Draft Assessment Report

Evaluation of Active Substances

Plant Protection Products

Prepared according to **Retained Regulation (EC) 1107/2009**
as it applies in Great Britain

Prosulfuron

Volume 1

GB Article 7 Amendment

Great Britain

September 2023

Version History

When	What
September 2023	HSE Initial Assessment

Table of contents

Level 1

Prosulfuron

1. STATEMENT OF SUBJECT MATTER AND PURPOSE FOR WHICH THIS REPORT HAS BEEN PREPARED AND BACKGROUND INFORMATION ON THE APPLICATION

1.1. CONTEXT IN WHICH THIS DRAFT ASSESSMENT REPORT WAS PREPARED

This draft assessment report (DAR) has been prepared to evaluate the application for amendment of the approval for the approved pesticidal active substance prosulfuron in Great Britain (GB). The application was submitted by Syngenta, the producer of the active substance (hereafter referred to as the "applicant") in September 2021 under retained Regulation (EC) No 1107/2009.

The approval of prosulfuron was renewed in the European Union (EU) in May 2017. The UK was a Member State (MS) of the EU at that time and therefore the approval of prosulfuron applied directly to the UK. Prosulfuron was renewed with the following restriction of the approval according to the provisions in Article 6(1) of Regulation (EC) No 1107/2009:

> *Use shall be limited to one application every three years on the same field at a maximum dose of 20 g active substance per hectare.*

The above restriction and all other details related to the approval of prosulfuron are included in the implementing regulation[1].

The applicant submitted an amendment application under Article 7 of Regulation (EC) 1107/2009 to the EU in 2016 to remove the restriction on the approval. The EU

[1] Commission Implementing Regulation (EU) No 2017/375 of 02 March 2017 renewing the approval of the active substance prosulfuron, as a candidate for substitution, in accordance with Regulation (EC) No 1107/2009 of the European Parliament and of the Council concerning the placing of plant protection products on the market, and amending the Annex to Commission Implementing Regulation (EU) No 540/2011 (OJ L 58, 4.3.2017, p. 6).

application was considered and evaluated by France as the Rapporteur Member State (RMS). The French competent authority completed the draft renewal assessment report (dRAR) in 2018. A revised dRAR was prepared in 2019 in response to submission of additional data requested by the European Food Safety Authority (EFSA) during the EU peer review process. An updated EFSA Conclusion was published in 2020[2]. The EU decided to amend the approval of prosulfuron to remove the restriction. This is detailed within the implementing Regulation (EU) 2021/574[3] published 30 March 2021. Since the publication of the regulation was after the UK withdrawal from the EU, it does not apply to GB.

Therefore, the producer of the active substance submitted an application to HSE as the reviewing competent authority for GB, to remove the restriction in GB. The applicant submitted the EU assessment and relevant documents from the EU assessment process to HSE to support the GB application. HSE has considered the EU assessment and supporting documentation in the GB assessment since the same guidance and data requirements are applicable to GB as in the EU. However, HSE has performed an independent consideration and assessment of the data and information submitted.

1.2. APPLICANT INFORMATION

1.2.1. Name and address of applicant(s) for approval of the active substance

Address : Syngenta Limited
European Regional Centre
30 Priestly Road
Surrey Research Park
Guildford, Surrey
GU2 7YH
United Kingdom

Contact person : Mr [redacted]

[2] EFSA (European Food Safety Authority), Anastassiadou, M, Arena, M, Auteri, D, Brancato, A, Bura, L, Carrasco Cabrera, L, Chaideftou, E, Chiusolo, A, Crivellente, F, De Lentdecker, C, Egsmose, M, Fait, G, Greco, L, Ippolito, A, Istace, F, Jarrah, S, Kardassi, D, Leuschner, R, Lostia, A, Lythgo, C, Magrans, O, Mangas, I, Miron, I, Molnar, T, Padovani, L, Parra Morte, JM, Pedersen, R, Reich, H, Santos, M, Sharp, R, Stanek, A, Sturma, J, Szentes, C, Terron, A, Tiramani, M, Vagenende, B and Villamar-Bouza, L, 2020. Conclusion on the peer review of the pesticide risk assessment of the active substance prosulfuron. EFSA Journal 2020;18(7):6181, 20 pp.

[3] Commission Implementing Regulation (EU) 2021/574 of 30 March 2021 amending Implementing Regulations (EU) 2017/375 and (EU) No 540/2011 as regards the conditions of approval of the active substance prosulfuron (OJ L 120, 8.4.2021, p. 9–12).

Head of Regulatory UK & Ireland
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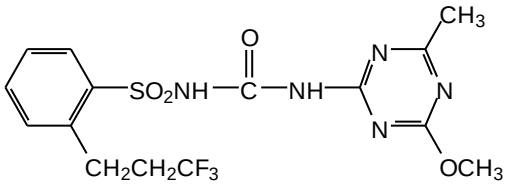
CPC4, Capital Park
Fulbourn
Cambridge
CB21 5XE
Tel: [redacted]
E-mail: [redacted]

1.2.3. Information relating to the collective provision of dossiers

Not relevant. Syngenta are the sole notifier for Prosulfuron.

1.3. IDENTITY OF THE ACTIVE SUBSTANCE

1.3.1. Common name proposed or ISO-accepted and synonyms	Prosulfuron
1.3.2. Chemical name (IUPAC and CA nomenclature)	
IUPAC	1-(4-methoxy-6-methyl-triazin-2-yl)-3-[2-(3,3,3-trifluoropropyl)-phenylsulfonyl]-urea
CA	N-[[(4-methoxy-6-methyl-1,3,5-triazin-2-yl)amino]carbonyl]-2-(3,3,3-trifluoropropyl)benzenesulfonamide
1.3.3. Producer's development code number	CGA 152005
1.3.4. CAS, EEC and CIPAC numbers	
CAS	94125-34-5
EEC	-
CIPAC	579
1.3.5. Molecular and structural formula, molecular mass	
Molecular formula	$C_{15}H_{16}F_3N_5O_4S$
Structural formula	
Molecular mass	419.4 g/mol

1.3.6. Method of manufacture (synthesis pathway) of the active substance	Confidential data see Volume 4 of RAR 2014
1.3.7. Specification of purity of the active substance in g/kg	Prosulfuron is manufactured with a minimum purity of 950 g/kg
1.3.8. Identity and content of additives (such as stabilisers) and impurities	
1.3.8.1. Additives	Confidential data see Volume 4 RAR 2014
1.3.8.2. Significant impurities	Confidential data see Volume 4 RAR 2014
1.3.8.3. Relevant impurities	Confidential data see Volume 4 RAR 2014
1.3.9. Analytical profile of batches	Confidential data see Volume 4 RAR 2014

1.4. INFORMATION ON THE PLANT PROTECTION PRODUCT

1.4.1. Applicant	Syngenta
1.4.2. Producer of the plant protection product	Confidential data see Volume 4 RAR 2014
1.4.3. Trade name or proposed trade name and producer's development code number of the plant protection product	Trade name : PEAK® 75 WG Development code number : A-8714 C
1.4.4. Detailed quantitative and qualitative information on the composition of the plant protection product	
1.4.4.1. Composition of the plant protection product	Confidential data see Volume 4 RAR 2014
1.4.4.2. Information on the active substances	Confidential data see Volume 4 RAR 2014
1.4.4.3. Information on safeners, synergists and co-formulants	Confidential data see Volume 4 RAR 2014
1.4.5. Type and code of the plant protection product	Water dispersible granules Code: WG
1.4.6. Function	Herbicide
1.4.7. Field of use envisaged	Agriculture
1.4.8. Effects on harmful organisms	Prosulfuron is absorbed via both the foliage and the plant roots. The compound is translocated within xylem as well as phloem to the site of action.

1.5. DETAILED USES OF THE PLANT PROTECTION PRODUCT

1.5.1. Details of representative uses

Crop and/or situation (a)	Member State	Product Name	F G I (b)	Pests or group of pests controlled (c)	Formulation		Application				Application rate per treatment			PHI (days) (l)	Remarks (m)
					Type (d-f)	Conc of a.i. g/kg (i)	Method kind (f-h)	Growth stage and season (j)	Number min max (k)	Interval between applications (min)	Kg a.i./hl min max (g/hl)	Water l/ha min max	Lk a.i./ha min max (*) (g/ha)		
Maize and sweet corn	GB	PEAK® 75 WG	F	Broad leaved weeds as cited on label	WG	750	Broadcast foliar application	BBCH 12-18 corresponding to 2-8 leaves	1	-	5-25	80-400	20	90 (grain) 60 (silage)	In combination with a nonionic surfactant at 0.1% to 0.25% of application volume
Maize and sweet corn	GB	PEAK® 75 WG	F	Broad leaved weeds as cited on label	WG	750	Broadcast foliar application	BBCH 12-18 corresponding to 2-8 leaves	1	-	3.75-18.75	80-400	15	90 (grain) 60 (silage)	In combination with a nonionic surfactant at 0.1% to 0.25% of application volume
Maize and Sweet corn	GB	PEAK® 75 WG	F	Broad leaved weeds as cited on label	WG	750	Broadcast foliar application	BBCH 12-19 corresponding to 2-9 leaves	1 (or split application)*	-	3.75-18.75	80-400	15 (total)	90 (grain) 60 (silage)	In combination with a nonionic surfactant at 0.1% to 0.25% of application volume [split app. is 2 apps to a total of 15g within BBCH 19]

* For uses where the column „Remarks“ in marked in grey further consideration is necessary. Uses should be crossed out when the notifier no longer supports this use(s).

(a) For crops, the EU and Codex classification (both) should be taken into account ; where relevant, the use situation should be described (e.g. fumigation of a structure)

(b) Outdoor or field use (F), greenhouse application (G) or indoor application (I)

(c) *e.g.* biting and suckling insects, soil born insects, foliar fungi, weeds

(i) g/kg or g/L. Normally the rate should be given for the active substance (according to ISO) and not for the variant in order to compare the rate for same active substances used in different variants (e.g. fluoroxypyr). In certain cases, where only one variant synthesised, it is more appropriate to give the rate for the variant (e.g. benthiavalicarb-isopropyl).

(j) Growth stage at 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

(d) *e.g.* wettable powder (WP), emulsifiable concentrate (EC), granule (GR)
(e) GCPF Codes – GIFAP Technical Monograph N° 2, 1989
(f) All abbreviations used must be explained: WG (water-dispersible granules)
(g) Method, e.g. high volume spraying, low volume spraying, spreading, dusting, drench
(h) Kind, e.g. overall, broadcast, aerial spraying, row, individual plant, between the plant – type of equipment used must be indicated (i) Concentration in g ai/kg of g ai/L.
(k) Indicate the minimum and maximum number of application possible under practical conditions of use
(l) PHI - minimum pre-harvest interval
(m) Remarks may include: extent of use / economic importance / restrictions

*split application is 2 applications to a total of 15 g/ha within BBCH 19

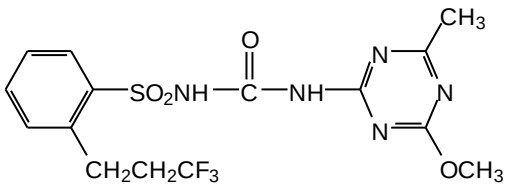
Level 2

Prosulfuron

2. SUMMARY OF ACTIVE SUBSTANCE HAZARD AND OF PRODUCT RISK ASSESSMENT

2.1. IDENTITY

Prosulfuron is a sulfonylurea herbicide, which acts through the inhibition of the enzyme acetolactate synthase (ALS). It is marketed in the form of water dispersible granules.



2.2. PHYSICAL AND CHEMICAL PROPERTIES

2.2.1. Summary of physical and chemical properties of the active substance

Prosulfuron is a white powder with no odour and low volatility (Henry's law constant = 3.5 x 10^{-4} Pa m^3 mol^{-1}). Its solubility in water (pH = 4.5) and in buffer solution (pH = 5) is low and is high at pH = 7.7. It is soluble in organic solvents and more particularly in halogenated hydrocarbon and ketone. This is not a fat soluble compound (log P_{ow} = 1.5 at pH = 5.0). Hydrolysis of prosulfuron is quite rapid at pH 5 ($t_{1/2} \cong$ 90d) and stable at pH 7 and pH 9 (t_{50} > 1 year). Some hydrolysis compounds were found after a 30 days study. Prosulfuron is not explosive and is not considered as an oxidizing substance.

Prosulfuron is stable after 2 weeks at 54°C and after 1 year at 20°C but results after 2 years at 20°C must be provided.

2.2.2. Summary of physical and chemical properties of the plant protection product

The formulation is under form of fine brown granules. It is not considered as explosive, oxidizing, highly flammable and shows no self-ignition. Its pH is within the range that naturally occurs. The formulation is stable for 2 weeks at 54°C and for at least 2 years at 20°C. Data on physical and chemical compatibility with other products have not been submitted.

2.3. DATA ON APPLICATION AND EFFICACY

For this Article 7 amendment application, data on application and efficacy is unchanged from the assessment in the existing RAR dated 2014.

2.4. FURTHER INFORMATION

For this Article 7 amendment application, further information is unchanged from the assessment in the existing RAR dated 2014.

2.5. METHODS OF ANALYSIS

For this Article 7 amendment application, methods of analysis is unchanged from the assessment in the existing RAR dated 2014.

