulfuron-methyl and expert consultation, the critical effect for the derivation of the AOEL was determined to be offspring effects: reduced pup body weight gain in the F1, F2a and F2b generations observed in the two-generation reproduction toxicity study conducted in rats (EFSA, 2012). Based on these findings, the lowest NOAEL was determined to be 6.3 mg/kg bw/day. No correction to account for oral absorption was required. Applying a standard safety factor of 100 to the NOAEL of 6.3 mg/kg bw/day, **the EU agreed AOEL was determined to be 0.063 mg/kg bw/day.**

It is noted that as part of the on-going EU renewal evaluation of halosulfuron-methyl, the RMS has proposed the same AOEL value as currently agreed at the EU level.

During the peer review evaluation for the active substance approval in 2012, EFSA concluded that a reference value for acute operator exposures (i.e.: an Acute Acceptable Operator Exposure Level, AAOEL value) was not required. While the RMS has proposed an AAOEL value of 0.5 mg/kg bw/day (based on a comparable derivation to the ARfD) in the context of the EU renewal, this reference value is currently tentative only and subject to agreement at the EU level and has not therefore been considered in the non-dietary risk assessment submitted to support the derogation.

6. References

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7. Supported products

Company	Product	Registration number
Farm-Ag International (Pty) Ltd	Brigadier 750 WG	L9218
ICA International Chemicals (Pty) Ltd	WeedO 750 WG	L11149
UPL South Africa (Pty) Ltd	Cyprex WG	L7665
Sharda International Africa (Pty) Ltd	Halosulfuron 750 WDG	L10855
Villa Crop Protection (Pty) Ltd	Halo 750 WDG	L8283
Rainbow Agrosciences (Pty) Ltd	Flagship 750 WDG	L10539
Green Island Investments Pty Ltd	Halo-Fron WG	L10152

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ENVIRONMENTAL (RISK) ASSESSMENT FOR THE PROPOSED APPLICATION OF PRODUCTS CONTAINING HALOSULFURON-METHYL

Prepared by:

Thomas Kratz

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Prepared for the Derogation Group consisting of:

Farm-Ag International (Pty) Ltd, ICA International Chemicals (Pty)
UPL South Africa (Pty) Ltd, Sharda International Africa (Pty) Ltd
Villa Crop Protection (Pty) Ltd, Rainbow Agrosciences (Pty) Ltd
Green Island Investments Pty Ltd

Project number: 2403474.UK0

Document number: EWC 2403474.UK0-0851

Date: 03/12/2024

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Background

The Halosulfuron-methyl Derogation Group comprising of: Farm-Ag International (Pty) Ltd, ICA International Chemicals (Pty) Ltd, UPL South Africa (Pty) Ltd, Sharda International Africa (Pty) Ltd, Villa Crop Protection (Pty) Ltd, Rainbow Agrosciences (Pty) Ltd and Green Island Investments Pty Ltd, is submitting a derogation for their water dispersible granule formulations (WG/WDG) containing 750 g/kg halosulfuron-methyl that includes dietary and non-dietary human health risk assessments as well as environmental risk assessments and hereby demonstrate safe use of these products, when used according to their recommended use pattern.

Product code(s) and name(s)	Halosulfuron 75 WDG (and similar products)
Formulation type	Water Dispersible Granules (WDG)
Category	herbicide
Active substance (incl. content)	Halosulfuron -methyl 750 g/kg

This report covers the environmental risk assessment.

Principle of Ecotoxicological assessment

The assessment of the environmental risks caused by agricultural remedies becomes increasingly important in practical environmental protection. Ecotoxicological risk assessment is used to assess the potential hazard of existing or new environmental chemicals regarding the ecosystem. The combination of exposure assessment and hazard assessment allows the assessment of hazards induced by an environmental chemical and the analysis and final evaluation of the potential risk.

Exposure: what are the environmental concentrations the non-target organisms are exposed to?

The expected environmental concentration is assessed with the aid of computer models and Predicted Environmental Concentrations (PECs) are derived for surface water PECsw, for soil PECsoil and for groundwater PECgw.

Hazard:

The hazard of a substance considers various ecotoxicological effects such as acute toxicity, chronic toxicity and bioaccumulation. Tests on non-target organisms are conducted according to widely accepted OECD guidance to determine the acute (LD/LC/EC_{50}) or chronic (NOEC/NOEL) toxicity endpoints. The LD/LC/EC_{50} is the "Concentration or dose where 50 % effect or mortality was observed/calculated "and the NOEC is the "No Observed Effect Concentration or Dose".

The assessment of the risks of agricultural remedies for the terrestrial environment is based on the calculation of risk indicators (e.g. TER, HQ) which compare the acute (LD/LC/EC_{50}) or chronic (NOEC/NOEL) toxicity endpoints generated from experimental data with the formulation or the active substance to the potential exposure in the environment. Currently TER 'Toxicity exposure ratio' values are used for the risk assessments of terrestrial vertebrates, earthworms and non-target plants when HQ 'Hazard quotients' values are used for the risk assessment of bees and non-target arthropods.

If the risk indicators (TER, HQ) are above the TER trigger or below the HQ trigger then the risk is considered acceptable.

The assessment of the risks of agricultural remedies for the aquatic environment is based on the calculation of PEC/RAC ratios. RAC is the "regulatory acceptable concentrations "which is derived by applying an assessment factor (AF) of 100 or 10 to the lowest acute or chronic toxicity value obtained from the respective tests. Both the trigger values and the assessment factors are conservative.

To assess the environmental risk to non-target organisms following the supported uses of the WG products containing 750 g/kg halosulfuron-methyl, the European model has been followed: The European model is well known for being very conservative in order to achieve the highly ambitious protection goal set out by the European commission. Furthermore, it is noted that the European

guidance sets are revised regularly, in order to reflect changes of test guidelines and of scientific knowledge. in EU Guidance documents (EFSA, SANCO, EPPO, etc.).

The risk assessments conducted reflect the South African Data requirements as per Appendix A&B "Toxicological Requirements for Registration of New Pesticides RSA", in order to cover all relevant areas considered under the South African Jurisdiction.

Overview of the risk assessment outcome

An assessment has been conducted to evaluate the environmental risks associated with the uses of the water dispersible granule products containing 750g halosulfuron-methyl/kg.

The comprehensive overview of the uses supported by the members of the derogation group as well as the outcome of the risk assessments for all non-target organisms in scope are presented below in Table 1.

Table 1: Identified uses for the halosulfuron 750 WDG

Use No.	Crop and/or situation	F, Fn, Fpn G, Gn, Gpn or I	Application				Application rate			PHI (days)	Conclusion						
			Method/Kind	Timing/Growth stage of crop & season	Max. number per crop/ season	Min. interval between applications (days)	L product/ha a) max. rate per appl. b) max. total rate per crop/season	g a.s./ha a) max. rate per appl. b) max. total rate per crop/season	Water L/ha min / max		Birds	Mammals	Aquatic organisms	Bees	Non-target arthropods	Soil organisms	Non-target plants
1	Maize	F	Knapsack sprayers or tractor mounted boom sprayers	Post emergence of the weeds (BBCH 10-14) BBCH 12-16 (2-6 leaf stage) of the crop	1	-	1	50	200 - 400	NA	A	A	R	A	A	A	R
2	Grain sorghum	F	Knapsack sprayers or tractor mounted boom sprayers	Post emergence of the weeds (BBCH 10-14) BBCH 12-16 (2-6 leaf stage) of the crop	1	-	1	50	200 - 400	NA	A	A	R	A	A	A	R
3	Wheat	F	Knapsack sprayers or tractor mounted boom sprayers	Post emergence of the weeds (BBCH 10-14) BBCH 12-21 (2 leaf stage to beginning of tillering) of the crop	1	-	1	50	200 - 400	NA	A	A	R	A	A	A	R
4	Sugarcane	F	Knapsack sprayers or tractor mounted boom sprayers	Post emergence of the weeds (BBCH 10-14) BBCH 12-16 (2-6 leaf stage) of the crop	1	-	1	50	200 - 400	NA	A	A	R	A	A	A	R
5	Avocado	F	Knapsack sprayers or tractor mounted boom sprayers	Post emergence of the weeds (BBCH 10-14) (BBCH 00-99 of the crop)	1	-	1	50	200 - 400	NA	A	A	R	A	A	A	R