2.6. EFFECTS ON HUMAN AND ANIMAL HEALTH

Background information

Prosulfuron was included into Annex I of Council Directive 91/414/EEC in 2002 (Commission Directive 2002/48/EC, 30 May 2002) and it is currently approved under

Commission Regulation (EC) 1107/2009 (repealing Commission Directive 91/414/EEC) as specified in Commission Implementing Regulation (EU) No. 540/2011 of 25 May 2011.

Following application for renewal, the Renewal Assessment Report (RAR) was peer reviewed by EFSA in 2014[4]. A critical area of concern was identified for the potential groundwater exposure above the parametric drinking water limit (0.1 µg/L) by the parent prosulfuron in all or the majority of the EU groundwater scenarios, even when use is limited to one application every third year. A data gap was identified for a relevance assessment for the groundwater metabolites CGA150829, CGA300406 and CGA325025. For CGA150829, genotoxic potential could not be ruled out, based on available data.

Implementing Regulation (EU) No 2017/375 of 2 March 2017, renewing the approval of prosulfuron, set out a restriction limiting the use of prosulfuron containing products to one application every three years on the same field at a maximum dose of 20 g active substance per hectare. The same regulation stated that the applicant shall provide further information confirming that the metabolite triazine-amine (CGA150829) does not have genotoxic potential and is not relevant for risk assessment. Shortly before the Implementing Regulation was published, Syngenta Crop Protection AG submitted an Article 7 application to the EU Rapporteur Member State (RMS) France, who prepared a revised renewal assessment report (RAR), which was submitted to EFSA in April 2018 and made available for commenting. Further information was requested from the applicant following the commenting stage, which was again evaluated by France and a further revised renewal assessment report was prepared (France, 2019[5]).

The Commission presented an addendum to the review report for prosulfuron and a draft Regulation to the Standing Committee on Plants, Animals, Food and Feed on 23 October 2020, establishing “that with respect to one or more representative uses of at least one plant protection product containing prosulfuron, when the plant

[4] Conclusion on the peer review of the pesticide risk assessment of the active substance prosulfuron, EFSA, 2014. Available: https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2014.3815

[5] France, 2019. Further revisions to the revised Renewal Assessment Report (RAR) on prosulfuron prepared by the Rapporteur Member State France in the framework of Regulation (EC) No 1107/2009, February 2019.

protection product is applied annually, the approval criteria provided for in Article 4 of Regulation (EC) No 1107/2009 are satisfied. It is therefore appropriate to remove the restriction limiting the use of prosulfuron to one application every three years on the same field at a maximum dose of 20 g active substance per hectare."

This GB application is supported by relevant data already submitted and evaluated at the EU level (included in the further revised RAR mentioned above; France, 2019), and the EFSA Conclusion[6]. The applicant has submitted new studies for this GB application to address data gaps identified during the peer review process and listed by EFSA in their conclusions in 2020. These studies concern groundwater metabolites CGA150829 and CGA325025 and their genotoxic potential, which impacts on the relevance assessment and decision on whether the restriction limiting the use of prosulfuron containing products to one application every three years can be lifted. With regard to the toxicological data on the active substance itself, the summaries of the endpoints have been reproduced below as this information may be important to the relevance assessment of the concerned groundwater metabolites.

2.6.1. Summary of absorption, distribution, metabolism and excretion in mammals

Absorption, distribution, metabolism and excretion (ADME)

There is no change to this section from the current assessment (RAR 2014) based on the information submitted for this GB application.

For completeness, the summary of the ADME properties of prosulfuron in mammals from the RAR 2014 is provided below as some groundwater metabolites could be major rat metabolites.

Prosulfuron was found to be rapidly absorbed and almost completely excreted in ADME studies conducted over 7 days using both triazine and phenyl labelled prosulfuron. The principal route of excretion was via the urine (about two thirds with the urine and one third with the faeces). A small amount (<10%) of prosulfuron or its

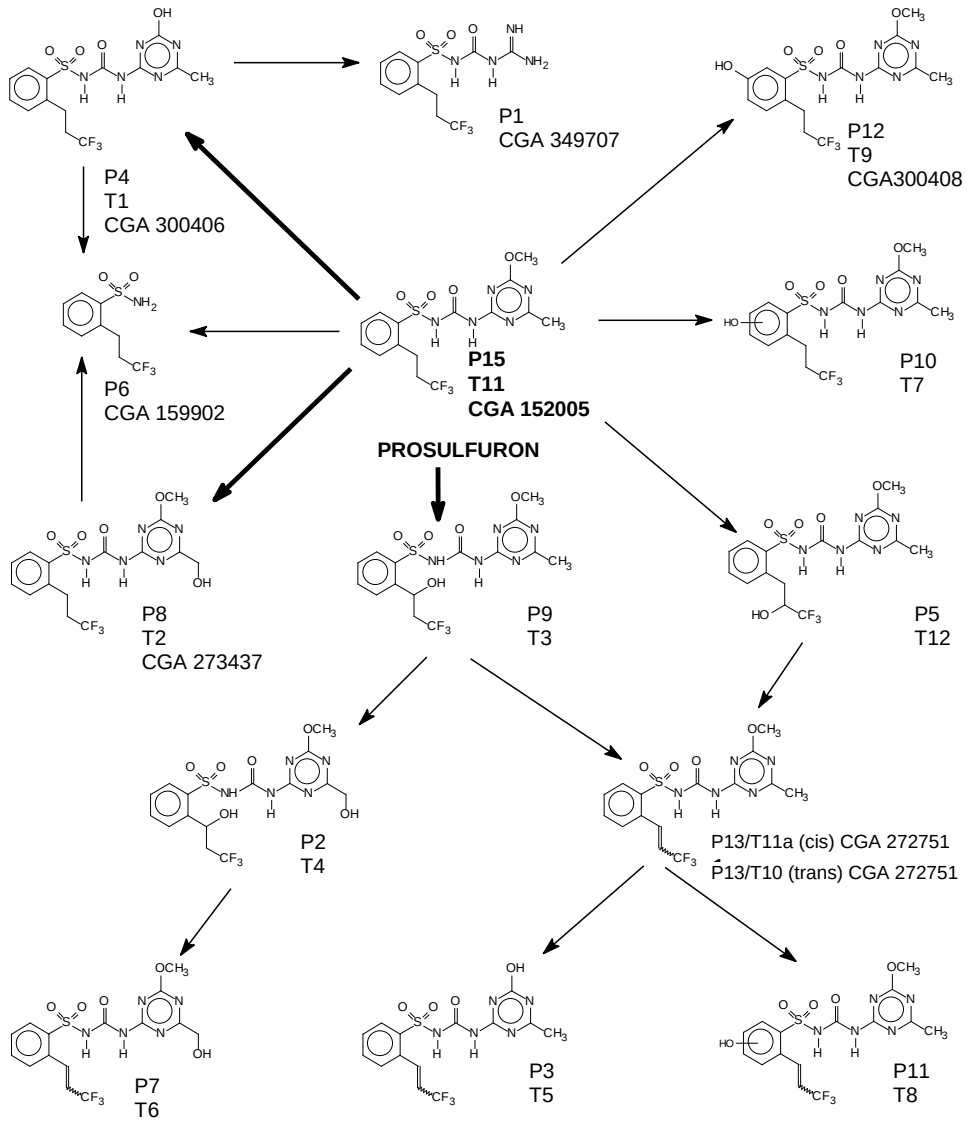
[6] Peer review of the pesticide risk assessment of the active substance prosulfuron. EFSA, June 2020. Available: https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2020.6181

metabolites were excreted with the bile. In a pharmacokinetic study using triazine labelled prosulfuron, peak plasma concentrations were reached 15 minutes and 4 hours following oral doses of 0.5 mg/kg and 400 mg/kg respectively, independent of sex. Pharmacokinetic parameters may have been affected by the different dosing vehicles used at the low and high dose levels in these studies.

Residual tissue levels were low after 7 days when a low dose (0.5 mg/kg) was administered, with most measurements of radioactivity being below the limit of quantification. Quantifiable levels of radioactivity were found in the whole blood (<0.0091 to 0.027% of the administered dose), plasma (<0.0045 to 0.018% of the applied dose) and liver (<0.0021 to 0.074% of the applied dose). Higher residues were observed after administration of an 800-fold dose (400 mg/kg). The highest residues were detected in the whole blood (0.014 to 0.050% of the applied dose), liver (0.012 to 0.044% of the applied dose), kidneys (0.0028 to 0.0053% of the applied dose), lungs (0.0018 to 0.0079% of the applied dose), and in the heart (<0.00074 to 0.0020% of the applied dose).

Prosulfuron was well metabolised (less than ca. 30% parent compound was excreted), 14 metabolites were identified in urine and faeces. Metabolism was almost independent of the administered dose but there were some differences between the sexes in the amount of individual metabolites. The predominant metabolic reactions included the hydroxylation at the side chains and the phenyl ring, O-demethylation of the triazine methoxy-group, and generation of a double bond on the trifluoropropyl group. Cleavage of the sulfonylurea bridge appears to be a minor metabolic pathway.

Figure 2.6.1-1 Proposed metabolic pathway of prosulfuron in rat



2.6.2. Summary of acute toxicity

No new data have been submitted. Please refer to original EU RAR 2014.

Table 2.6.2-1 Summary of the acute toxicity of prosulfuron

Type of Study	Result		Classification	References
Acute oral LD_{50} in rats	LD_{50} (male)	949 mg/kg	Harmful if swallowed: R22 H302, Acute	[redacted] 1991e
	LD_{50} (female)	546 mg/kg		
	LD_{50} (both)	986 mg/kg		
Acute oral LD_{50} in mice	LD_{50} (male)	1208		[redacted] 1991d

		mg/kg	Tox. Cat. 4	
	LD_{50} (female)	1262 mg/kg		
	LD_{50} (both)	1247 mg/kg		
Acute dermal LD_{50} in rabbits	LD_{50}> 2000 mg/kg		None	[redacted] 1991c
Acute inhalation LC_{50} in rats	LC_{50}> 5.4 mg/L		None	[redacted] 1991
Primary skin irritation in rabbits	Non irritant		None	[redacted] 1991b
Primary eye irritation in rabbits	Slight irritant		None	[redacted] 1991a
Skin sensitisation (Buehler 3 applications) in Guinea pigs	Non sensitizing		None	[redacted] 1991f
Skin sensitization (M&K) in Guinea pigs	Non sensitizing		None	[redacted] 1992a

Prosulfuron is classified for **acute toxicity by the oral route, category 4 (H302, harmful if swallowed)** according to Regulation 1272/2008. Although prosulfuron was not a skin sensitiser in two skin sensitization studies, the presence of an impurity CGA159902 classified for skin sensitisation present at 1% in the technical specification and not sufficiently tested in these studies (tested at 0.1%), triggers the classification of prosulfuron with **H317, may cause an allergic skin reaction**.

2.6.3. Summary of short-term toxicity

No new data have been submitted. Please refer to original EU RAR 2014.

Table 2.6.3-1 Summary of adverse effects in short-term toxicity studies

Studies	**NOAEL** approx. mg/kg bw/day	**Dose/ adverse effects** approx. mg/kg bw/day	**References**
28-day rat Gavage	100	300: Liver effects (weights/clinical chemistry), decreases in red blood cell counts/hematocrit	[redacted], 1992
28-day rat Diet	107	209: Decreased body weight gains (changes in clinical chemistry indicative of possible liver	[redacted] ad [redacted],

		effects)	1991
28-day mouse Diet	14	169: Liver effects (weights/clinical chemistry)	[redacted], 1991a
28-day dog Diet	None*	19 (lowest dose): Liver weight effects	[redacted], 1991b
28-day dog Diet	None*	32 (lowest dose): Liver, adrenal and spleen weight effects	[redacted], 1992
90–day rat Diet	3	33: Reduced body weight and body weight gain, liver weights 255: Liver effects (decreased triglycerides and 5'-nucleotidase activities in males)	[redacted] and [redacted], 1991
90–day mouse Diet	69	264: Liver effects (increased liver weights, hepatocyte hypertrophy, and changes of liver-associated clinical chemistry parameters), some changes of red blood cell parameters 504: heart effects (vacuolative degeneration)	[redacted] and [redacted], 1991
90–day dog Diet	5.9	56: Decreased body weight gain/ body weight loss, liver effects (increased liver weights, and changes clinical chemistry parameters), hematopoietic system (decreased RBC counts, decreased hematocrit, decreased haemoglobin concentration, abnormal erythrocyte morphology, thrombocytopenia and changes in leukocyte counts, erythroid hyperplasia of the bone marrow) 110: heart effects (myocardial necrosis and degeneration)	[redacted], 1991
21-day rabbit Dermal	None	No valid study	[redacted], 1992

* Due to the limited nature of these studies, it is not appropriate to set a No-observed-adverse-effect level (NOAEL).

In subchronic studies in rats the liver was shown to be a target organ with weight and clinical chemistry changes, though no histopathological effects. Body weight effects and changes in haematological parameters were seen at higher dose levels.

In mice the liver was also a target organ with increased weights, hepatocyte hypertrophy, and changes of liver-associated clinical chemistry parameters. The heart also appeared to be a target organ with multifocal vacuolative degeneration (precise location not stated). Additionally, some changes of red blood cell parameters were observed.

At high doses administration of prosulfuron to dogs caused decreased body weight gain or even body weight loss. The main effects were noted in the liver (increased weights, changes in clinical chemistry parameters and pigment accumulation, possibly lipofuscin), the heart (myocardial necrosis and degeneration), kidney (pigment accumulation, renal proximal tubular epithelial fatty change) and in the hematopoietic system.

The inconsistency between NOAEL in mice after 28 days (14 mg/kg bw/day) and after 90 days (69 mg/kg bw/day) is only apparent. Both studies were performed in the same lab, with the same strains. The slight effect on the liver, target organ for all species, was considered as non adaptative in the 28-day assay (due to the lack of histopathological data in this assay, thus setting of a conservative NOAEL) and adaptative in the 90-day assay. In fact, if the same criteria are used, NOAEL could be respectively 1000 ppm (155 mg/kg bw/day) and 500 ppm (69 mg/kg bw/day) after 28 and 90 days.

The NOAEL of the 90-day rat study was set at 3 mg/kg bw/day based on marginal but clear effects on body weight and body weight gain seen at 33 mg/kg bw/day. Nevertheless, a clear NOAEL for the rat was seen in the 2-year study at 8.6 mg/kg bw/day. The lower NOAEL set in the 90-day study compared to the 2-year study is due to an inadequation between ranges of doses used in these studies.

Consequently, the relevant lowest oral NOAEL for short term toxicity is 5.9 mg/kg bw/day based on the 90-day dog study.

2.6.4. Summary of genotoxicity

No new data have been submitted. Please refer to original EU RAR 2014.

Table 2.6.4-1 Summary of genotoxicity studies with prosulfuron

Test system	Test species/cells	Prosulfuron concentration	Result	Reference
In vitro assays				
In vitro	*Salmonella*	2.4 to 39.1	Negative	[redacted],

bacterial reverse mutation assay (Ames)	*typhimurium* (TA1535, TA1537, TA98, TA100) and *Escherichia coli* (WP2 uvrA)	μg/plate (*S. typhimurium*), 312.5 to 5000 μg/plate (*E. coli*)	(with and without S9)	1991
In vitro bacterial reverse mutation assay (Ames)	*Salmonella typhimurium* (TA1535, TA1537, TA98, TA100) and *Escherichia coli* (WP2 uvrA pKM101, WP2 pKM101)	Up to 5000 μg/plate	Negative (with and without S9)	[redacted], 2011
In vitro bacterial reverse mutation assay (Ames)	*Salmonella typhimurium* (TA1535, TA1537, TA98, TA100) and *Escherichia coli* (WP2 uvrA pKM101, WP2 pKM101)	Up to 5000 μg/plate	Negative (with and without S9)	[redacted], 2011a
In vitro mammalian cell gene mutation assay	Chinese hamster V79 cells	Up to 1400 μg/ml	Negative (with and without S9)	[redacted], 1991
In vitro cytogenetic test	Chinese hamster ovary cells	Up to 500 μg/ml	No increased number of cell chromosome aberrations (with and without S9)	[redacted], 1991
In vitro autoradiographic DNA-repair test	Rat hepatocytes	Up to 1000 μg/ml	No increase in unscheduled DNA-repair	[redacted], 1991
In vivo assays				
In vivo micronucleus test	Mouse bone marrow cells	Up to 1600 mg/kg bw (single dose)	Negative	[redacted], 1991

When tested in vitro, prosulfuron was negative in an Ames test (with *Salmonella typhimurium* and *Escherichia coli*), a mammalian cell gene mutation assay with V79 cells, a cytogenetic test in Chinese hamster ovary cells, and an autoradiographic DNA-repair test in rat hepatocytes. Prosulfuron was also negative in two recent Ames tests performed due to new manufacturing specification for prosulfuron and submitted during the renewal process of prosulfuron.

When tested in vivo, prosulfuron did not induce micronuclei in a bone marrow micronucleus test in the mouse, although no evidence of bone marrow toxicity data was presented, the test was conducted at or close to the maximum tolerated dose and distribution data (in the rat) indicate that prosulfuron appears to reach the bone.

2.6.5. Summary of long-term toxicity and carcinogenicity

No new data have been submitted. Please refer to original EU RAR 2014.

Table 2.6.5-1 Summary of the results of the long-term toxicity and carcinogenicity studies

Studies	NOAEL approx. mg/kg bw/day	Dose/adverse effects approx. mg/kg bw/day	References
Rat 2-year oral (diet)	8.6	88: Decreased body weights/body weight gain, effects on red blood cell parameters, possible treatment related increased incidence of testicular interstitial cell tumours/early onset mammary gland adenocarcinomas in females 183: Increased incidence of uterine endometrial hyperplasia and uterine horn dilatation in females and increased incidence of acinar atrophy of the mammary gland in males: indication of hormonal disruption (uterus and mammalian gland in rats) at high dose levels	[redacted], [redacted] and [redacted], 1994
Mouse 18-month oral (diet)	1.71	82: increased incidence of centrilobular hepatocyte hypertrophy in males 410: decreased body weight gain, effects on red blood cells (increased hematocrit, decreased MCHC) and on the liver (weights, centrilobular hepatocyte hypertrophy)	[redacted] and [redacted], 1993
Dog 1-year oral (diet)	1.9	19: Decreased red blood cell parameters, liver effects (increased liver weights, and changes clinical chemistry parameters), accumulation of lipofuscin in the liver and kidney	[redacted] and [redacted], 1993

In a lifetime study in the rat there was a slightly increased incidence of testicular interstitial cell tumours in males, and a small increase in the incidence of mammary gland adenocarcinomas in females at the same dose levels, however the changes were not significant when the increased survival in these groups was considered. There was also an apparent earlier onset of mammary gland adenocarcinomas in females, although no significant difference existed for adenocarcinoma onset time between the control and any treatment group. Additionally, there was an increased incidence of uterine endometrial hyperplasia and uterine horn dilation in females as well as an increased incidence of acinar atrophy of the mammary gland in males.

No evidence of carcinogenicity was seen in mice.

2.6.6. Summary of reproductive toxicity

No new data have been submitted. Please refer to original EU RAR 2014.

Table 2.6.6-1 Summary of the results of the multigeneration study (oral route)

Species	NOAEL approx. mg/kg bw/day	Dose/reproductive effects approx. mg/kg bw/day	References
Rat (diet)	Parental: 12 Offspring: 12 Reproductive: 251	135: Body weight changes in parental animals and pups No effect on reproductive performance at any dose level.	[redacted] and [redacted], 1993

In a two generation study in the rat the NOAEL was 200 ppm (equivalent to approximately 12 mg/kg bw/day) based on the body weight effects seen in both parental animals and pups. In the P0 generation there was no indication of any treatment-related effects on precoital interval, mating index, parturition index, or gestation length. The pregnancy and gestation indices were comparable between all groups except for the low dose group, where slightly lower indices were obtained. In the P1 generation there was no indication for treatment-related effects on precoital interval, mating index, parturition index, or gestation length. The pregnancy, fertility, and gestation indices were comparable between all groups except for the low and top

dose groups, where lower indices were obtained. This is nevertheless considered incidental.

Table 2.6.6-2 Summary of the results of the developmental toxicity studies (oral route)

Species	NOAEL mg/kg bw/day	Dose/developmental effects mg/kg bw/day	References
Rat (gavage, GD 6-15)	Maternal: 200 Developmental: 50	Maternal: 400: reduced body weight gain and food consumption Developmental: 200: slightly increased incidence of skeletal variations (primarily extra-rudimentary ribs and lobed and/or constricted thoracic vertebrae centra)	[redacted], 1992
Rabbit (gavage, GD 7-19)	Maternal: 10 Developmental: 10	Maternal: 100: reduced body weight gain and food consumption Developmental: 100: increased incidence of resorptions	[redacted], 1992

Prosulfuron was not teratogenic in either rats or rabbits. The no effect level for maternal toxicity and developmental toxicity was 200 and 50 mg/kg bw/day respectively in rats, while in rabbits the no effect level for maternal toxicity and developmental toxicity was 10 mg/kg bw/day. It should be noted that although no maternal toxicity was seen in the rat developmental study at 200 mg/kg bw/day, based on other short term studies in the rat it is likely that some maternal toxicity was present.

Prosulfuron was shown not to have endocrine disruptive effects in vivo, and it is considered unlikely that in vitro tests would add any relevant information. Therefore, prosulfuron is unlikely to be an endocrine disruptor (EFSA, 2014).

2.6.7. Summary of neurotoxicity

No new data have been submitted. Please refer to original EU RAR 2014.

Table 2.6.7-1 Summary of the results of the neurotoxicity studies (oral route)

Species	NOAEL mg/kg bw/day	Dose/neurotoxic effects mg/kg bw/day	References
Rat Acute (gavage)	10	250: slight effects on neurological parameters 3 hours after dosing, apparently reversible, in presence of general toxicity 1000: decreased survival in females, decreased bw gain in males	[redacted] and [redacted], 1994
Rat 90-day (diet)	12	152: decreased body weight gain and decreased forelimb grip strength, likely due to general toxicity	[redacted] and [redacted], 1994

2.6.8. Literature review

The applicant provided a literature review report on the toxicology of prosulfuron.

Since the first registration of prosulfuron, none of the published papers gives new/unknown information compared to data provided in the first review.

2.6.9. Summary of toxicological data on impurities and metabolites

Toxicity data on potential groundwater metabolites CGA349707, CGA159902, CGA150829 (triazine amine), SYN542604, CGA325025, SYN547308 and CGA300406 were evaluated in the EU RAR (2014 and Article 7 revised RAR, 2019). Two new in vitro micronucleus studies ([redacted], 2020 and [redacted], 2021) have been submitted with the amendment application in GB to clarify the genotoxic potential of CGA150829 and CGA325025. An additional repeated dose 28-day study on CGA150829 in rat ([redacted], 2014) and its benchmark dose analysis ([redacted], 2015), both considered at the renewal of another sulfonyl urea herbicide tribenuron-methyl (RAR, 2017), are also mentioned – please refer to Volume 3CA B6 for details. Short summaries of all available information are presented below.

CGA349707 and CGA159902 are minor rat metabolites, while CGA300406 is considered a major rat metabolite. CGA150829, SYN542604, CGA325025 and SYN547308 are not rat metabolites.

CGA349707

The potential genotoxicity of CGA349707 has been investigated in an Ames test, in an in vitro gene mutation assay (MLA/TK) and in an in vitro chromosomal aberration test using human lymphocytes. Negative results were obtained in these tests. It is concluded that CGA349707 has no genotoxic activity.

Table 2.6.9-1: Summary of genotoxicity data for metabolite CGA349707

Parameter	Result	Reference
In vitro tests		
Bacterial reverse mutation (Ames) assay with *S. typhimurium and E. coli*	Negative	[redacted] 2005
L5178Y $TK^{+/-}$ mouse lymphoma mutation assay	Negative	[redacted] 2005
In vitro cytogenetics assay in human lymphocytes	Negative	[redacted] 2005

CGA159902

CGA159902 is not acutely toxic via the oral and dermal route, is not a skin or eye irritant but is a skin sensitiser.

The potential genotoxicity of CGA159902 has been investigated in a battery of in vitro and higher tier in vivo genotoxicity tests. Negative results were obtained in an Ames test and in an in vivo unscheduled DNA synthesis assay. Positive results were obtained in in vitro tests (cytogenetics assay in human lymphocytes and MLA/TK assay showing increased numbers of small colonies) and are indicative of an in vitro clastogenic effect of this compound. Nevertheless, the in vivo mouse bone marrow micronucleus test showed negative results. It is concluded that CGA159902 is not an in vivo genotoxicant.

Table 2.6.9-2: Summary of toxicity data for metabolite CGA159902 (=CA1118A)

Genotoxicity			
In vitro tests			
Parameter		**Result**	**Reference**
Bacterial reverse mutation (Ames) assay with *S. typhimurium and E. coli*		Negative	[redacted] 1993*
L5178Y $TK^{+/-}$ mouse lymphoma mutation assay		(-S9) Negative (+S9) Positive (small colonies)	[redacted] 2005a
In vitro cytogenetic assay in human lymphocytes		(-S9) Positive (+S9) Negative	[redacted] 2005a
In vivo tests			
Parameter	**Species**	**Result**	**Reference**
Rat liver unscheduled DNA synthesis assay	Rat	Negative	[redacted] 2005b
Mouse bone marrow micronucleus test	Mouse	Negative	[redacted] 2005c
Acute toxicity			
Parameter	**Species**	**Result (mg/kg or effect)**	**Reference**
Acute oral LD_{50}	Rat	> 2000 mg/kg	[redacted] 1993*
Acute dermal LD_{50}	Rat	> 2000 mg/kg	[redacted] 1993a*
Skin irritation	Rabbit	Non-irritant	[redacted] 1993*
Eye irritation	Rabbit	Non-irritant	[redacted] 1993a*
Skin Sensitization (Maximization Test)	Guinea pig	Sensitizer – H317	[redacted] 1993b*

* Although these studies were already submitted during the first evaluation process of prosulfuron, they were not cited in the original draft assessment report. They are thus reported here for a better understanding of the full toxicology package of the metabolite CGA159902.