Use No.	Crop and/or situation	F, Fn, Fpn G, Gn, Gpn or I	Application				Application rate			PHI (days)	Conclusion						
			Method/Kind	Timing/Growth stage of crop & season	Max. number per crop/ season	Min. interval between applications (days)	L product/ha a) max. rate per appl. b) max. total rate per crop/season	g a.s./ha a) max. rate per appl. b) max. total rate per crop/season	Water L/ha min / max		Birds	Mammals	Aquatic organisms	Bees	Non-target arthropods	Soil organisms	Non-target plants
6	Citrus	F	Knapsack sprayers or tractor mounted boom sprayers	Post emergence of the weeds (BBCH 10-14) (BBCH 00-99 of the crop)	1	-	1	50	200 - 400	NA	A	A	R	A	A	A	R
7	Mango	F	Knapsack sprayers or tractor mounted boom sprayers	Post emergence of the weeds (BBCH 10-14) (BBCH 00-99 of the crop)	1	-	1	50	200 - 400	NA	A	A	R	A	A	A	R
8	Kikuyu and/or Cynodon lawn	F	Knapsack sprayers or tractor mounted boom sprayers	Post emergence of the weeds (BBCH 10-14) (BBCH 21-65 of the crop)	1	-	1	50	200 - 400	NA	A	A	R	A	A	A	R

Explanation for column "Conclusion"

A	Acceptable, Safe use
R	Risk mitigation measures required

List of endpoints used for ecotoxicological assessment

The following tables present the endpoints for the active substance halosulfuron-methyl and its metabolites as well as the representative formulation halosulfuron-methyl 75WG according to data requirements presented in the Appendices A[1] and B[2] of the 'Toxicological requirements for registration of new pesticides in South Africa' for active substances and plant protection products, respectively.

It has to be noted that the representative formulated product 'Halosulfuron-methyl 75WG' used in the studies for the EU evaluation of the active substance halosulfuron-methyl is a surrogate for the supported product Halosulfuron 75 WDG and similar products presented at the end of the document.

These endpoints are taken from the EFSA Conclusion on the peer review of the pesticide risk assessment of the active substance halosulfuron (EFSA Journal 2012;10(12):2987). The most sensitive endpoints that have been used the risk assessment are shown in bold.

Summary of effects on birds and other terrestrial vertebrates

Halosulfuron-methyl has been tested for acute and chronic toxicity in a number of different bird and mammal species under standard laboratory conditions.

Table 2: Summary of endpoints for toxicity of halosulfuron-methyl and its metabolites to birds and mammals

Species	Test substance	Test type	End point	Toxicity	Reference / Owner
Birds					
Bobwhite quail (*Colinus virginianus*)	Halosulfuron-methyl	Acute oral	**LD_{50}**	> 2250 mg a.s./kg bw **(extrapolated 4248 mg a.s./kg bw)[1]**	EFSA Journal 2012
Mallard duck (*Anas platyrhynchos*)	Halosulfuron-methyl	Subchronic and reproduction (22 weeks)	**NOEL**	1000 ppm (**119 mg a.s./kg bw/d (males))**	EFSA Journal 2012
Mammals					
Rat	Halosulfuron-methyl	Acute oral	**LD_{50}**	**7758 mg a.s./kg bw**	EFSA Journal 2012
Rat	Halosulfuron-methyl	Reproductive toxicity two generation	**NOAEL**	**6.3 mg a.s./kg bw/day**	EFSA Journal 2012

[1] According to the EFSA Guidance Document (2009), since no mortality was observed at the limit dose, the LD50 value can be extrapolated by a factor of 1.888 as 10 birds (5 male and 5 female) were treated at the top rate, which results in a LD50 of 4248 mg/kg for risk assessment purposes.

Summary of effects on aquatic organisms

The active substance halosulfuron-methyl and its major aquatic metabolites were tested in a number of species under standard laboratory conditions. Resulting acute and chronic endpoints are presented in the following table.

Table 3: Summary of endpoints for toxicity of halosulfuron-methyl and its metabolites to aquatic organisms

[1] APPENDIX A: Toxicological requirements for registration of new pesticides in South Africa registration of agricultural remedies (act 36 of 1947), Evaluation of complete dossier for plant protection active substances)
[2] APPENDIX B: Toxicological requirements for registration of new pesticides in South Africa registration of agricultural remedies (act 36 of 1947), Evaluation of complete dossier for plant protection products (formulation)

Species	Test substance	Test type	End point	Toxicity	Reference / Owner
Fish					
Rainbow trout *Oncorhynchus mykiss*	Halosulfuron-methyl	Acute - Flow-through	96 h LC_{50}	>131 mg a.s./L (mm)	EFSA Journal 2012
Bluegill sunfish *Lepomis macrochirus*	Halosulfuron-methyl	Acute - Flow-through	96 h LC_{50}	>118 mg a.s./L (mm)	EFSA Journal 2012
Rainbow trout *Oncorhynchus mykiss*	Halosulfuron-methyl rearrangement	Acute – semi-static	96 h LC_{50}	>15.3 mg/L (mm)	EFSA Journal 2012
Rainbow trout *Oncorhynchus mykiss*	Halosulfuron-methyl	ELS – flow-through	87 d NOEC Survival and growth	34 mg a.s./L (mm)	EFSA Journal 2012
Aquatic invertebrates					
Daphnia magna	Halosulfuron-methyl	Acute - Flow-through	48 h EC_{50}	>107 mg a.s./L (mm)	EFSA Journal 2012
Daphnia magna	Halosulfuron-methyl rearrangement	Acute –-static	48 h EC_{50}	>19.2 mg/L (mm)	EFSA Journal 2012
Mysidopsis bahia	Halosulfuron-methyl	Acute - Flow-through	96 h LC_{50}	109 mg a.s./L (mm)	EFSA Journal 2012
Lymnaea peregra [1]	Halosulfuron-methyl	Acute - semi-static	96 h LC_{50}	>89.9 mg a.s./L (mm)	EFSA Journal 2012
Daphnia magna	Halosulfuron-methyl	Full Life-Cycle – Flow-through	21 d NOEC Survival and reproduction	7.2 mg a.s./L (mm)	EFSA Journal 2012
Daphnia magna	Halosulfuron-methyl	Full Life-Cycle – Flow-through	21 d NOEC Survival and reproduction	6.9 mg a.s./L (mm)	EFSA Journal 2012
Sediment-dwelling organisms					
Chironomus riparius	Halosulfuron-methyl	Chronic / Development, water-spiked – static	28 d E C_{50} 28 d NOEC Emergence and development	>10 mg a.s./L (mm) 5 mg a.s./L (mm) (4.94 mg a.s./kg dw sed (mm))	EFSA Journal 2012
Algae					
Green algae *Pseudokirchneriella subcapitata*	Halosulfuron-methyl	Static	72 h E_rC_{50}	0.00507 mg a.s./L (nom)	EFSA Journal 2012
Navicula pelliculosa	Halosulfuron-methyl	Static	120 h E_rC_{50}	>0.35 mg/L (mm)	EFSA Journal 2012
Skeletonema costatum	Halosulfuron-methyl	Static	120 h E_rC_{50}	>0.40 mg/L (mm)	EFSA Journal 2012

Species	**Test substance**	**Test type**	**End point**	**Toxicity**	**Reference / Owner**
Green algae *Pseudokirchneriella subcapitata*	Halosulfuron	Static	72 h E_rC_{50}	>98 mg a.s./L (mm)	EFSA Journal 2012
Green algae *Pseudokirchneriella subcapitata*	Halosulfuron-methyl rearrangement	Static	72 h E_rC_{50}	>20.3 mg/L (mm)	EFSA Journal 2012
Green algae *Pseudokirchneriella subcapitata*	Aminopyrimidine	Static	72 h E_rC_{50}	521 mg/L (nom)	EFSA Journal 2012
Higher plant					
Lemna gibba	Halosulfuron-methyl	Semi-static	7 d E_bC_{50} **7 d E_rC_{50}**	0.000217 mg a.s./L (mm) **0.000491 mg a.s./L (mm)**	EFSA Journal 2012
Lemna gibba modified exposure (+ sediment)	Halosulfuron-methyl	Static	7 d E_bC_{50} **7 d E_rC_{50}**	0.000942 mg a.s./L (mm) **0.00342 mg a.s./L (mm)**	EFSA Journal 2012
Lemna gibba	Halosulfuron-methyl rearrangement	Semi-static	**7 d E_rC_{50}**	**0.000491 mg/L $(mm)^2$**	n.a.
Lemna gibba	Halosulfuron rearrangement	Semi-static	**7 d E_rC_{50}**	**0.000491 mg/L $(mm)^2$**	n.a.
Lemna gibba	Chlorosulfonamide acid	Semi-static	**7 d E_rC_{50}**	**0.000491 mg/L $(mm)^2$**	n.a.
Lemna gibba	Halosulfuron	Semi-static	**7 d E_rC_{50}**	**0.000491 mg/L $(mm)^2$**	n.a.
Lemna gibba	Chlorosulfonamide	Semi-static	**7 d E_rC_{50}**	**0.000491 mg/L $(mm)^2$**	n.a.
Lemna gibba	Aminopyrimidine	Semi-static	**7 d E_rC_{50}**	**0.000491 mg/L $(mm)^2$**	n.a.
Further testing on aquatic organisms					
Echinochloa oryzicola, Schoenoplectus juncoides, Monochoria vaginalis and *Eleocharis kuroguwai*	HSM, technical, halosulfuron, O-demethyl halosulfuron-methyl, halosulfuron-methyl rearrangement, halosulfuron-rearrangement, aminopyrimidine, chlorosulfonamide and chlorosulfonamide acid	Herbicidal activity 17 d pre or post emergence treatment	-	≥63 reduction in toxicity vs halosulfuron-methyl	EFSA Journal 2012