CGA150829 – triazine amine [evaluated in the RAR, 2014 + one new study ([redacted], 2020) and one 28-day study ([redacted], 2014) and its benchmark dose modelling ([redacted], 2015) considered in the RAR of tribenuron-methyl, 2017]

CGA150829, also named IN-A4098 or AE F059411 or triazine amine, is a common metabolite to several sulfonyl urea herbicides (e.g. metsulfuron-methyl, thifensulfuron-methyl, triasulfuron, tribenuron-methyl, iodosulfuron-methyl). CGA150829 is harmful if swallowed, not acutely toxic via the dermal route and via inhalation, not a skin or eye irritant and not a skin sensitiser. During the renewal of tribenuron-methyl (RAR, 2017) a GLP and OECD 407 compliant repeat dose 28-day study in rats ([redacted], 2014) and its benchmark dose analysis ([redacted], 2015) were considered. Based on lower body weight and nutritional parameters the 95% lower confidence limit ($BMDL_{10}$) was calculated as 0.7 mg/kg bw/day and this value was regarded as the NOAEL in the 28-day study.

CGA150829 was shown to be negative in the Ames tests. Available in vitro gene mutation assays in mammalian cells showed negative and equivocal results. It should be noted that the equivocal results were observed in the absence of metabolic activation. CGA150829 was shown not to induce chromosomal aberrations in vitro and in vivo, and concluded not to be clastogenic.

Two additional GLP and OECD test guideline compliant in vitro studies not included in the EU RAR: mammalian cell gene mutation assays in mouse lymphoma L5178Y cells ([redacted], 2019) and Chinese hamster ovary (CHO) cells ([redacted] and [redacted], 2019), showed that there was no concern for the potential of CGA150829 to induce gene mutations and clastogenicity. However, the EFSA PPR Panel (2020)[7] agreed that an additional in vitro micronuclei test would be needed to conclude on its aneugenic potential.

In response to this, in their Article 7 GB application, the applicant provided an additional in vitro micronucleus assay in human lymphocytes ([redacted], 2020), which was GLP and OECD compliant and provided clear negative results.

[7] Scientific Opinion of the Scientific Panel on Plant Protection Products and their Residues (PPR Panel) on the genotoxic potential of triazine amine (metabolite common to several sulfonylurea active substances). EFSA Journal, February 2020. Available: https://efsa.onlinelibrary.wiley.com/doi/pdf/10.2903/j.efsa.2020.6053

Table 2.6.9-3: Summary of toxicity data for metabolite CGA150829 – triazine amine (includes studies evaluated in the EU RAR, 2014, Article 7 revised EU RAR, 2019; in the EFSA PPR Panel Opinion, 2020; tribenuron-methyl RAR, 2017 and one new study)

Studies evaluated in the RAR, 2014, and Article 7 revised EU RAR, 2019 - presented here for completeness as applicable to GB)			
Genotoxicity			
In vitro tests			
Parameter		**Result**	**Reference**
Bacterial reverse mutation (Ames) assay with *S. typhimurium and E. coli*		Negative (+/- S9)	[redacted] 1991
Bacterial reverse mutation (Ames) assay with *S. typhimurium and E. coli*		Negative (+/- S9)	[redacted], 2009
Bacterial reverse mutation (Ames) assay with *S. typhimurium and E. coli*		Negative (+/- S9)	[redacted], 1998
L5178Y $TK^{+/-}$ mouse lymphoma gene mutation assay		Negative *Choice of highest tested dose is questionable*	[redacted], 2015
CHO/HGPRT gene mutation assay		Equivocal (-S9) Negative (+S9)	[redacted], 2009
In vitro cytogenetics assay in Chinese Hamster cells		Negative (+/- S9)	[redacted] 1991
In vitro cytogenetics assay in human lymphocytes		Positive (+S9) Negative (-S9)	[redacted] 1987
In vitro cytogenetics assay in human lymphocytes		Negative (+/- S9)	[redacted], 2009
Unscheduled DNA synthesis assay on rat hepatocytes		Negative	[redacted] 1988
Unscheduled DNA synthesis assay on human fibroblasts		Negative	[redacted] 1988
In vivo tests			
Parameter	**Species**	**Result**	**Reference**

Chromosome studies on somatic cells	Chinese Hamster	Negative	[redacted] 1988
Acute toxicity			
Parameter	**Species**	**Result (mg/kg or effect)**	**Reference**
Acute oral LD_{50}	Rat	> 2000 mg/kg bw in males = 1000 mg/kg bw in females (**H302**)	[redacted] 1991
Acute dermal LD_{50}	Rat	> 2000 mg/kg bw	[redacted] 1991a
Acute inhalation LC_{50}	Rat	> 5.2 mg/L	[redacted] 1991b
Skin irritation	Rabbit	Non-irritant	[redacted] 1991
Eye irritation	Rabbit	Non-irritant	[redacted] 1991a
Skin Sensitization (Maximization Test)	Guinea pig	Non sensitizer	[redacted] 1991b
Studies evaluated in the EFSA PPR Panel Opinion, 2020 - presented here for completeness as applicable to GB			
In Vitro Mammalian Cell Forward Gene Mutation (CHO/HPRT) Assay	Chinese hamster ovary (CHO) cells	Negative	[redacted] and [redacted] V., 2019
In Vitro Mammalian Cell Mutation Assay	Mouse Lymphoma L5178Y Cells	Negative	[redacted], 2019
Studies evaluated in the tribenuron-methyl EU RAR, 2017 - presented here for completeness as applicable to GB			
Repeat dose 28 day study	Rat	NOAEL < the lowest tested dose	[redacted]., 2014
Benchmark dose modelling of IN-A4098 Repeated-dose oral toxicity 28-day feeding study in rats ([redacted], 2014).		$BMDL_{10}$ 0.7 mg/kg bw/day	[redacted], R., 2015
Study submitted with Article 7 (Reg. 1107/2009) application to support the amendment of approval conditions in GB (October, 2022)			

In Vitro Mammalian Cell Micronucleus Test	Human Peripheral Lymphocytes	Negative	[redacted], 2020

SYN542604

The potential genotoxicity of SYN542604 has been investigated in an Ames test, in an in vitro gene mutation assay (MLA/TK) and in an in vitro chromosomal aberration test using human lymphocytes. Negative results were obtained in these tests. It is concluded that SYN542604 has no genotoxic activity.

Table 2.6.9-4: Summary of toxicity data for metabolite SYN542604

Genotoxicity		
In vitro tests		
Parameter	**Result**	**Reference**
Bacterial reverse mutation (Ames) assay with *S. typhimurium and E. coli*	Negative (+/- S9)	[redacted], 2010
L5178Y $TK^{+/-}$ mouse lymphoma gene mutation assay	Negative (+/- S9)	[redacted], 2010
In vitro cytogenetics assay in human lymphocytes	Negative (+/- S9)	[redacted], 2010

CGA325025 (evaluated in the EU RAR, 2014, Article 7 revised EU RAR, 2019 - presented here for completeness as applicable to GB + one new study by [redacted], 2021)

The potential genotoxicity of CGA325025 has been investigated in an Ames test, in an in vitro gene mutation assay (MLA/TK) and in an in vitro chromosomal aberration test using human lymphocytes. Negative results were obtained in the Ames test and in the in vitro gene mutation assay. It was concluded that CGA325025 was not a mutagenic compound in vitro. Nevertheless, as the in vitro chromosomal aberration assay showed equivocal results, no conclusion could be drawn on the clastogenic properties of CGA325025.

The available data were assessed at an EFSA expert meeting and it was noted that the genotoxic potential of metabolite CGA325025 could not be finalised. All experts agreed that CGA325025 did not induce gene mutation; however, the chromosome aberration test showed equivocal results and an in vitro micronucleus assay, which could allow a conclusion on the genotoxic potential (clastogenicity and aneugenicity) of the metabolite was missing, leading to a data gap (EFSA, 2020).

In response to that, in their GB application, the applicant provided an additional GLP and OECD compliant in vitro micronucleus assay in human lymphocytes ([redacted], 2021) which showed clear negative results (see evaluation in Volume 3 CA B6). Overall, CGA325025 is not genotoxic.

Table 2.6.9-5: Summary of toxicity data for metabolite CGA325025 (from Article 7 revised EU RAR, 2019 + one new study)

Studies evaluated in the EU RAR, 2014; Article 7 revised EU RAR, 2019 - presented here for completeness as applicable to GB			
Genotoxicity			
In vitro tests			
Parameter		**Result**	**Reference**
Bacterial reverse mutation (Ames) assay with *S. typhimurium and E. coli*		Negative (+/- S9)	[redacted], 2013
L5178Y $TK^{+/-}$ mouse lymphoma gene mutation assay		Negative (+/- S9)	[redacted], 2013
In vitro cytogenetics assay in human lymphocytes		Equivocal (+/- S9)	[redacted], 2013
Study submitted with Article 7 (Reg. 1107/2009) application to support the amendment of approval conditions in GB (October, 2022)			
In Vitro Mammalian Cell Micronucleus Test	Human Peripheral Lymphocytes	Negative (+/- S9)	[redacted], 2021

SYN547308

The potential genotoxicity of SYN547308 has been investigated in an Ames test, in an in vitro gene mutation assay (MLA/TK) and in an in vitro chromosomal aberration test using human lymphocytes as well as in an in vivo mouse bone marrow micronucleus test. Negative results were obtained in the Ames test and in the in vitro gene mutation assay. As the in vitro chromosomal aberration assay showed positive results without metabolic activation, an in vivo micronucleus assay was conducted and gave negative results. Therefore, SYN547308 can be considered as devoid of genotoxic properties.

Table 2.6.9-6: Summary of toxicity data for metabolite SYN547308

Genotoxicity			
***In vitro* tests**			
Parameter		**Result**	**Reference**
Bacterial reverse mutation (Ames) assay with *S. typhimurium and E. coli*		Negative (+/- S9)	[redacted], 2014
L5178Y $TK^{+/-}$ mouse lymphoma gene mutation assay		Negative (+/- S9)	[redacted], 2014
In vitro cytogenetics assay in human lymphocytes		(-S9) Positive (+S9) Negative	[redacted], 2014
***In vivo* tests**			
Parameter	**Species**	**Result**	**Reference**
Mouse bone marrow micronucleus test	Mouse	Negative	[redacted], 2014

CGA300406

The potential genotoxicity of CGA300406 has been investigated in an Ames test, in an in vitro gene mutation assay (MLA/TK) and in an in vitro chromosomal aberration test using human lymphocytes as well as in an in vivo mouse bone marrow micronucleus test. Negative results were obtained in the Ames test and in the in vitro

gene mutation assay. As the in vitro chromosomal aberration assay showed positive results with and without metabolic activation, an in vivo micronucleus assay was conducted and gave negative results. Therefore, CGA300406 can be considered as devoid of genotoxic properties.

Table 2.6.9-7: Summary of toxicity data for metabolite CGA300406

Genotoxicity			
In vitro tests			
Parameter		**Result**	**Reference**
Bacterial reverse mutation (Ames) assay with *S. typhimurium and E. coli*		Negative (+/- S9)	[redacted], 2015a
L5178Y $TK^{+/-}$ mouse lymphoma gene mutation assay		Negative (+/- S9)	[redacted], 2015
In vitro cytogenetics assay in human lymphocytes		(-S9) Positive (+S9) Positive	[redacted], 2015b
In vivo tests			
Parameter	**Species**	**Result**	**Reference**
Mouse bone marrow micronucleus test	Mouse	Negative	[redacted], 2015

2.6.10. Summary of mammalian toxicity

Prosulfuron was found to be rapidly absorbed and almost completely excreted in ADME studies conducted over 7 days using both triazine and phenyl labelled prosulfuron. The principal route of excretion was via the urine (about two thirds with the urine and one third with the faeces). A small amount (<10%) of prosulfuron or its metabolites were excreted with the bile. In a pharmacokinetic study using triazine labelled prosulfuron, peak plasma concentrations were reached 15 minutes and 4 hours following oral doses of 0.5 mg/kg and 400 mg/kg respectively, independent of sex. Pharmacokinetic parameters may have been affected by the different dosing vehicles used at the low and high dose levels in these studies.

Residual tissue levels were low after 7 days when a low dose (0.5 mg/kg) was administered, with most measurements of radioactivity being below the limit of quantification. Quantifiable levels of radioactivity were found in the whole blood (<0.0091 to 0.027% of the administered dose), plasma (<0.0045 to 0.018% of the applied dose) and liver (<0.0021 to 0.074% of the applied dose). Higher residues were observed after administration of an 800-fold dose (400 mg/kg). The highest residues were detected in the whole blood (0.014 to 0.050% of the applied dose), liver (0.012 to 0.044% of the applied dose), kidneys (0.0028 to 0.0053% of the applied dose), lungs (0.0018 to 0.0079% of the applied dose), and in the heart (<0.00074 to 0.0020% of the applied dose).

Prosulfuron was well metabolised (less than ca. 30% parent compound was excreted), 14 metabolites were identified in urine and faeces. Metabolism was almost independent of the administered dose but there were some differences between the sexes in the amount of individual metabolites. The predominant metabolic reactions included the hydroxylation at the side chains and the phenyl ring, O-demethylation of the triazine methoxy-group, and generation of a double bond on the trifluoropropyl group. Cleavage of the sulfonylurea bridge appears to be a minor metabolic pathway.

Prosulfuron was moderately toxic by the oral route. The classification of prosulfuron as harmful if swallowed (**Xn, R22**) was already agreed at European level. Prosulfuron is also classified for acute toxicity by oral route, category 4 (**H302**, harmful if swallowed) according to the criteria of the regulation (EC) n°1272/2008. Although prosulfuron is not a skin sensitiser in two skin sensitization studies, the presence of an impurity classified as Xi, R43 in the technical specifications and not sufficiently tested in these studies triggers the classification **Xi, R43** for prosulfuron (**H317**, may cause an allergic skin reaction).

In subchronic studies in rats the liver was shown to be a target organ with weight and clinical chemistry changes, though no histopathological effects. Body weight effects and changes in haematological parameters were seen at higher dose levels. In mice the liver was also a target organ with increased weights, hepatocyte hypertrophy, and changes of liver-associated clinical chemistry parameters. The heart also appeared to be a target organ with multifocal vacuolative degeneration (precise location not

stated). Additionally, some changes of red blood cell parameters were observed. At high doses administration of prosulfuron to dogs caused decreased body weight gain or even body weight loss. The main effects were noted in the liver (increased weights, changes in clinical chemistry parameters and pigment accumulation, possibly lipofuscin), the heart (myocardial necrosis and degeneration), kidney (pigment accumulation, renal proximal tubular epithelial fatty change) and in the hematopoietic system.

When tested in vitro, prosulfuron was negative in an Ames test, a mammalian cell gene mutation assay, a cytogenetic test, and an autoradiographic DNA-repair test. Prosulfuron was also negative in two recent Ames tests. When tested in vivo, prosulfuron did not induce micronuclei in a bone marrow micronucleus test in the mouse.

In a lifetime study in the rat there was a slightly increased incidence of testicular interstitial cell tumours in males, and a small increase in the incidence of mammary gland adenocarcinomas in females at the same dose levels, however the changes were not significant when the increased survival in these groups was considered. There was also an apparent earlier onset of mammary gland adenocarcinomas in females, although no significant difference existed for adenocarcinoma onset time between the control and any treatment group. There was also an increased incidence of uterine endometrial hyperplasia and uterine horn dilation in females as well as an increased incidence of acinar atrophy of the mammary gland in males. No evidence of carcinogenicity was seen in mice.

In a two generation study in the rat body weight effects were seen in both parental animals and pups. In the P0 generation there was no indication of any treatment-related effects on precoital interval, mating index, parturition index, or gestation length. The pregnancy and gestation indices were reduced in the low dose group. In the P1 generation there was no indication for treatment-related effects on precoital interval, mating index, parturition index, or gestation length. Low indices were obtained for pregnancy, fertility, and gestation in the low and top dose groups. This is nevertheless considered incidental.

Prosulfuron was not teratogenic in either rats or rabbits. Developmental toxicity (a slightly increased incidence of skeletal variations, primarily extra rudimentary ribs and lobed and/or constricted thoracic vertebrae centra) was seen in the rat, at levels where some maternal toxicity was likely to be present, based on other studies. Increased incidence of resorptions was observed in the rabbit in the presence of maternal toxicity.

In neurotoxicity studies in the rat, acute and repeat dose, no neurotoxic potential was demonstrated.

Prosulfuron was shown not to have endocrine disruptive effects in vivo, and it is considered unlikely that in vitro tests would add any relevant information. Therefore, prosulfuron is unlikely to be an endocrine disruptor (EFSA, 2014).

Table B.6.10.1-1 Summary of NOAELs for toxicology studies

Studies	**NOAEL** approx. mg/kg bw/day	**LOAEL and effects** approx. mg/kg bw/day	**References**
Rat, 28-day (gavage)	100	300: Liver effects (weights/clinical chemistry), decreases in red blood cell counts/hematocrit	[redacted], 1992
Rat, 28–day (diet)	107	209: Decreased body weight gains (changes in clinical chemistry indicative of possible liver effects)	[redacted] ad [redacted], 1991
Mouse, 28-day (diet)	14	169: Liver effects (weights/clinical chemistry)	[redacted], 1991a
Dog, 28-day (diet)	None	19 (lowest dose): Liver weight effects	[redacted], 1991b
Dog, 28-day (diet)	None	32 (lowest dose): Liver, adrenal and spleen weight effects	[redacted], 1992
Rat, 90–day (diet)	3	33: Reduced body weight and body weight gain, liver weights	[redacted] and [redacted], 1991
Mouse, 90–day (diet)	69	264: Liver effects (increased liver weights, hepatocyte hypertrophy, and changes of liver-associated clinical chemistry parameters), some changes in red blood cells parameters	[redacted] and [redacted], 1991
Dog, 90-day (diet)	5.9	56: Decreased body weight gain/ body weight loss, liver effects (increased liver weights, and changes clinical chemistry	[redacted], 1991

		parameters), hematopoietic system (decreased RBC counts, decreased hematocrit, decreased haemoglobin concentration, abnormal erythrocyte morphology, thrombocytopenia and changes in leukocyte counts, erythroid hyperplasia of the bone marrow)	
Rabbit, 21-day dermal	None	No valid study	[redacted], 1992
Rat, 2-year (diet)	8.6	88: Decreased body weights, body weight gain, effects on red blood cell parameters, possible treatment related increased incidence of testicular interstitial cell tumours/early onset mammary gland adenocarcinomas in females	[redacted], [redacted] and [redacted], 1994
Mouse, 18-month (diet)	1.71	82: Increased incidence of centrilobular hepatocyte hypertrophy in males	[redacted] and [redacted], 1993
Dog, 1-year (diet)	1.9	19: Decreased red blood cell parameters, liver effects (increased liver weights, and changes clinical chemistry parameters), accumulation of lipofuscin in the liver and kidney	[redacted] and [redacted], 1993
Rat, multigeneration (diet)	Parental: 12 Offspring: 12 Reproductive: 251	135: Body weight changes in parental animals and pups No effect on reproductive performance at any dose level.	[redacted] and [redacted], 1993
Rat developmental (gavage)	Maternal: 200 Developmental: 50	Maternal: 400: reduced body weight gain and food consumption Developmental: 200: slightly increased incidence of skeletal variations (primarily extra-rudimentary ribs and lobed and/or constricted thoracic vertebrae centra)	[redacted], 1992
Rabbit developmental (gavage)	Maternal: 10 Developmental: 10	Maternal: 100: reduced body weight gain and food consumption Developmental: 100: increased incidence of resorptions	[redacted], 1992
Rat, acute neurotoxicity (gavage)	10	250: slight effects on neurological parameters 3 hours after dosing, apparently reversible, in presence of general toxicity	[redacted] and [redacted], 1994
Rat, 90-day neurotoxicity (diet)	12	152: decreased body weight gain and decreased forelimb grip strength	[redacted] and [redacted], 1994

2.6.11. Toxicological end point for assessment of risk following long-term dietary exposure – ADI (Acceptable daily intake)

The **ADI was set at 0.02 mg/kg bw/d** based on the 1-year dog (NOAEL of 1.9 mg/kg bw/d based on decreased red blood cell parameters and liver effects) and the 18-month mouse (NOAEL of 1.7 mg/kg bw/d based on liver effects) studies and by using a safety factor of 100 (EFSA Conclusions, 2014).

2.6.12. Toxicological end point for assessment of risk following acute dietary exposure - ARfD (acute reference dose)

An ARfD was set based on the lowest NOAEL observed in the short-term and teratology toxicity studies. The most relevant study appeared to be the developmental toxicity study performed in rabbits, where the NOAEL was 10 mg/kg bw/day, based on the increased incidence of resorptions observed at the dose level of 100 mg/kg bw/day. Therefore the following ARfD was derived, with a safety factor (SF) of 100 (EFSA Conclusion, 2014):

ARfD = NOAEL / SF = 10 mg/kg bw/d / 100 = **0.1 mg/kg bw**

2.6.13. Toxicological end point for assessment of occupational, bystander and residents risks – AOEL (Acceptable operator exposure level)

The **AOEL was set at 0.06 mg/kg bw/d** based on the 90-day dog study (NOAEL of 5.9 mg/kg bw/d based on liver effects and effects on the hematopoietic system) and by using a safety factor of 100 (EFSA Conclusion, 2014).

2.6.14. Proposal for a maximum allowable concentration (MAC) in drinking water / drinking water limit (DWL)

The maximum admissible concentration of a pesticide active substance is 0.1 μg/L, as established by Council Directive 98/83/EC[8] (still applicable to GB).

2.7. RESIDUE

The residue definitions have been reconsidered as a result of the additional toxicological data evaluated in the current assessment. This is summarized below:

For the renewal of the approval of prosulfuron, the residue definition for risk assessment (RD-RA) and enforcement (RD- Enf) in plants were proposed as:

- prosulfuron (Draft subject to the data gap on the genotoxicity of CGA150829)

However, the RD-Enf currently in force is:

- prosulfuron

The residue definition for enforcement and risk assessment was considered provisional, pending the addressment of the data gap on the genotoxicity of CGA150829 (EFSA conclusion, 2014).

Within the current assessment, the genotoxic potential of the metabolite CGA150829 was excluded (See B.6.8.1), therefore the data gap above has been addressed (See B.7.1. for details). The residue definitions for risk assessment and enforcement are no longer considered draft.

The residue definition for risk assessment (RD-RA) in plant commodities is therefore proposed as:

- prosulfuron

[8] Council Directive 98/83/EC of November 1998 on the quality of water intended for human consumption (OJ L 330, 05.12.98, p. 32-54).

The residue definition for enforcement (RD-Enf) in plant commodities is proposed as:

- prosulfuron

This conclusion is based on the current intended uses for prosulfuron (see table B.7.4-1). If in future the uses are changed and a more critical GAP is considered, the metabolism of prosulfuron and the subsequent residue definition for risk assessment will need to be re-considered. The residue definitions will also be re-considered at the next renewal of the active.

There were additional data gaps relating to the metabolites CGA159902, CGA349707, CGA325025 and SYN547308 and the need for further toxicological assessment the potential for consumer risk assessments. Additional toxicological data has been submitted; toxicological reference values (TRVs) have been established for all relevant metabolites and chronic exposure assessments have been undertaken. The data gaps relating to exposure from these metabolites has been addressed.

It is further noted that data is only available on maize; for the setting of a general residue definition for risk assessment, additional data on a wider range of crops is required.

As all MRLs are currently set at LOQ, it is appropriate to maintain the residue definition for enforcement as prosulfuron only. If in future, substantive MRLs are proposed, this may require further consideration.

2.8. FATE AND BEHAVIOUR IN THE ENVIRONMENT

2.8.1. Summary of fate and behaviour in soil

Route of degradation in soil

The route of degradation of prosulfuron, radio-labelled in either the triazine or phenyl-ring has been studied in laboratory soils under aerobic, anaerobic, and aerobic-sterile conditions at 20 and 25°C. In the original DAR six studies were reported, which were all considered to be acceptable. Two additional laboratory soil degradation studies

were conducted to address degradation over a wider range of pH values, due to pH dependence for hydrolysis and its potential impact on the route of degradation. In summary, aerobic degradation of prosulfuron in soil mainly occurs via a biological process and is enhanced by temperature and moisture. Under anaerobic conditions degradation of prosulfuron is similar to under aerobic conditions, at least in poorly active soils. Photolysis is not a major route of degradation.

The degradation of prosulfuron proceeds via formation of several metabolites and the same metabolic pathway is followed for all of the main metabolites, irrespective of soil characterization.

Degradation proceeds via cleavage of the sulfonylurea bridge yielding CGA159902 (phenyl sulfonamide; maximum 47.4 % after 12 months) and CGA150829 (triazine amine; maximum 40.6 % after 62 days). Another pathway involves O-demethylation of prosulfuron yielding CGA300406 (maximum 24.0 % after 30 days). This metabolite may be further degraded to CGA325025 (demethoxy amino prosulfuron) reaching a maximum of 17.4 % after 274 days; or undergoes either opening of the triazine ring leading to CGA349707 reaching a maximum of 22.6 % after 12 months, SYN542604 (previously also known as M5) reaching 30.8 % after 62 days and minor metabolites (CGA325028 and CGA325027 (<10 %)) or cleavage of the sulfonylurea bridge to give G28533 (dihydroxy triazine; <10 %). A minor pathway involves hydroxylation of prosulfuron yielding small amounts of CGA300408.

During aerobic degradation of prosulfuron, two unknown soil metabolites M17 and M18 were detected, which would trigger a risk assessment for groundwater contamination according to SANCO/221/2000. Metabolite M17 reached 6.1% of the applied radioactivity (on day 120; study end) in sandy clay loam soil after application of phenyl-labelled prosulfuron. Metabolite M18 accounted for 9.9% of the applied radioactivity (on day 120; study end) in loam soil treated with triazine-labelled prosulfuron. The applicant has been able to identify M18 (now designated as SYN547308). Despite a significant amount of work by the applicant, identification of M17 has not been possible and therefore no information of its properties or concentrations in the environment is available. HSE accepts the position of the

applicant that identification of M17 is not technically feasible in accordance with SANCO/221/2000 and therefore no further work is necessary.

Prosulfuron is mineralised (up to 21.5 %) and bound residues are formed in significant amounts (up to 57 % (phenyl; within one year) or 34.3 % (triazine; within 120 days).

Rate of degradation in soil

The aerobic degradation rate of phenyl or triazine labelled prosulfuron in laboratory conditions is available in ten soils at 20 - 25°C. Prosulfuron degradation followed Single First-Order (SFO) Rate Model kinetics with DT50 of 15.4 - 198 days and DT90 51.1 - 657 days. The geometric mean of normalised (20°C, pF2) DT50 values to be used for modelling is 62.1 days.