nom: based on nominal concentrations; mm: based on mean measured concentrations; im: based on initial measured concentrations

n.a.: not applicable
[1] Toxicity data for *Lymnaea peregra* was not considered in the risk assessment during EU review as it is not a standard/recognised species for EU registration.
[2] As no E_rC_{50} is available for the metabolites, to be precautionary, the E_rC_{50} of halosulfuron-methyl was used as a surrogate without a safety factor.

The representative formulation Halosulfuron-methyl 75WG were tested in a number of species under standard laboratory conditions. Resulting acute and chronic endpoints are presented in the following table.

Table 4: Summary of endpoints for toxicity of Halosulfuron-methyl 75WG to aquatic organisms

Species	Test substance	Test type	End point	Toxicity	Reference / Owner
Fish					
Rainbow trout *Oncorhynchus mykiss*	Halosulfuron-methyl 75WG	Acute – static	96 h LC_{50}	>97.3 mg a.s./L (mm)	EFSA Journal 2012
Aquatic invertebrates					
Daphnia magna	Halosulfuron-methyl 75WG	Acute – static	48 h EC_{50}	121 mg a.s./L (mm)	EFSA Journal 2012
Sediment-dwelling organisms					
-					
Algae					
Green algae *Pseudokirchneriella subcapitata*	Halosulfuron-methyl 75WG	Static	72 h E_bC_{50} 72 h E_rC_{50}	0.00295 mg a.s./L (mm) 0.0189 mg a.s./L (mm)	EFSA Journal 2012
Higher plant					
Lemna gibba	Halosulfuron-methyl 75WG	Semi-static	7 d E_bC_{50} **7 d E_rC_{50}**	0.000863 mg a.s./L (mm) **0.00142 mg a.s./L (mm)**	EFSA Journal 2012
Lemna gibba modified exposure (+ sediment)	Halosulfuron-methyl 75WG	Static	7 d E_bC_{50} **7 d E_rC_{50}**	0.000845 mg a.s./L (mm) **0.00445 mg a.s./L (im)**	EFSA Journal 2012
Elodea canadensis (+ sandy loam soil)	Halosulfuron-methyl 75WG	Static	15 d NOEC	0.00816 mg a.s./L (nom)	EFSA Journal 2012
Ceratophyllum demersum (+ sandy loam soil)	Halosulfuron-methyl 75WG	Static	15 d NOEC	0.0032 mg a.s./L (mm)	EFSA Journal 2012
Myriophyllum proserpinacoides (+ sandy loam soil)	Halosulfuron-methyl 75WG	Static	14 d NOEC	0.01 mg a.s./L (mm)	EFSA Journal 2012
Saggitaria saggitifolia (+ sandy loam soil)	Halosulfuron-methyl 75WG	Static	21 d NOEC	0.00156 mg a.s./L (mm)	EFSA Journal 2012
Further testing on aquatic organisms					
Bacillariophyceae, Chlorophyceae, Cyanophyceae, Xanthophyceae	Halosulfuron-methyl 75WG	Field test - Paddy treated at 37.5 g a.s./ha Field test on paddy	-	No adverse effects at 37.5 g a.s./ha 63 days after flooding	EFSA Journal 2012

mm: based on mean measured concentrations

Summary of effects on arthropods

Bees

Acute laboratory studies with honey bees have been performed with halosulfuron-methyl and Halosulfuron-methyl 75WG.

Table 5: Summary of endpoints for toxicity of halosulfuron-methyl and Halosulfuron-methyl 75WG to bees

Species	Test substance	Test type	End point	Toxicity	Reference / Owner
Adult honey bee (*Apis mellifera*)	Halosulfuron-methyl	Acute oral	48 h-LD_{50}	**>100 µg a.s/bee**	EFSA Journal 2012
		Acute contact	48 h-LD_{50}	**>100 µg a.s/bee**	
Adult honey bee (*Apis mellifera*)	Halosulfuron-methyl 75WG	Acute oral	48 h-LD_{50}	**>100 µg a.s/bee**	EFSA Journal 2012
		Acute contact	48 h-LD_{50}	**>100 µg a.s/bee**	

Non-target arthropods other than bees

A set of laboratory standard laboratory studies have been performed with Halosulfuron-methyl 75WG.

Table 6: Summary of endpoints from laboratory tests with Halosulfuron-methyl 75WG on non-target arthropods

Species	Test Substance	Test substrate	End point	Toxicity	Reference / Owner
Laboratory test / Tier I					
Aphidius rhopalosiphi	Halosulfuron-methyl 75WG	Glass plate, 2-D	48 h-LR_{50}	**> 300 g a.s./ha**	EFSA Journal 2012
Typhlodromus pyri	Halosulfuron-methyl 75WG	Glass plate, 2-D	14 d-LR_{50}	**> 300 g a.s./ha**	EFSA Journal 2012

Summary of effects on non-target soil meso- and macrofauna

Earthworms

The active substance halosulfuron-methyl was tested on potential acute effects on earthworms (*Eisenia fetida*).

For the potentially relevant soil metabolites halosulfuron-methyl rearrangement, halosulfuron, chlorosulfonamide, chlorosulfonamide acid, chlorosulfonamide acid guanidine, chlorosulfonamide guanidine, aminopyrimidine and O-demethyl halosulfuron methyl for which endpoints are not available it is proposed an endpoint derived using the parent endpoint to which an extra assessment factor of 10 was applied as a conservative approach proposed previously by EFSA. All endpoints are summarised in the table below.

Table 7: Summary of endpoints for toxicity of halosulfuron-methyl and its metabolites to earthworms

Test organism	Test substance	Test type	End point	Toxicity	Reference / Owner
Eisenia foetida	**Acute toxicity**				
	Halosulfuron-methyl	Acute 14 day	14d-LD_{50}	**> 1000 mg a.s./kg dw soil**	EFSA Journal 2012
	Halosulfuron-methyl rearrangement	Parent end point/10	14d-LD_{50}	**> 100 mg/kg dw soil** [1]	n.a.
	Halosulfuron	Parent end point/10	14d-LD_{50}	**> 100 mg/kg dw soil** [1]	n.a.
	Chlorosulfonamide	Parent end point/10	14d-LD_{50}	**> 100 mg/kg dw soil** [1]	n.a.
	Chlorosulfonamide acid	Parent end point/10	14d-LD_{50}	**> 100 mg/kg dw soil** [1]	n.a.
	Chlorosulfonamide acid guanidine	Parent end point/10	14d-LD_{50}	**> 100 mg/kg dw soil** [1]	n.a.
	Chlorosulfonamide guanidine	Parent end point/10	14d-LD_{50}	**> 100 mg/kg dw soil** [1]	n.a.
	Aminopyrimidine	Parent end point/10	14d-LD_{50}	**> 100 mg/kg dw soil** [1]	n.a.
	O-demethyl halosulfuron methyl	Parent end point/10	14d-LD_{50}	**> 100 mg/kg dw soil** [1]	n.a.

n.a.: not applicable

[1] Parent endpoint with safety factor of 10 applied as proposed in EFSA Journal 2012: 10(12):2987

Soil meso- and macrofauna (other than earthworms)

No data are available for chronic effects of halosulfuron-methyl on collembolan (*Folsomia candida*), and soil mites (*Hypoaspis aculeifer*) as there were not required during the previous EU evaluation.

Summary of effects on soil nitrogen transformation

The active substance halosulfuron-methyl was tested on potential effects on the process of microbial nitrogen and carbon transformation in soil. For the potentially relevant soil metabolites halosulfuron-methyl rearrangement, halosulfuron, chlorosulfonamide, chlorosulfonamide acid, chlorosulfonamide acid guanidine, chlorosulfonamide guanidine, aminopyrimidine and O-demethyl halosulfuron methyl for which endpoints are not available it is proposed an endpoint for nitrogen transformation derived using the parent endpoint to which an extra assessment factor of 10 was applied as a conservative approach proposed previously by EFSA. All endpoints are summarised in the table below.

Table 8: Summary of endpoints for toxicity of halosulfuron-methyl and its metabolites to soil micro-organisms

Test substance	Test type	End point	Reference
Halosulfuron-methyl	Carbon and Nitrogen transformation	**28 day <25% effect (200 g a.s./ha)**	EFSA Journal 2012

Halosulfuron-methyl rearrangement	Nitrogen transformation (Parent end point/10)	**28 day <25% effect (20 g/ha)**	n.a.
Halosulfuron	Nitrogen transformation (Parent end point/10)	**28 day <25% effect (20 g/ha)**	n.a.
Chlorosulfonamide	Nitrogen transformation (Parent end point/10)	**28 day <25% effect (20 g/ha)**	n.a.
Chlorosulfonamide acid	Nitrogen transformation (Parent end point/10)	**28 day <25% effect (20 g/ha)**	n.a.
Chlorosulfonamide acid guanidine	Nitrogen transformation (Parent end point/10)	**28 day <25% effect (20 g/ha)**	n.a.
Chlorosulfonamide guanidine	Nitrogen transformation (Parent end point/10)	**28 day <25% effect (20 g/ha)**	n.a.
Aminopyrimidine	Nitrogen transformation (Parent end point/10)	**28 day <25% effect (20 g/ha)**	n.a.
O-demethyl halosulfuron methyl	Nitrogen transformation (Parent end point/10)	**28 day <25% effect (20 g/ha)**	n.a.

n.a.: not applicable

[1] Parent endpoint with safety factor of 10 applied as proposed in EFSA Journal 2012: 10(12):2987

Summary of effects on terrestrial non-target higher plants

Potential effects of halosulfuron-methyl on vegetative vigour and seedling emergence have been tested in two studies. The results of the studies are summarised in the table below.

Table 9: Summary of endpoints for toxicity of halosulfuron-methyl to terrestrial non target higher plants

Test type	Test substance	Most sensitive species	End point	Toxicity	Reference / Owner
Seedling emergence	Halosulfuron-methyl	Lettuce	**ER_{50}**	**0.12 g a.s./ha (plant dry weight)**	EFSA Journal 2012
Vegetative vigour	Halosulfuron-methyl	Radish	**ER_{50}**	**0.21565 g a.s./ha (plant dry weight)**	EFSA Journal 2012
		Tomato, cucumber, ryegrass, corn, onion, soybean, cabbage, lettuce, radish, oat	**HC_5**	**0.1 g a.s./ha (plant dry weight)**	EFSA Journal 2012

Summary of effects on biological methods for sewage treatment

The chronic effect of halosulfuron-methyl on biological methods for sewage treatment was assessed and are summarised in the table below.

Table 10: Summary of endpoints for effects of halosulfuron-methyl on biological methods for sewage treatment

Test organism	Test substance	Test type	End point	Toxicity	Reference / Owner
Activated sludge	Halosulfuron-methyl	Respiration Inhibition test	EC_{50}	> 100 mg a.s./L	EFSA Journal 2012

Birds and other terrestrial vertebrates

The available acute and chronic toxicity studies demonstrate that Halosulfuron-methyl exhibits low toxicity to birds, reflected in the limit endpoint LD_{50} > 2250 mg a.s./kg bw and the long-term NOEL of 119 mg/kg bw/day from the Mallard duck study.

Halosulfuron-methyl is of low acute toxicity to mammals with a LD_{50} of 7758 mg a.s./kg bw in rats. The offspring toxicity NOAEL of 100 ppm in the two-generation reproduction study in rat corresponds to average intake of 6.3 mg/kg bw/day for males.

Since no data are required for the formulation Halosulfuron-methyl 75WG, the risk assessments can be carried out with the endpoints for the active substance.

Since the available data for the relevant metabolites Halosulfuron-methyl rearrangement and Chlorosulfonamide acid indicate that they are not more acutely toxic to mammals than the parent, it is reasonable to assume that the avian and mammalian risk assessment for these metabolites is covered by that for the parent.

The results of the acute and reproductive screening assessments, according to the EFSA Guidance Document on Risk Assessment for Birds and Mammals (2009), are summarised in the following tables.

Dietary risk assessment for birds

Screening Step

Uses no. 1 to 4 on maize, cereals (wheat and sorghum) and sugarcane

Table 11: Screening assessment of the acute and long-term/reproductive risk for birds due to the use of Halosulfuron-methyl 75WG in maize, cereals and sugarcane (uses no. 1-4; risk envelope)

Intended use	Maize, sorghum, wheat and sugarcane				
Active substance	Halosulfuron-methyl				
Application rate (kg a.s./ha)	1 × 0.05				
Acute toxicity (mg a.s./kg bw)	4248				
TER criterion	10				
Crop scenario Growth stage	**indicator species for screening**	**SV_{90}**	**MAF_{90}**	**DDD_{90} (mg/kg bw/d)**	**TER_a**
Cereals BBCH 12-21	Small omnivorous bird	158.8	n.a.	7.94	535.2
Reprod. toxicity (mg a.s./kg bw/d)	119				
TER criterion	5				
Crop scenario Growth stage	**indicator species for screening**	**SV_m**	**MAF_m × TWA**	**DDD_m (mg/kg bw/d)**	**TER_{lt}**
Cereals BBCH 29 - 59	Small omnivorous bird	64.8	1.0 x 0.53	1.72	69.3

SV: shortcut value; MAF: multiple application factor; TWA: time-weighted average factor; DDD: daily dietary dose; TER: toxicity to exposure ratio. TER values shown in **bold** fall below the relevant trigger.

Based on the available data and risk assessment, a low acute and long-term risk via dietary exposure to birds can be concluded for the foliar spray application of the product to cereals, maize and sugarcane covering the risk envelope for all uses.

Dietary risk assessment for mammals

Screening Step

Uses no. 1, 5 to 8 in maize, orchards (avocado, citrus and mango) and grassland (Kikuyu and/or Cynodon lawn)

Table 12: Screening assessment of the acute and long-term/reproductive risk for mammals due to the uses of Halosulfuron-methyl 75WG in maize (surrogate for sugarcane), orchards and grassland (uses no. 1 and 4-8; risk envelope)

Intended use	Maize (surrogate for sugarcane), avocado, citrus and mango, Kikuyu and/or Cynodon lawn				
Active substance	Halosulfuron-methyl				
Application rate (kg a.s./ha)	1 × 0.05				
Acute toxicity (mg a.s./kg bw)	7758				
TER criterion	10				
Crop scenario Growth stage	**indicator species for screening**	**SV_{90}**	**MAF_{90}**	**DDD_{90} (mg/kg bw/d)**	**TER_a**
Orchards BBCH 00-99	Small herbivorous mammal	136.4	n.a.	6.82	1137.9
Reprod. toxicity (mg a.s./kg bw/d)	6.3				
TER criterion	5				
Crop scenario Growth stage	**indicator species for screening**	**SV_m**	**MAF_m × TWA**	**DDD_m (mg/kg bw/d)**	**TER_{lt}**
Orchards BBCH 00-99	Small herbivorous mammal	72.3	1.0 x 0.53	1.92	**3.3**

SV: shortcut value; MAF: multiple application factor; TWA: time-weighted average factor; DDD: daily dietary dose; TER: toxicity to exposure ratio. TER values shown in **bold** fall below the relevant trigger.

Based on the available data and risk assessment, a low acute risk via dietary exposure to mammals can be concluded for the foliar spray application of the product to maize, sugarcane, avocado, citrus and mango, Kikuyu and/or Cynodon lawn cereals, covering the risk envelope for all uses. Therefore no further assessment of the acute risk is required. However, an acceptable long-term risk cannot be demonstrated. Therefore, an assessment of the long-term risk for mammals following the uses in cereals has been conducted and presented in the table below.

Uses no. 2 and 3 on cereals (wheat and sorghum)

Table 13: Screening assessment of the long-term/reproductive risk for mammals due to the use of Halosulfuron-methyl 75WG in cereals (use no. 2-3)

Intended use	sorghum, wheat
Active substance	Halosulfuron-methyl
Application rate (kg a.s./ha)	1 × 0.05

Reprod. toxicity (mg a.s./kg bw/d)	6.3				
TER criterion	5				
Crop scenario Growth stage	**indicator species for screening**	**SV_m**	**MAF_m × TWA**	**DDD_m (mg/kg bw/d)**	**TER_{lt}**
Cereals BBCH 12-21	Small herbivorous mammal	48.3	1.0 x 0.53	1.28	**4.9**

SV: shortcut value; MAF: multiple application factor; TWA: time-weighted average factor; DDD: daily dietary dose; TER: toxicity to exposure ratio. TER values shown in **bold** fall below the relevant trigger.