The aerobic degradation rate of metabolite CGA150829 was studied in 11 different soils and followed SFO or biphasic kinetics. The non-normalised DT50 values varied between 22.5 and >1000 days and the DT90 values were 97 to >1000 days. The median of normalised (20°C, pF2) DT50 values to be used for modelling is 216 days.

The aerobic degradation rate of metabolite CGA159902 was studied in four different soils and followed either SFO or biphasic kinetics. The non-normalised DT50 values, recalculated to represent SFO model, varied between 89.7 and >1000 days and the DT90 values were 301 to >1000 days. The geometric mean of normalised (20°C, pF2) DT50 values to be used for modelling is 188 days.

The aerobic degradation rate for metabolite CGA300406 was calculated in four different soils within four studies dosed with prosulfuron. The non-normalised SFO DT50 values were 2.6-47.5 days and DT90 values 8.8-158 days. The minimum and maximum normalised (20°C, pF2) DT50 values to be used for modelling are 2.6 and 30.2 d.

Soil degradation rate of CGA325025 was determined only in studies dosed with metabolite itself. The non-normalised SFO DT50 values were 47.4-102 days and

DT90 values 157-340 days. The geometric mean of normalised (20°C, pF2) DT50 values to be used for modelling is 62.4 days.

The aerobic degradation rate for metabolite SYN542604 was calculated within five studies dosed with either prosulfuron or metabolite. The non-normalised SFO DT50 values ranged between 25 and 184 days and DT90 values were 83.2-611 days. The geometric mean of normalised (20°C, pF2) DT50 values to be used for modelling is 84.6 days.

The aerobic rate of degradation of metabolite CGA349707 was calculated in four different soils within three studies dosed with either prosulfuron or metabolite. The non-normalised SFO DT50 values ranged between 91.9 and 737 days and DT90 values were 305 to >1000 days. The geometric mean of normalised (20°C, pF2) DT50 values to be used for modelling is 153 days.

The aerobic rate of degradation of metabolite SYN547308 (M18) was calculated in three different soils dosed with metabolite. The DT50 values ranged between 7.8 and 174 days and DT90 values were 120 to 654 days. The geometric mean of normalised (20°C, pF2) DT50 values to be used for modelling is 67.1 days (derived conservatively from biphasic kinetic fits).

The rate of degradation of prosulfuron under anaerobic conditions is similar to that in aerobic conditions (DT50 of 89-138 days).

During a 30-day soil photolysis study prosulfuron slowly degraded in darkness (89.7% (phenyl) and 93.2% (triazine) remained at the end of the study). Sunlight slightly enhanced degradation (83.7% (phenyl) and 79.8% (triazine) remained after 30 days sunlight exposure). It was concluded in the original DAR that photodegradation of prosulfuron is not a significant route of dissipation in the environment. This is in good agreement with the UV-spectrum which shows no absorption at wavelength greater than 270 nm. No novel metabolites > 5% were detected compared to aerobic conditions.

A total of 18 field dissipation studies were carried out at various locations across Europe (France, Germany, Italy, Austria and Switzerland). Of these eighteen studies

eleven were selected by the applicant for kinetic analysis to derive trigger and modelling endpoints for the risk assessment. The best fit kinetics DT50,field were 3.8-38.9 days and the corresponding DT90,field were 15.2-129 days, and these are found acceptable to be used for triggering additional work. However, it is not justified to use these field studies to derive modelling endpoints. Several of these studies are very briefly reported and the information available does not correspond to current guidelines.

During 2014-2015 six new field studies dosed with prosulfuron were conducted by the applicant in Northern and Southern Europe. These studies followed the EFSA guidance (2014) to obtain $DegT_{50}$ values in soil and are considered acceptable to be used in FOCUS modelling. The normalised (20°C, pF2) DegT50 ranged from 9.96 days to 43.5 days, with a geometric mean of 18.7 days.

In one US residue study, due to rapid degradation prosulfuron residues in soil were < 1 µg/kg after about 100 days. Residues of metabolites CGA159902 and CGA150829 were 7 - 9 µg/kg after the same period.

Accumulation studies in one site in France and in two sites in Switzerland show that, after spring application to corn, prosulfuron is rarely detected in soil at harvest (< 1.8 µg/kg) demonstrating no risk for soil accumulation. Metabolites are likely to be more persistent but US studies show no significant residue after one year.

Mobility in soil

Adsorption of prosulfuron has been determined in two acceptable studies and the validated organic-carbon normalised Freundlich distribution coefficient (K_{foc}) and associated Freundlich exponent (1/n) values range from 3.9 to 37.3 mL/g and 0.81 to 0.94, respectively. The geometric mean K_{foc} of 11.7 mL/g and arithmetic mean 1/n of 0.869 are considered appropriate for exposure modelling.

The metabolite CGA150829 is common for several sulfonylureas and the consolidated endpoints are presented in the (List of endpoints) LoEP (n=27). The

geometric mean K_{foc} of 45.6 mL/g and arithmetic mean 1/n of 0.9 are considered appropriate for exposure modelling.

One study in four soils is available for CGA159902, where the K_{foc} and 1/n values range from 44.3 to 88.1 mL/g and 0.81 to 0.94, respectively. The geometric mean K_{foc} of 68.0 mL/g and arithmetic mean 1/n of 0.88 are considered for exposure assessment.

Adsorption of metabolite CGA300406 was studied in four soils but one soil was excluded due to 1/n value outside the expected range of values of 0.7-1.1. The K_{foc} and 1/n values range from 42.3 to 49.4 mL/g and 0.87 to 0.93, respectively. The geometric mean K_{foc} of 46.8 mL/g and arithmetic mean 1/n of 0.9 are considered appropriate for exposure modelling.

The adsorption K_{foc} and 1/n values of CGA325025 in four soils were 20.7-32.2 mL/g and 0.853-1.057, respectively. The geometric mean K_{foc} of 26.2 mL/g and arithmetic mean 1/n of 0.973 are considered appropriate for exposure modelling.

Adsorption of SYN542604 was studied in five soils. The K_{foc} and 1/n values were 58-223 mL/g and 0.80-0.88, respectively. The geometric mean K_{foc} of 111 mL/g and arithmetic mean 1/n of 0.85 are considered for exposure assessment.

Adsorption of metabolite CGA349707 was studied in three soils. The K_{foc} and 1/n values range from 36.7 to 51.7 mL/g and 0.85 to 1.08, respectively. The geometric mean K_{foc} of 44.0 mL/g and arithmetic mean 1/n of 0.96 are considered for exposure assessment.

Adsorption of metabolite SYN547308 (M18) was investigated in five soils. The K_{foc} and 1/n values were 65-288 mL/g and 0.91-0.95, respectively. Adsorption of SYN547308 is pH dependent at soil pH(H2O) <6.5. The geometric mean K_{foc} for soils with pH ≥6.5 of 89.5 mL/g and arithmetic mean 1/n of 0.929 are considered correct for exposure assessment.

No pH dependency was observed for prosulfuron or metabolites other than SYN547308.

As expected from adsorption studies, column leaching studies confirmed the high mobility of prosulfuron. With both labels, more than 80% of applied radioactivity (AR) was found in leachates for soils with %OC <2.6. In soils with high organic carbon content (>2.6 %OC) 1.0-54% AR was found in leachate. Ageing of residues reduced leaching of prosulfuron in columns to some extent. In the study aged for 30 days, up to 59% of radioactivity was found in leachates mainly as prosulfuron. Ageing up to 180 days reduced the amount prosulfuron to 12% AR in leachate. Metabolites were detected in soil residues but they represented less than 4% AR in leachates.

Three lysimeter studies, one in Switzerland and two in USA, are available for prosulfuron. In Swiss lysimeter in sandy soil the yearly average concentrations of total radioactivity in leachate during the 3-year study period were 0.07-0.23 µg/L when applied only once and 0.22-0.31 µg/L when applied on two consecutive years. However, the concentrations of prosulfuron, CGA159902, CGA300406, CGA349707, SYN542604 and CGA325025 were <0.1 µg/L each. In US lysimeters in silt loam and sand soils the total residues represented a mean of 0.08-0.98 µg/L. Prosulfuron was seen at trace amounts at soil depth of 0.9 m, probably due to preferential flow at early stage of the study. Metabolite CGA159902 was seen at maximum concentration of 2.4 µg/L, CGA300406 at 0.08 µg/L, CGA325028 at 0.74 µg/L and M5 (derivative of CGA159902) at 1 µg/L. The triazine moiety is less mobile than the phenyl moiety.

2.8.2. Summary of fate and behaviour in water and sediment

Prosulfuron is rapidly hydrolysed at pH 5 with DT_{50} of 5-12 days but at higher pH hydrolysis is significantly slower (DT_{50} 424-651 days at pH 7 and 682-1690 days at pH 9). Therefore, in natural environmental conditions hydrolysis is not expected to be significant route of degradation.

Photolytic degradation in water is not significant for prosulfuron.

Prosulfuron is not readily biodegradable. Therefore classification R53 is suggested for prosulfuron.

Behaviour of prosulfuron in aerobic water/sediment systems has been investigated in four studies. Prosulfuron forms mainly the same metabolites as in soil: CGA150829, CGA159902, CGA300406, CGA325025, SYN542604 and CGA349707 (max. 7.9, 21.6, 34.3, 7.0, 24.8 and 16.1% in whole system, respectively).

Only two studies were used for calculation of degradation rates for prosulfuron, the study duration being too short in remaining two studies (30 days). When applied to water/sediment systems, prosulfuron is slowly dissipated from water phase. In sediment, prosulfuron peaked at 27.1% after 60 days in systems at 20°C. In a system kept at 9°C the maximum amount was 35.4% after 140 days. The half-lives measured at 20°C were 86.2-127 days in water phase, with a geometric mean of 103 days. In whole system, the DT_{50} values at 20°C ranged from 119 to 216 days, with geometric mean of 173 days.

2.8.3. Summary of fate and behaviour in air

The vapour pressure of prosulfuron is $<3.5 \times 10^{-6}$ Pa at 25°C. According to FOCUS Air Guidance this indicates negligible volatilisation. In the original DAR, studies on volatilisation from soil and plants were reported, which show that volatilisation is negligible over 24-hour study period. If prosulfuron was to volatilise, it will degrade with a half-life in air of 4.7-46 hours (Atkinson method, assuming 1.5×10^6 OH/cm^3 and 12-hour day).

The vapour pressure of metabolite CGA150829 is 9.6×10^{-5} Pa at 20°C. According to FOCUS Air Guidance this indicates volatilisation from plant surface but not from soil. However, no further evaluation is considered necessary for this metabolite.

2.8.4. Summary of monitoring data concerning fate and behaviour of the active substance, metabolites, degradation and reaction products

None provided as part of this application.

2.8.5. Definition of the residues in the environment requiring further assessment

Soil: Prosulfuron, CGA159902, CGA150829, CGA300406, CGA325025, CGA349707, SYN542604, SYN547308

Groundwater: Prosulfuron, CGA159902, CGA150829, CGA300406, CGA325025, CGA349707, SYN542604, SYN547308

Surface water: Prosulfuron, CGA159902, CGA150829, CGA300406, CGA325025, CGA349707, SYN542604

Sediment: Prosulfuron, CGA159902, CGA300406

2.8.6. Summary of exposure calculations and product assessment

Predicted Environmental Concentrations (PEC) values in groundwater were calculated for prosulfuron and its metabolites using FOCUS PEARL 4.4.4 at an application rate of 20 g as/ha with either annual applications or applications restricted to 1 year in 2. Earlier modelling had indicated that FOCUS PEARL gave the highest concentrations compared to FOCUS PELMO or MACRO simulations.

Using the prosulfuron field DT_{50} value, for annual application at 20 g/ha, the concentrations of prosulfuron were >0.1 µg/L in two out of four GB relevant scenarios with PEARL 4.4.4 (0.106 µg/L in Hamburg and 0.111 µg/L in Okehampton scenario). Concentrations of prosulfuron were <0.1 µg/L in all four GB relevant scenarios when uses were restricted to a 1 in 2 year interval in all GB relevant scenarios.

The current conditions of approval of prosulfuron limit use to one application every three years at a maximum dose of 20 g/ha. The groundwater modelling presented here demonstrates that the current restriction to a 1 in 3 year application interval is no longer required. Since annual applications at a maximum dose of 20 g/ha do result in the identification of safe uses (i.e. based on 2 out of 4 GB relevant FOCUS scenarios giving rise to concentrations <0.1 µg/L) no restriction on the approval is considered necessary. However the risk to groundwater resources may still need to be mitigated at individual product level.

To protect groundwater resources, products authorised in GB must demonstrate acceptable assessment for all four GB relevant scenarios (i.e. concentration of prosulfuron <0.1 µg/L). HSE may determine at the product level that restriction of use may be required for applications of 20 g/ha to protect groundwater resources.

The metabolites CGA150829 and CGA325025 occur up to 0.234 µg/L and 0.123 µg/L respectively following annual applications. For CGA150829 the trigger was still breached in one GB relevant scenario when uses were restricted to a 1 in 2 year application (0.107 µg/L in the Hamburg scenario). For CGA325025 the trigger was not breached in any GB relevant scenario when uses were restricted to 1 year in 2. The metabolites CGA159902 and SYN547308 occur at >0.1 µg/L and CGA349707 occurs at >0.75 µg/L following annual applications of 20 g/ha.