Based on the available data and risk assessments, a potential long-term risk via dietary exposure to wild mammals can be concluded for the foliar spray application of the product to all crops on GAP. Therefore, a first-tier risk assessment is required for these uses.

Tier 1 Step

Table 14: First-tier assessment of the reproductive risk for mammals due to the uses of Halosulfuron-methyl 75WG

Active substance	Halosulfuron-methyl				
Application rate (kg a.s./ha)	1 × 0.05				
Reprod. toxicity (mg a.s./kg bw/d)	6.3				
TER criterion	5				
Crop scenario Growth stage	**Generic focal species**	**SV_m**	**MAF_m × TWA**	**DDD_m (mg/kg bw/d)**	**TER_{lt}**
Intended use	Maize and sugarcane (uses no. 1 and 4, BBCH 12-16)				
Maize, BBCH 10-19	Small insectivorous mammal “shrew”	4.2	1.0 x 0.53	0.11	57.0
Maize, BBCH 10-29	Small herbivorous mammal “vole”	72.3	1.0 x 0.53	1.90	**3.3**
Maize, BBCH 10-29	Small omnivorous mammal “mouse”	7.8	1.0 x 0.53	0.21	30.7
Intended use	Sorghum and wheat (uses no. 2-3, BBCH 12-21)				
Cereals, BBCH 10-19	Small insectivorous mammal “shrew”	4.2	1.0 x 0.53	0.11	57.0
Cereals, BBCH ≥ 20	Small insectivorous mammal “shrew”	1.9	1.0 x 0.53	0.05	125.9
Cereals, BBCH 10-29	Small omnivorous mammal “mouse”	7.8	1.0 x 0.53	0.21	30.7
Intended use	avocado, citrus and mango (uses no. 5 to 7, BBCH 00-99 (Between the rows, avoid contact with crop foliage))				
Orchards BBCH < 10 or not crop directed	Small insectivorous mammal “shrew”	1.9	1.0 x 0.53	0.05	125.9
Orchards BBCH < 10 or not crop directed	Small herbivorous mammal “vole”	72.3	1.0 x 0.53	1.90	**3.3**
Orchards	Large herbivorous mammal “lagomorph”	14.3	1.0 x 0.53	0.38	16.7

BBCH < 10 or not crop directed					
Orchards BBCH < 10 or not crop directed	Small omnivorous mammal "mouse"	7.8	1.0 x 0.53	0.21	30.7
Intended use	Kikuyu and/or Cynodon lawn (use no. 8, BBCH 21-65)				
grassland All season	Large herbivorous mammal "lagomorph"	17.3	1.0 x 0.53	0.46	13.8
grassland late	Small insectivorous mammal "shrew"	1.9	1.0 x 0.53	0.05	125.9
grassland All season	Small herbivorous mammal "vole"	72.3	1.0 x 0.53	1.90	**3.3**
grassland Late season (seed heads)	Small omnivorous mammal "mouse"	6.6	1.0 x 0.53	0.17	36.2

SV: shortcut value; MAF: multiple application factor; TWA: time-weighted average factor; DDD: daily dietary dose; TER: toxicity to exposure ratio. TER values shown in **bold** fall below the relevant trigger.

Based on the first-tier risk assessment the TER_{lt} values for Halosulfuron-methyl are above the trigger value indicating an acceptable chronic risk, except for small herbivorous mammal "vole" following the proposed uses in maize, sugarcane, avocado, citrus, mango and Kikuyu and/or Cynodon lawn. However, the vole is not a relevant mammalian species in South Africa. Therefore, an acceptable long-term risk to mammals can be concluded following the proposed uses in Halosulfuron-methyl.

Risks for birds and mammals through drinking water

Table 15: Ratios of effective application rate (AR_{eff}) to acute and long-term endpoints for Halosulfuron-methyl following the uses of Halosulfuron-methyl 75WG - puddle scenario

Birds			
Effective application rate (g a.s./ha) =	50		
Dietary toxicity (mg a.s./kg bw/d) =	4248	quotient =	0.0118
Reprod. toxicity (mg a.s./kg bw/d) =	119	quotient =	0.4202
Mammals			
Effective application rate (g a.s./ha) =	50		
Dietary toxicity (mg a.s./kg bw/d) =	7758	quotient =	0.0064
Reprod. toxicity (mg a.s./kg bw/d) =	6.3	quotient =	7.9365

The ratios of effective application rate (AR_{eff}) to acute and long-term endpoints fall below the trigger of 50 (K_{oc} < 500 L/kg) indicating that further assessment of the acute and long-term risk to birds and mammals from drinking water from puddles is not required for **halosulfuron-methyl**.

Effects of secondary poisoning

Not expected as log Pow of halosulfuron-methyl and relevant metabolites (soil and surface water) are <3.

Overall, the risk of halosulfuron-methyl for birds and mammals was assessed as low for all representative uses of Halosulfuron-methyl 75WG. The risk for birds and mammals from the consumption of contaminated drinking water was assessed as low.

Aquatic life

Toxicity studies on fish, daphnids, sediment-dwellers, algae and aquatic plants are available. In addition to the usual study with *Lemna gibba*, higher tier studies on aquatic plants with sediment present in the aquaria are also available. The studies indicate that *Lemna gibba* is the most sensitive species investigated, so effects on *Lemna gibba* drive the risk assessment. In addition to the standard guideline *Lemna gibba* effects studies, two *Lemna gibba* studies are available (active substance and formulated product), where the exposure pattern in the study was modified (this is achieved by including sediment in the test system to which the halosulfuron-methyl partitioned). The pattern of decline of halosulfuron-methyl concentrations in the water column was measured in these tests.
EFSA agrees that *Lemna gibba* was the most sensitive aquatic macrophyte species on the basis of the available higher tier studies.

The available acute aquatic toxicity data for fish, aquatic invertebrates, algae and aquatic plants demonstrate that there is no increase in toxicity apparent due to formulating as Halosulfuron-methyl 75WG, as the endpoints are within the same order of magnitude.

The evaluation of the risk for aquatic and sediment-dwelling organisms was performed in accordance with the methods followed in the European union. In the following tables, the ratios between predicted environmental concentrations in surface water bodies (PEC_{SW}) and regulatory acceptable concentrations (RAC) are given for the most sensitive organism in freshwater.

PEC_{SW} values have been calculated assuming entry to the waterbody via spray drift for the active substance and metabolites observed in the aquatic environment in environmental fate studies. As calculations have been performed for exposure to water from the spray drift pathway, only metabolites formed in surface water or sediment have been included in the assessment (either from the aquatic photolysis study or from the water/sediment study). The PEC_{SW} calculations considered an application rate of 1 x 50 g a.s./ha to cover application to all crops. The GAP includes both field crops and application around tree crops. However, application for orchard and citrus crops, are to treat weeds around the crops and care must be taken not to apply the herbicide to the foliage. Therefore, applications will be made in a downwards direction and therefore, the drift values for field crops (downward spray) have been used rather than a traditional air blast upwards and sidewards spray. Therefore, as the drift values are the same, the calculations for field crops also cover application beneath tree crops to treat weeds.

Halosulfuron-methyl is recommended for application to maize, cereals, sugarcane, fruit crops and lawn and therefore exposure to marine or estuarine environments is not expected to arise.

In accordance with the EFSA Aquatic Guidance Document, risk assessment for higher aquatic plants has been performed considering only the more relevant endpoint “growth rate” (E_rC_{50}).

Since *Lemna gibba* is the most sensitive species investigated, the risk assessment for the active substance is only presented for *Lemna gibba*. The 7 d E_rC_{50} values of 0.491 µg a.s./L and 1.42 µg a.s./L from the standard laboratory tests with halosulfuron-methyl and Halosulfuron-methyl 75WG have been used to derive the Tier 1 RAC values of 0.0491 µg a.s./L and 0.142 µg a.s./L (assessment factor of 10), respectively. The 7 d E_rC_{50} values of 3.42 µg a.s./L and 4.45 µg a.s./L from the modified exposure tests with halosulfuron-methyl and Halosulfuron-methyl 75WG have been used to derive the Tier 2 RAC values of 0.342 µg a.s./L and 0.445 µg a.s./L (assessment factor of 10), respectively. A low risk can then be justifiably extrapolated to all other aquatic species if safe use is shown using the macrophyte endpoints.

The calculated PEC/RAC ratios are presented in the table below. Safe use is demonstrated when PEC/RAC < 1.

Table 16: Aquatic organisms: Acceptability of risk (PEC/RAC < 1) for halosulfuron-methyl for aquatic plants for all uses of Halosulfuron-methyl 75WG (1 × 50 g a.s./ha)

Group		**Higher plant**	**Higher plant (modified exposure)**
Test species		***Lemna gibba***	***Lemna gibba*+ sediment**
Endpoint		E_rC_{50}	E_rC_{50}
(µg/L)		0.491	3.42
AF[a]		10	10
RAC (µg/L)		0.0491 (Tier 1)	0.342 (Tier 2)
Drift rate	**PEC_{SW} (µg/L)**	**PEC/RAC ratio**	
2.77% at 1 m (default distance)	0.462	**9.409**	**1.351**
0.57% at 5 m	0.095	**1.935**	0.278
0.29% at 10 m	0.048	0.978	-

AF: Assessment factor; PEC: Predicted environmental concentration; RAC: Regulatory acceptable concentration; PEC/RAC ratios above the relevant trigger of 1 are shown in **bold**

[a] Assessment factor adjusted in line with EFSA/2013/3290

Table 17: Aquatic organisms: Acceptability of risk (PEC/RAC < 1) for Halosulfuron-methyl 75WG for aquatic plants for all uses of Halosulfuron-methyl 75WG (1 × 50 g a.s./ha)

Group		**Higher plant**	**Higher plant (modified exposure)**
Test species		***Lemna gibba***	***Lemna gibba*+ sediment**
Endpoint		E_rC_{50}	E_rC_{50}
(µg/L)		1.42	4.45
AF[a]		10	10
RAC (µg/L)		0.142 (Tier 1)	0.445 (Tier 2)
Drift rate	**PEC_{SW} (µg/L)**	**PEC/RAC ratio**	
2.77% at 1 m (default distance)	0.462	**3.254**	**1.038**
0.57% at 5 m	0.095	0.669	0.213

AF: Assessment factor; PEC: Predicted environmental concentration; RAC: Regulatory acceptable concentration; PEC/RAC ratios above the relevant trigger of 1 are shown in **bold**

[a] Assessment factor adjusted in line with EFSA/2013/3290

The risk assessments for halosulfuron-methyl and Halosulfuron-methyl 75 WG, based on PEC_{SW} values from entry via drift, demonstrates an acceptable chronic risk to aquatic plants (most sensitive aquatic organisms) with a 5 m buffer zone for all uses of Halosulfuron-methyl 75 WG at 1 x 50 g a.s./ha when using higher tier studies.

For the potentially relevant metabolites of halosulfuron-methyl, no study data are available on the most sensitive species for halosulfuron-methyl, i.e. aquatic plants (*Lemna gibba*). However, the toxicity data available on the green algae for the metabolites halosulfuron, halosulfuron-methyl rearrangement and aminopyrimidine show that that these metabolites are more than 1000 fold less toxic than the parent. Therefore, the risk assessment for the metabolites was conducted assuming the toxicity of these metabolites is equal to the toxicity of the parent, i.e. an E_rC_{50} of 0.491 µg/L is used for the potentially relevant metabolites halosulfuron-methyl rearrangement (HSMR), halosulfuron (HS), halosulfuron

rearrangement (HSR), chlorosulfonamid (CSE), chlorosulfonamide acid (CSA) and aminopyrimidine (AP).

Table 18: Aquatic organisms: Acceptability of risk (PEC/RAC < 1) for the metabolites of Halosulfuron-methyl for aquatic plants for all uses of Halosulfuron-methyl 75WG (1 × 50 g a.s./ha)

Metabolite	**HSMR**	**HSR**	**CSA**	**HS**	**CSE**	**AP**
Group	**Higher plant**					
Test species[a]	***Lemna gibba***					
Endpoint	E_rC_{50}	E_rC_{50}	E_rC_{50}	E_rC_{50}	E_rC_{50}	E_rC_{50}
(µg/L)	0.491	0.491	0.491	0.491	0.491	0.491
AF[b]	10	10	10	10	10	10
RAC (µg/L)	0.0491	0.0491	0.0491	0.0491	0.0491	0.0491
PEC_{SW} (µg/L)[c]	0.107	0.102	0.017	0.041	0.014	0.012
PEC/RAC ratio	2.179	2.077	0.346	0.835	0.285	0.244

AF: Assessment factor; PEC: Predicted environmental concentration; RAC: Regulatory acceptable concentration; PEC/RAC ratios above the relevant trigger of 1 are shown in **bold**

[a] Most sensitive test species

[b] Assessment factor adjusted in line with EFSA/2013/3290

[c] PEC_{sw} for a drift value of 2.77% for one application at the default distance of 1 m

The risk assessments for the potentially relevant metabolites of halosulfuron-methyl, based on PEC_{SW} values from entry via drift, demonstrates an acceptable risk to aquatic organisms without mitigation measures for all uses of Halosulfuron-methyl 75 WG at 1 x 50 g a.s./ha when using standard laboratory testing outcomes.

Overall, for halosulfuron-methyl and its potentially relevant metabolites there is low risk to aquatic organisms following the uses of Halosulfuron-methyl 75WG when using a 5 m buffer zone.

According to the EFSA Guidance Document, substances with a log Pow ≥3 have the potential for bioaccumulation. The log Pow of halosulfuron-methyl of 1.67 at pH 5, -0.0186 at pH 7 and -0.542 at pH 9 which is lower than the trigger value of 3 and therefore indicates low potential for bioaccumulation.
The log Pow of halosulfuron-methyl rearrangement is 2.313. For halosulfuron rearrangement, halosulfuron, chlorosulfonamide, chlorosulfonamide acid and aminopyrimidine EPI Suite KOWWIN version 1.68 (version 4.1) estimates the log Pow value as 2.31, 0.45, -0.54, -0.49 and 0.95, respectively. These values are lower than the trigger value of 3 and therefore indicate low potential for bioaccumulation. Therefore, no further consideration of metabolites is considered necessary and BCF studies are not required.

Bees

According to the 'Guidelines on the management of the risk of Agricultural Remedies on insect pollinators (DAFF, 2017)' with a contact LD_{50} of >100 µg a.s./bee from a study conducted in conformance with the OECD guidelines 214 (see Table 5), halosulfuron-methyl can be classified as non-toxic ($LD_{50} \geq 11$ µg/bee) to bees. Therefore, no additional toxicology data will be required for any residues that may be present in pollen and nectar.

As the EFSA guidance (EFSA Journal 2013;11(7):3295) is not agreed at EU level, the evaluation of the risk (acute oral and contact) for bees (honey bees and bumble bees) is performed according to the

existing guidance in force in the EU namely the Guidance Document on Terrestrial Ecotoxicology (SANCO/10329/2002 rev.2 (final), October 17, 2002) and the revised EPPO scheme (OEPP/EPPO, 2010).

The risk assessment for honey bees is based on the maximum single application rate of Halosulfuron-methyl 75WG of 50 g a.s./ha.

Table 19: First-tier assessment following SANCO/10329/2002 rev.2 of the acute risk for bees due to the uses of Halosulfuron-methyl 75WG (1 x 50 g a.s./ha)

Intended use **Active substance** **Application rate (g a.s./ha)**		Maize, sorghum, wheat, sugarcane, avocado, citrus, mango and lawn Halosulfuron-methyl 1 × 50		
Species	**Test design**	**LD_{50} (lab.) (µg a.s./bee)**	**Single application rate (g a.s./ha)**	**Q_{HO}, Q_{HC} criterion: $Q_H \leq 50$**
Apis mellifera	Oral toxicity	> 100	50	< 0.5
	Contact toxicity	> 100		< 0.5
Product **Application rate (g a.s./ha)**		Halosulfuron-methyl 75WG 1 × 50		
Species	**Test design**	**LD_{50} (lab.) (µg a.s./bee)**	**Single application rate (g a.s./ha)**	**Q_{HO}, Q_{HC} criterion: $Q_H \leq 50$**
Apis mellifera	Oral toxicity	>100	50	< 0.5
	Contact toxicity	>100		< 0.5

Q_{HO}, Q_{HC}: Hazard quotients for oral and contact exposure. Q_H values shown in **bold** breach the relevant trigger.

The calculated oral and contact Hazard Quotients for halosulfuron-methyl and Halosulfuron-methyl 75WG are well below the trigger value of 50, indicating an acceptable acute risk to honeybees following the proposed uses of Halosulfuron-methyl 75WG according to the GAP.

Overall, it can be concluded that the risk to bees from the application of Halosulfuron-methyl 75WG according to good agricultural practice is acceptable.