Since all 5 metabolites included in the residue definition for groundwater assessment are now considered non-relevant according to SANCO/221/2000, no additional restrictions on timing of application of prosulfuron products applied at up to 20 g/ha are required to mitigate risks to groundwater from these metabolites. Further details of the groundwater metabolite relevance assessment is included in Section 2.11, including an assessment up to Step 5 of the SANCO/221/2000 guidance for metabolite CGA349707 which breaches the 0.75 µg/L trigger limit following annual applications.

PEC values in soil, surface water and sediment for prosulfuron and metabolites were not recalculated as part of this review, since the removal of the 1 in 3 year application restriction does not have an impact on PECs in these compartments.

2.9. EFFECTS ON NON-TARGET SPECIES

For this Article 7 amendment application, methods of analysis is unchanged from the assessment in the original RAR dated 2014.

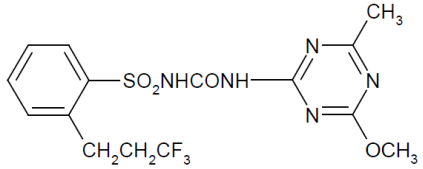
2.10. CLASSIFICATION AND LABELLING

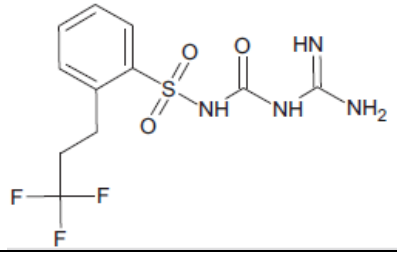
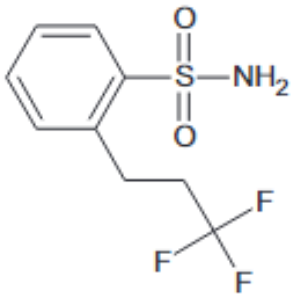
For this Article 7 amendment application, the classification and labelling is unchanged from the assessment in the original RAR dated 2014.

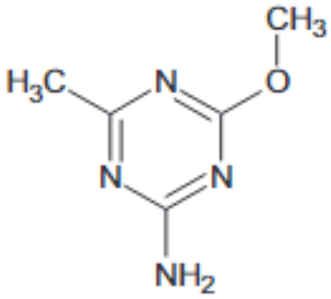
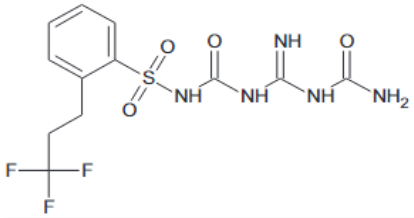
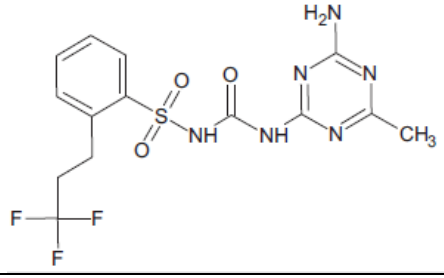
2.11. RELEVANCE OF METABOLITES IN GROUNDWATER

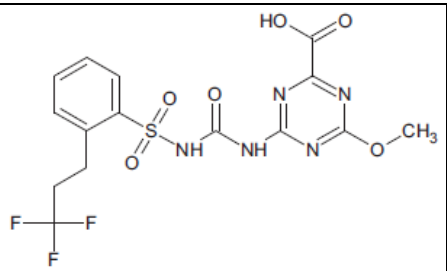
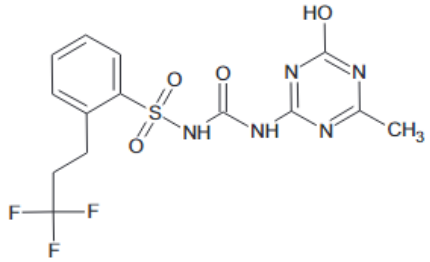
A relevance assessment of the following groundwater metabolites, CGA150829 (triazine amine), CGA159902, CGA349707, CGA325025 and SYN547308 has been conducted in line with SANCO guidance (Sanco/221/2000 –rev.10- final).

Table 2.11-1 Toxicological studies available on prosulfuron and its metabolites

Substance	Structure	Available studies	New studies submitted with this GB Article 7 application
Prosulfuron		In vitro: - Ames test – [redacted], 1991; [redacted], 2011 and 2011a - Gene mutation assay – [redacted], 1991 - Cytogenetic test – [redacted], 1991 - Unscheduled DNA repair test – [redacted], 1991 In vivo: - Bone marrow MN test (mouse) – [redacted], 1991 - Acute oral (rats/mice) – [redacted], 1991e and 1991d - Acute dermal (rabbits) – [redacted], 1991c - Acute inhalation (rats) – [redacted], 1991 - Skin/eye irritation (rabbits) – [redacted], 1991b and 1991a - Skin sensitisation (guinea pigs) – [redacted], 1991f and [redacted], 1992a - 28 day studies (rat/mouse/dog) – [redacted], 1992; [redacted] and [redacted], 1991; [redacted], 1991a,b and 1992 - 90 day studies (rat/mouse/dog) – [redacted] and [redacted], 1991; [redacted] and [redacted], 1991; [redacted], 1991 - 21 day study (rabbit) – [redacted], 1992 - 1 year study (dog) – [redacted] and [redacted], [redacted], 1993 - 18 month study (mouse) – [redacted] and [redacted], 1993 - 2 year study (rat) – [redacted], [redacted] and [redacted], 1994 - Multigeneration study (rat) – [redacted] and [redacted], 1993 - Developmental studies (rat/rabbit) – [redacted], 1992 and [redacted], 1992 - Neurotoxicity studies (rat) – [redacted] and [redacted], 1994; [redacted] and [redacted], 1994	n/a

CGA349707		<u>In vitro:</u> - Ames test – [redacted], 2005 - Gene mutation assay – [redacted], 2005 - Cytogenetic test – [redacted], 2005	n/a
CGA159902 (=CA1118A; prosulfuron phenyl sulfonamide)		<u>In vitro:</u> - Ames test – [redacted], 1993 - Gene mutation assay – [redacted], 2005a - Cytogenetic test – [redacted], 2005a <u>In vivo:</u> - Unscheduled DNA repair test – [redacted], 2005b - Bone marrow MN test (mouse) – [redacted], 2005c - Acute oral (rat) – [redacted], 1993 - Acute dermal (rat) – [redacted], 1993a - Skin/eye irritation (rabbit) – [redacted], 1993 and 1993a - Skin sensitisation (guinea pig) – [redacted], 1993b	n/a

CGA150829 (=IN-A4098 or AE F059411 or triazine amine)		<u>In vitro:</u> - Ames test – [redacted], 1991; [redacted], 1998; [redacted], 2009 - Gene mutation assays – [redacted], 2009; [redacted], 2015; [redacted] and [redacted], 2019 - Cytogenetic test – [redacted], 1991; [redacted], 1987; [redacted], 2009 - Unscheduled DNA repair test – [redacted], 1988 and [redacted], 1988 <u>In vivo:</u> - Chromosome aberration test (hamster) – [redacted], 1988 - Acute oral (rat) – [redacted], 1991a - Acute dermal (rat) – [redacted], 1993a - Acute inhalation (rat) – [redacted], 1991b - Skin/eye irritation (rabbit) – [redacted], 1991 and 1991a - Skin sensitisation (guinea pig) – [redacted], 1991b - 28-day study (rat) – [redacted], 2014 (RAR – tribenuron-methyl, 2017) - Benchmark dose modelling based on [redacted], 2014 – [redacted], 2015 (RAR - tribenuron-methyl, 2017)	<u>In vitro:</u> - Mammalian cell MN test – [redacted], 2020
SYN542604 (M5)		<u>In vitro:</u> - Ames test – [redacted], 2010 - Gene mutation assays – [redacted], 2010 - Cytogenetic test – [redacted], 2010	n/a
CGA325025 (=demethoxy amino-prosulfuron)		<u>In vitro:</u> - Ames test – [redacted], 2013 - Gene mutation assays – [redacted], 2013 - Cytogenetic test – [redacted], 2013	<u>In vitro:</u> - Mammalian cell MN test – [redacted], 2021

SYN547308 (M18)		<u>In vitro:</u> - Ames test – [redacted], 2014 - Gene mutation assays – [redacted], 2014 - Cytogenetic test – [redacted], 2014 <u>In vivo:</u> - Bone marrow MN test (mouse) – [redacted], 2014	n/a
CGA300406 (O-desmethyl-prosulfuron)		<u>In vitro:</u> - Ames test – [redacted], 2015a - Gene mutation assays – [redacted], 2015 - Cytogenetic test – [redacted], 2015b <u>In vivo:</u> - Bone marrow MN test (mouse) – [redacted], 2015	n/a

2.11.1. STEP 1: Exclusion of degradation products of no concern

Metabolites CGA150829 (traizine amine), CGA159902, CGA349707, CGA325025 and SYN547308 cannot be excluded as degradation products of no concern. Further assessment is therefore required.

2.11.2. STEP 2: Quantification of potential groundwater contamination

Metabolites CGA150829 (triazine amine), CGA159902, CGA349707, CGA325025 and SYN547308 were shown to exceed 0.1 µg/L in groundwater and as such needed further consideration in terms of their relevance.

Metabolite	80th Percentile PECgw (µg/L)	Model and Version Number	Scenario
CGA150829	0.234	PEARL v4.4.4.	Hamburg
CGA159902	0.370	PEARL v4.4.4.	Hamburg
CGA349707	0.962	PEARL v4.4.4.	Hamburg
CGA325025	0.123	PEARL v4.4.4.	Hamburg
SYN547308	0.220	PEARL v4.4.4.	Okehampton

2.11.3. STEP 3: Hazard assessment – identification of relevant metabolites

2.11.3.1. STEP 3, Stage 1: screening for biological activity

Metabolites CGA150829 (triazine amine), CGA159902, CGA349707, CGA325025 and SYN547308 have been confirmed based on the available evidence to have less than 50% comparable biological activity to parent and are not considered to be biologically active. Therefore, they are not relevant at Stage 1 and can proceed to Stage 2.

2.11.3.2. STEP 3, Stage 2: screening for genotoxicity

CGA349707

The potential genotoxicity of CGA349707 was investigated in an Ames test, in a mouse lymphoma assay/ thymidine kinase (MLA/TK) test and in an in vitro chromosomal aberration test using human lymphocytes (further details in Section 2.6.8 of this document and the revised EU RAR, 2019). Negative results were obtained in these in vitro tests. Moreover, SAR analysis (DEREK) showed that CGA349707 did not have alert for genotoxicity. It is concluded that **CGA349707 has no genotoxic activity**. Therefore it is not relevant at Stage 2 and can proceed to Stage 3.

CGA159902

Negative results with CGA159902 were obtained in an Ames test and in an in vivo unscheduled DNA synthesis assay. Positive results were obtained in in vitro tests (cytogenetics assay in human lymphocytes and MLA/TK assay showing increased numbers of small colonies) indicating a potential clastogenic effect. Nevertheless, the in vivo mouse bone marrow micronucleus test showed negative results (further details in Section 2.6.8 of this document and the revised EU RAR, 2019). Moreover, SAR (structure-activity relationship) analysis (DEREK) showed that CGA159902 did not have any alerts for genotoxicity. It is concluded that **CGA159902 is not an in vivo genotoxicant**. Therefore it is not relevant at Stage 2 and can proceed to Stage 3.

CGA150829 (triazine amine)

Negative results with CGA150829 were obtained in a number of Ames tests and overall negative results in the in vitro and in vivo chromosome aberration assays.

Available in vitro gene mutation assays in mammalian cells showed negative and equivocal results. It should be noted that the equivocal results were observed in the absence of metabolic activation. The EU RMS considered that a mutagenic potential of the metabolite CGA150829 could not be ruled out based on the available data. Two additional GLP and OECD test guideline compliant in vitro studies not included in the EU RAR: mammalian cell gene mutation assays in mouse lymphoma L5178Y cells and Chinese hamster ovary (CHO) cells, were considered by the EFSA PPR (plant protection products and their residues) Panel (2020), who based on the overall weight of evidence concluded that there is no concern for the potential of CGA150829 to induce gene mutations and clastogenicity. It was agreed that an additional in vitro micronuclei test would be needed to conclude on its aneugenic potential.

An additional in vitro micronucleus assay in human lymphocytes ([redacted], 2020) submitted with the Article 7 application to GB, which was GLP and OECD compliant, provided clear negative results. Based on the available studies (further details in Volume 3 CA B6) it can be concluded that **overall CGA150829 has no genotoxic activity**. Therefore it is not relevant at Stage 2 and can proceed to Stage 3.

CGA325025

The potential genotoxicity of CGA325025 was investigated in vitro. Negative results were obtained in the Ames test and in the gene mutation assay in mammalian cells (MLA/TK) indicating that CGA325025 is not a mutagenic compound in vitro. However, the in vitro chromosomal aberration assay with human lymphocytes showed equivocal results, and no conclusion could be drawn on the clastogenic properties of CGA325025. The EFSA PPR Panel (2020) concluded that an additional in vitro micronucleus assay was required to make a decision on the overall genotoxic potential of CGA325025.