Non-target arthropods (other than bees)

Valid and reliable Tier I data are available for standard sensitive species of non-target arthropods, *Aphidius rhopalosiphi* and *Typhlodromus pyri*. Please refer to Table 6.

The risk to non-target arthropods is assessed using the approach recommended in the published ESCORT 2 document (Candolfi *et al.* 2001) and the EC Guidance Document on Terrestrial Ecotoxicology (SANCO/10329/2002).

The potential risk of Halosulfuron-methyl 75WG to in-field and off-field non-target arthropods has been assessed by calculation of the hazard quotient (HQ = exposure/toxicity) based on the predicted environmental rate (PER) and the lethal rate (LR_{50}) values for the species *Aphidius rhopalosiphi* and *Typhlodromus pyri*.

Table 21: First-tier assessment of the in-field risk for non-target arthropods following the uses of Halosulfuron-methyl 75WG (1 x 50 g a.s./ha)

Intended use	Maize, sorghum, wheat, sugarcane, avocado, citrus, mango and lawn		
Product	Halosulfuron-methyl		
Application rate (g a.s./ha)	1 × 50		
MAF	1		
Test species **Tier I**	**LR_{50} (lab.)** **(g a.s./ha)**	**$PER_{in\text{-}field}$** **(g a.s./ha)**	**$HQ_{in\text{-}field}$** **criterion: HQ ≤ 2**
Aphidius rhopalosiphi	> 300	50	< 0.17
Typhlodromus pyri	> 300		< 0.17

MAF: Multiple application factor; PER: Predicted environmental rate; HQ: Hazard quotient.

Based on the available Tier I studies, the resulting in-field HQ values for *A. rhopalosiphi* and *T. pyri* are well below the trigger of concern. Consequently, an acceptable risk to non-target arthropods from all proposed uses of Halosulfuron-methyl 75WG can be assumed, and an assessment of the off-field non-target arthropods is not necessary.

Exposure to Halosulfuron-methyl 75WG poses no risk to survival within the in-field and off-field habitats for non-target arthropods when the outcomes from standard laboratory studies are considered for all uses according to label recommendations.

Non-target soil meso- and macrofauna

The evaluation of the risk for non-target soil meso- and macrofauna was performed in accordance with the recommendations of the "Guidance Document on Terrestrial Ecotoxicology", as provided by the Commission Services (SANCO/10329/2002 rev 2 (final), October 17, 2002) and taking into account the data requirements given in the Regulation (EC) No 1107/2009. The available toxicity data with halosulfuron-methyl can be extrapolated to Halosulfuron-methyl 75WG. For the potentially relevant soil metabolites (i.e. halosulfuron-methyl rearrangement, halosulfuron, chlorosulfonamide, chlorosulfonamide acid, chlorosulfonamide acid guanidine, chlorosulfonamide guanidine, aminopyrimidine and O-demethyl halosulfuron methyl), for which no experimental data are available for earthworms, an assessment factor of 10 was applied to the parent endpoints.

First-tier risk assessment

An acute risk assessment is no longer required in the EU but is still required in South Africa. The potential acute risk of Halosulfuron-methyl/Halosulfuron-methyl 75WG, halosulfuron-methyl rearrangement, halosulfuron, chlorosulfonamide, chlorosulfonamide acid, chlorosulfonamide acid guanidine, chlorosulfonamide guanidine, aminopyrimidine and O-demethyl halosulfuron methyl to soil macro-organisms was assessed by calculating acute and long-term TER values by comparing the LC_{50} values and the maximum (initial) PEC_{soil} values. PEC_{soil} values have been calculated in accordance with FOCUS (1997) assuming a soil density of 1.5 g/cm^3 and a soil mixing depth of 5 cm. An application rate of 1 x 50 g a.s./ha (or 0.067 kg product/ha) has been assumed for application to all crops (field and around tree crops). This will cover the risk envelope for all crops.

The results of the first-tier risk assessments for eartwormsare summarised in the following tables.

Table 22: First-tier assessment of the acute risk for earthworms due to the uses of Halosulfuron-methyl 75WG in all crops (1 x 50 g a.s./ha, risk envelope)

Intended uses	All crops
Acute effects on earthworms	

Test species	Compound	LC_{50} (mg/kg dw)	$PEC_{soil\ max}$[a] (mg/kg dw)	TER_a (criterion TER ≥ 10)
Eisenia fetida	Halosulfuron-methyl/Halosulfuron-methyl 75WG	>1000	0.0658	>15198
	Halosulfuron-methyl rearrangement	>100[b]	0.0055	>18182
	Halosulfuron	>100 [b]	0.016	>6250
	Chlorosulfonamide	>100 [b]	0.0127	>7874
	Chlorosulfonamide acid	>100 [b]	0.0103	>9709
	Chlorosulfonamide acid guanidine	>100 [b]	0.0116	>8621
	Chlorosulfonamide guanidine	>100 [b]	0.0055	>18182
	Aminopyrimidine	>100 [b]	0.0079	>12658
	O-demethyl halosulfuron methyl	>100 [b]	0.0049	>20408

[a] The PEC_{soil} values cover all uses.
[b] Parent endpoint with safety factor of 10 applied

The above risk assessments demonstrate an acceptable risk to earthworms from all proposed uses of Halosulfuron-methyl 75WG.

Soil micro-organisms

The evaluation of the risk for soil micro-organisms was performed in accordance with the recommendations of the "Guidance Document on Terrestrial Ecotoxicology", as provided by the Commission Services (SANCO/10329/2002 rev 2 (final), October 17, 2002). The available toxicity data with halosulfuron-methyl can be extrapolated to Halosulfuron-methyl 75WG. For the potentially relevant soil metabolites (i.e. halosulfuron-methyl rearrangement, halosulfuron, chlorosulfonamide, chlorosulfonamide acid, chlorosulfonamide acid guanidine, chlorosulfonamide guanidine, aminopyrimidine and O-demethyl halosulfuron methyl), for which no experimental data are available for soil micro-organisms (N-transformation), an assessment factor of 10 was applied to the parent endpoints.

The relevant PEC_{soil} for risk assessments covering the proposed use pattern are already used in the risk assessment for earthworms and other non-target soil organisms (meso- and macrofauna).

The results of the risk assessment for soil micro-organisms are summarised in the following table.

Table 23: Assessment of the risk for effects on soil micro-organisms due to the use of Halosulfuron-methyl 75WG in all crops (1 x 50 g a.s./ha, risk envelope)

Intended use	All crops		
N-mineralisation			
Compound	**NOEC (mg/kg dw)**	**$PEC_{soil\ max}$[a] (mg/kg dw)**	**Risk acceptable?**
Halosulfuron-methyl/ Halosulfuron-methyl 75WG	0.267[b]	0.0658	Yes
Halosulfuron-methyl rearrangement	0.027	0.0055	Yes
Halosulfuron	0.027	0.016	Yes
Chlorosulfonamide	0.027	0.0127	Yes
Chlorosulfonamide acid	0.027	0.0103	Yes
Chlorosulfonamide acid guanidine	0.027	0.0116	Yes
Chlorosulfonamide guanidine	0.027	0.0055	Yes
Aminopyrimidine	0.027	0.0079	Yes
O-demethyl halosulfuron methyl	0.027	0.0049	Yes

[a] The PEC_{soil} values cover all uses.
[b] 200 g a.s./ha converted to mg a.s./kg equivalent of 0.267 mg a.s./kg assuming soil depth 5 cm and soil bulk density of 1.5 g/cm^3

The above risk assessments demonstrate an acceptable risk to non-target soil micro-organisms from all proposed uses of Halosulfuron-methyl 75WG.

Terrestrial non-target higher plants

The risk assessment is based on the "Guidance Document on Terrestrial Ecotoxicology", (SANCO/10329/2002 rev.2 final, 2002). It is restricted to off-field situations, as non-target plants are non-crop plants located outside the treated area. Spray drift from the treated areas may produce residues of a product in adjacent off-crop areas.

Deterministic approach

The effect of halosulfuron-methyl on plant dry weight was the most sensitive parameter in both the pre- and post–emergence studies, with the worst case (lowest) ER_{50} of 0.12 g a.s./ha (lettuce, dry weight, seedling emergence study) and ER_{50} of 0.21565 g a.s./ha (radish, dry weight, vegetative vigour).

Effects on non-target plants are of concern in the off-field environment, where they may be exposed to spray drift. The amount of spray drift reaching off-crop habitats is calculated using the 90th percentile estimates derived by the BBA (2000) from the spray-drift predictions of Ganzelmeier & Rautmann (2001). It has to be noted that for applications in fruit for herbicides that are applied to the ground, the category "field crops" is applicable.

The results of the Tier 1 deterministic risk assessment for non-target terrestrial plants are shown below.

Table 24: Assessment of the deterministic risk for non-target plants due to the uses of Halosulfuron-methyl 75WG

Active substance	Halosulfuron-methyl			
Application rate (g a.s./ha)	50			
Intended use	Maize, sorghum, wheat, sugarcane avocado, citrus and mango (field crops) Kikuyu and/or Cynodon lawn (ornamentals, < 50 cm high)			
Scenario	**ER_{50} (g a.s./ha)**	**Drift rate [a]**	**$PER_{off\text{-}field}$ (g a.s./ha)**	**TER criterion: TER ≥ 5**
Seedling emergence	0.12 (plant dry weight)	2.77% at 1 m	1.39	**0.09**
		0.57% at 5 m	0.29	**0.42**
		0.29% at 10 m	0.15	**0.83**
		0.15% at 20 m	0.08	**1.60**
		0.10% at 30 m	0.05	**2.40**
		0.07% at 40 m	0.04	**3.43**
		0.06% at 50 m	0.03	**4.00**
		0.04% at 75 m	0.02	6.00
Vegetative vigour	0.21565 (plant dry weight)	2.77% at 1 m	1.39	**0.16**
		0.57% at 5 m	0.29	**0.76**
		0.29% at 10 m	0.15	**1.49**
		0.15% at 20 m	0.08	**2.88**
		0.10% at 30 m	0.05	**4.31**
		0.07% at 40 m	0.04	6.16

PER: Predicted environmental rate; TER: toxicity to exposure ratio. TER values in **bold** fall below the relevant trigger
[a] Drift value for one application (90^{th} percentiles)

The above risk assessment demonstrates that in the case of seedling emergence acceptable risk is demonstrated at a distance of 70 m (i.e. TER >5). For vegetative vigour acceptable risk is demonstrated at a distance of 40 m (i.e. TER >5).
Where permitted the use of drift reducing nozzles would reduce the mitigation required for acceptable risk for seedling emergence and for vegetative vigour endpoints.

Table 25: Assessment of the deterministic risk for non-target plants due to the uses of Halosulfuron-methyl 75WG with drift reducing nozzles

Active substance	Halosulfuron-methyl				
Application rate (g a.s./ha)	50				
Intended use	Maize, sorghum, wheat, sugarcane avocado, citrus and mango (field crops) Kikuyu and/or Cynodon lawn (ornamentals, < 50 cm high)				
Scenario	**ER_{50} (g a.s./ha)**	**Drift rate [a]**	**Drift reduction**	**$PER_{off\text{-}field}$ (g a.s./ha)**	**TER criterion: TER ≥ 5**
Seedling emergence	0.12 (plant dry weight)	0.07% at 40 m	50%	0.018	6.86
		0.10% at 30 m	50%	0.025	**4.80**
		0.15% at 20 m	75%	0.019	6.40
		0.20% at 15 m	75%	0.025	**4.80**
		0.29% at 10 m	90%	0.015	8.28
		0.57% at 5 m	90%	0.029	**4.21**
Vegetative vigour	0.21565 (plant dry weight)	0.15% at 20 m	50%	0.038	5.75
		0.20% at 15 m	50%	0.050	**4.31**
		0.29% at 10 m	75%	0.036	5.95
		0.57% at 5 m	90%	0.029	7.57
		2.77% at 1 m	90%	0.139	**1.56**

PER: Predicted environmental rate; TER: toxicity to exposure ratio. TER values in **bold** fall below the relevant trigger
[a] Drift value for one application (90^{th} percentiles)

For seedling emergence, an acceptable risk is demonstrated at a distance of 10 m with 90% drift reducing nozzles or a distance of 20 m with 75% drift reducing nozzles or a distance of 40 m with 50% drift reducing nozzles (i.e. TER >5).

For vegetative vigour, an acceptable risk is demonstrated at a distance of 5 m with 90% drift reducing nozzles or at a distance of 10 m with 75% drift reducing nozzles or at a distance of 20 m with 50% drift reducing nozzles (i.e. TER >5).

Probabilistic approach

Since the deterministic risk assessment illustrated potential risk from the uses of Halosulfuron-methyl 75WG with the need for mitigation based on the plant dry weight seedling emergence and seedling growth study data; the data from the vegetative vigour study is considered in this probabilistic risk assessment, since this was the worst case, as proposed in the Addendum Volume 1, September 2012 included in the EFSA conclusion (Conclusion on the peer review of the pesticide risk assessment of the active substance halosulfuron (evaluated variant halosulfuron-methyl). EFSA Journal 2012;10(12):2987)). The HC_5 value of 0.1 g a.s./ha reported in Table 9 was determined from the ER_{50} data in the vegetative vigour study based on plant dry weight using ETX2 model.

As for the deterministic approach, the probabilistic approach uses the 90^{th} percentile drift deposition data to determine the off-field exposure. Table 26 presents toxicity exposure ratios (TERs) using the HC_5 endpoint.

Table 26: Assessment of the probablistic risk for non-target plants due to the uses of Halosulfuron-methyl 75WG with drift reducing nozzles

Active substance	Halosulfuron-methyl				
Application rate (g a.s./ha)	50				
Intended use	Maize, sorghum, wheat, sugarcane avocado, citrus and mango (field crops) Kikuyu and/or Cynodon lawn (ornamentals, < 50 cm high)				
Scenario	**HC_5 (g a.s./ha)**	**Drift rate [a]**	**Drift reduction**	**$PER_{off\text{-}field}$ (g a.s./ha)**	**TER criterion: TER ≥ 1**
Vegetative vigour	0.10 (plant dry weight)	0.20% at 15 m	-	0.100	1.00
		0.29% at 10 m	50%	0.073	1.38
		0.57% at 5 m	75%	0.071	1.40
		2.77% at 1 m	90%	0.139	**0.72**

PER: Predicted environmental rate; TER: toxicity to exposure ratio. TER values in **bold** fall below the relevant trigger
[a] Drift value for one application (90^{th} percentiles)

For vegetative vigour, based on the HC_5 endpoint, an acceptable risk is demonstrated at a distance of 5 m with 75% drift reducing nozzles or at a distance of 10 m with 50% drift reducing nozzles or at a distance of 15 m without drift reduction (i.e. TER >1).

The acceptable risk for vegetative vigour will be protective of seedling emergence.

It is concluded that the risk to terrestrial non-target plants following all uses of Halosulfuron-methyl 75WG is acceptable at a distance of 5 m with the use of 75% drift reducing nozzles or at a distance of 10 m with the use of 50% drift reducing nozzles or at a distance of 15 m without drift reduction.

Biological methods for sewage treatment

Halosulfuron-methyl had no significant inhibitory effect on the respiration rate of activated sludge at the concentrations tested. The 3- hour EC_{50} was > 100 mg a.s./L based on nominal concentrations. Therefore, an acceptable risk can be concluded for biological methods of sewage treatment.

Conclusion

The quantitative risk assessment of the halosulfuron-methyl mammalian toxicology, eco-toxicology and environmental fate data package concludes that it is highly unlikely that the environment will be at unacceptable risk due to the use and application of the product Halosulfuron 750WDG to cereals, sugarcane, avocado, citrus, mango and lawn, according to Good Agricultural Practices (GAP).

References

EFSA (European Food Safety Authority), 2012. Conclusion on the peer review of the pesticide risk assessment of the active substance halosulfuron (evaluated variant halosulfuron-methyl). EFSA Journal 2012;10(12):2987.

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EFSA (European Food Safety Authority), 2013. Guidance on tiered risk assessment for plant protection products for aquatic organisms in edge-of-field surface waters EFSA Journal 2013;11(7):3290.

European Commission, 2002a. Guidance Document on Terrestrial Ecotoxicology Under Council Directive 91/414/EEC. SANCO/10329/2002 rev.2 final, 17 October 2002.

SETAC (Society of Environmental Toxicology and Chemistry), 2001. Guidance Document on Regulatory Testing and Risk Assessment procedures for Plant Protection Products with Non-Target Arthropods. ESCORT 2.

Supported products

Company	Product	Registration number
Farm-Ag International (Pty) Ltd	Brigadier 750 WG	L9218
ICA International Chemicals (Pty) Ltd	WeedO 750 WG	L11149
UPL South Africa (Pty) Ltd	Cyprex WG	L7665
Sharda International Africa (Pty) Ltd	Halosulfuron 750 WDG	L10855
Villa Crop Protection (Pty) Ltd	Halo 750 WDG	L8283
Rainbow Agrosciences (Pty) Ltd	Flagship 750 WDG	L10539
Green Island Investments Pty Ltd	Halo-Fron WG	L10152