An additional in vitro micronucleus assay in human lymphocytes ([redacted], 2021) submitted with the Article 7 application to GB, which was GLP and OECD compliant, provided clear negative results. Based on the available studies (further details in

Section 2.6.8 of this document, and in Volume 3 CA B6) it can be concluded that overall **CGA325025 has no genotoxic activity**. Therefore it is not relevant at Stage 2 and can proceed to Stage 3.

SYN547308

The potential genotoxicity of SYN547308 was investigated in vitro in an Ames test, in a gene mutation assay (MLA/TK) with negative results, and in a chromosomal aberration test using human lymphocytes where positive results without metabolic activation were reported. An in vivo micronucleus assay was conducted and gave negative results (further details in Section 2.6.8 of this document). Therefore, overall it was concluded that **SYN547308 has no genotoxic activity**. Therefore it is not relevant at Stage 2 and can proceed to Stage 3.

2.11.3.3. STEP 3, Stage 3: screening for toxicity

Parent compound prosulfuron is classified as Harmful if swallowed: H302 – Acute Tox. Cat 4. Prosulfuron is not classified as acutely (Cat 1-3) or chronically toxic or very toxic. It is not classified for carcinogenicity, reproductive toxicity or mutagenicity. Consequently, according to Guidance Document Sanco/221/2000, further toxicity testing with the metabolites is not required based on these criteria and based on the hazard profile of the parent substance, they are not relevant at Stage 3. The only metabolites with available acute toxicity data are CGA159902 and CGA150829. CGA159902 was shown to be of low acute toxicity by both the oral and dermal routes. It is not a skin or eye irritant. It was a skin sensitiser in the guinea pig maximization assay; nevertheless, according to the guidance document Sanco/221/2000, this is not considered relevant. CGA150829 is harmful if swallowed, not acutely toxic via the dermal route and via inhalation, not a skin or eye irritant and not a skin sensitiser.

2.11.4. STEP 4: Exposure assessment – threshold of concern approach

CGA349707

Toxicology assessment

The metabolite CGA349707 is present in groundwater at 0.962 µg/L: as this exceeds the 0.75 µg/L threshold of toxicological concern, a refined risk assessment is required to further consider potential relevance (see Step 5).

Residues assessment

The PECgw of CGA349707 is 0.962 µg/L. The metabolite cannot be deemed as non-relevant based on exposure assessment using the threshold of toxicological concern approach described in Step 4 because estimated intakes from drinking water alone exceed 0.75 µg/L (equivalent to 0.02 µg/kg bw/day), therefore Step 5 is required.

CGA159902

Toxicology assessment

The maximum PECgw value for CGA159902 is 0.370 µg/L. This is below the 0.75 µg/L threshold of toxicological concern, and the applicant concluded that further refinement of risk assessment is not required. EFSA (2020) however noted that residue levels in plants for CGA159902 need to be taken into account to characterise the total consumer intake from food and water. As the exposure from foodstuffs and drinking water in the critical consumer group (infants) is above the threshold of toxicological concern, the assessment has to proceed to Step 5 (see below).

Residues assessment

The PECgw of CGA159902 is 0.370 µg/L. The metabolite cannot be deemed as non-relevant based on exposure assessment using the threshold of toxicological concern approach described in Step 4 because the combined consumer intakes from food and

water were investigated (see discussion below) and estimated intakes from all sources (food and drinking water) exceeds 0.02 µg/kg bw/day, therefore Step 5 is required.

CGA150829 (triazine amine)

Toxicology assessment

The maximum PECgw value for CGA150829 is 0.234 µg/L. This is below the 0.75 µg/L threshold of toxicological concern; however EFSA (2020) noted that CGA150829 (triazine amine) is a major plant metabolite and a common residue of other active substances in food. Therefore, the residue levels in plants for CGA150829 need to be taken into account to characterise the total consumer intake from food and water. As the exposure from foodstuffs and drinking water in the critical consumer group (infants) is above the threshold of toxicological concern, the assessment has to proceed to Step 5 (see below).

Residues assessment

The PEC_{gw} of CGA150829 is 0.234 µg/L. The metabolite cannot be deemed as non-relevant based on exposure assessment using the threshold of toxicological concern approach described in Step 4 because the combined consumer intakes from food and water were investigated (see discussion below) and estimated intakes from all sources (food and drinking water) exceeds 0.02 µg/kg bw/day, therefore Step 5 is required.

CGA325025

Toxicology assessment

The maximum PECgw value for CGA325025 is 0.123 µg/L. This is below the 0.75 µg/L threshold of toxicological concern; however EFSA (2020) noted that it is not possible to confirm that both metabolites do not contribute to consumer exposure via food. Therefore, the residue levels in plants for CGA325025 need to be taken into account to

characterise the total consumer intake from food and water. As the exposure from foodstuffs and drinking water in the critical consumer group (infants) is above the threshold of toxicological concern, the assessment has to proceed to Step 5 (see below).

Residues assessment

The PECgw of CGA325025 is 0.123 µg/L. The metabolite cannot be deemed as non-relevant based on exposure assessment using the threshold of toxicological concern approach described in Step 4 because the combined consumer intakes from food and water were investigated (see discussion below) and estimated intakes from all sources (food and drinking water) exceeds 0.02 µg/kg bw/day, therefore Step 5 is required.

SYN547308

Toxicology assessment

The maximum PECgw value for SYN547308 is 0.220 µg/L. This is below the 0.75 µg/L threshold of toxicological concern; however EFSA (2020) noted that it is not possible to confirm that this metabolite does not contribute to consumer exposure via food. Therefore, the residue levels in plants for SYN547308 need to be taken into account to characterise the total consumer intake from food and water. As the exposure from foodstuffs and drinking water in the critical consumer group (infants) is above the threshold of toxicological concern, the assessment has to proceed to Step 5 (see below).

Residues assessment

The PECgw of SYN547308 is 0.220 µg/L. The metabolite cannot be deemed as non-relevant based on exposure assessment using the threshold of toxicological concern approach described in Step 4 because the combined consumer intakes from food and water were investigated (see discussion below) and estimated intakes from all sources (food and drinking water) exceeds 0.02 µg/kg bw/day, therefore Step 5 is required.

2.11.5. STEP 5: Refined risk assessment

CGA349707

Toxicology assessment

CGA349707 is a metabolite of prosulfuron in the rat, representing up to 5% of the applied dose. No toxicity studies on CGA349707 are available to set an ADI. The applicant took a conservative approach and, assuming that CGA349707 is entirely responsible for the toxicity of prosulfuron, proposed an ADI of 0.001 mg/kg bw/day (derived by multiplying the ADI of prosulfuron 0.02 mg/kg bw/day, by 5%). Therefore the **ADI of 0.001 mg/kg bw/day** can be used for the consumer risk assessment for **CGA349707**.

Residues assessment

The metabolite CGA349707 of prosulfuron could be present in groundwater at levels requiring further consideration. Based upon worst case modelling conducted in the assessment for maize (1 x 20 g a.s./ha, annual application) resulting in worst case PEC_{gw} estimation, it is indicated that metabolite CGA349707 is present above the trigger value of 0.1 µg/L in groundwater.

* CGA349707 is not in the plant or animal residue definition for risk assessment; It was not considered in the food during the consumer risk assessment.

* PEC_{gw} calculations after leaching from soil for CGA349707 indicates that the potential exposure to metabolite CGA349707 is > 0.75 µg/L but < 10 µg/L, with maximum PEC_{gw} of 0.962 µg/L.

* In relation to the drinking water contribution, the highest intake is expected for infants (< 4 months). EFSA Guidance on pesticides in foods for infants and young children estimates the water consumption of bottle-fed infants as 1.135 L/day, equating to 227 ml/kg bw/day (EFSA 2018). Estimated intakes of CGA349707 from drinking water for the critical consumer group infants are 0.00022 mg/kg bw/day. This is 21.8 % of the established ADI (0.001 mg/kg bw/day).

Conclusion

As the estimated intake of CGA349707 from drinking water is ≤ 100 % of the established ADI, and dietary intakes from other sources is not expected, no further consideration is required. In conclusion, CGA349707 contributes 21.8 % of the established ADI. As the estimated intakes of CGA349707 following the proposed use of prosulfuron are below the ADI of 0.001 mg/kg bw/day no harmful effect on human health is expected.

CGA159902

Toxicology assessment

CGA159902 is a metabolite of prosulfuron in the rat, representing up to 6.7% of the applied dose. It is not acutely toxic via the oral and dermal route, is not a skin or eye irritant but is a skin sensitiser. No toxicity studies on CGA159902 are available to set an ADI. Assuming that CGA159902 is entirely responsible for the toxicity of prosulfuron, an ADI of 0.0013 mg/kg bw/day (derived by multiplying the ADI of prosulfuron 0.02 mg/kg bw/day, by 6.7%) is proposed. Therefore the **ADI of 0.0013 mg/kg bw/day** can be used for the consumer risk assessment for **CGA159902**.

Residues assessment

The metabolite CGA159902 of Prosulfuron could be present in groundwater at levels requiring further consideration. Based upon worst case modelling conducted in the assessment for maize (1 x 20 g a.s./ha, annual application) resulting in worst case PECgw estimation, it is indicated that metabolite CGA159902 is present above the trigger value of 0.1 µg/L in groundwater.

* CGA159902 is not in the plant or animal residue definition for risk assessment; It was not considered in the food during the consumer risk assessment.

* PEC_{gw} calculations after leaching from soil for CGA159902 indicates that the potential exposure to metabolite CGA159902 is < 0.75 µg/L, with maximum PEC_{gw} of 0.370 µg/L.
* In relation to the drinking water contribution, the highest intake is expected for an infant (< 4 months). EFSA Guidance on pesticides in foods for infants and young children estimates the water consumption of bottle-fed infants as 1.135 L/d (EFSA Journal 2018; 16(6) 5286, 75 pp.). Estimated intakes of CGA159902 from drinking water for the critical consumer group infants are 0.00008 mg/kg bw/day. This is 6.5 % of the established ADI (0.0013 mg/kg bw/day).

Conclusion

As the estimated intake of CGA159902 from drinking water is ≤ 100 % of the established ADI, and dietary intakes from other sources is not expected, no further consideration is required. In conclusion, CGA159902 contributes 6.5 % of the established ADI. As the estimated intakes of CGA159902 following the proposed use of prosulfuron are below the ADI of 0.0013 mg/kg bw/day no harmful effect on human health is expected.

CGA150829 (triazine amine)

Toxicology assessment

CGA150829 (triazine amine) is a major plant metabolite and a common residue of other active substances in food. It has similar acute oral toxicity to prosulfuron (harmful if swallowed) based on an acute oral toxicity study but it is only a very minor rat metabolite. A 28-day study is available and based on the results of this study, a specific **ADI of 0.0007 mg/kg bw/day** can be set. This ADI should be used for the consumer risk assessment for CGA150829.

Residues assessment

The metabolite CGA150829 of Prosulfuron could be present in groundwater at levels requiring further consideration. Based upon worst case modelling conducted in the

assessment for maize (1 x 20 g a.s./ha, annual application) resulting in worst case PECgw estimation, it is indicated that metabolite CGA150829 is present above the trigger value of 0.1 µg/L in groundwater.

* CGA150829 is not in the plant or animal residue definition for risk assessment; It was not considered in the food during the consumer risk assessment.
* PEC_{gw} calculations after leaching from soil for CGA150829 indicates that the potential exposure to metabolite CGA150829 is < 0.75 µg/L, with maximum PEC_{gw} of 0.234 µg/L.
* In relation to the drinking water contribution, the highest intake is expected for an infant (< 4 months). EFSA Guidance on pesticides in foods for infants and young children estimates the water consumption of bottle-fed infants as 1.135 L/d (EFSA Journal 2018; 16(6) 5286, 75 pp.). Estimated intakes of CGA150829 from drinking water for the critical consumer group infants are 0.00005 mg/kg bw/day. This is 7.6 % of the established ADI (0.0007 mg/kg bw/day).

Conclusion

As the estimated intake of CGA150829 from drinking water is ≤ 100 % of the established ADI, and dietary intakes from other sources is not expected, no further consideration is required. In conclusion, CGA150829 contributes 7.6 % of the established ADI. As the estimated intakes of CGA150829 following the proposed use of prosulfuron are below the ADI of 0.0007 mg/kg bw/day no harmful effect on human health is expected.

CGA325025

Toxicology assessment

CGA325025 is not a rat metabolite. No toxicological studies are available for this metabolite to be able to set a specific ADI. The metabolite has been shown not to be

genotoxic. Therefore, the TTC Cramer Class III value (1.5 µg/kg bw/day) is proposed for the consumer risk assessment.

Residues assessment

The metabolite CGA325025 of prosulfuron could be present in groundwater at levels requiring further consideration. Based upon worst case modelling conducted in the assessment for maize (1 x 20 g a.s./ha, annual application) resulting in worst case PECgw estimation, it is indicated that metabolite CGA325025 is present above the trigger value of 0.1 µg/L in groundwater.

* CGA325025 is not in the plant or animal residue definition for risk assessment; It was not considered in the food during the consumer risk assessment.

* PEC_{gw} calculations after leaching from soil for CGA325025 indicates that the potential exposure to metabolite CGA325025 is < 0.75 µg/L, with maximum PEC_{gw} of 0.123 µg/L.

* In relation to the drinking water contribution, the highest intake is expected for an infant (< 4 months). EFSA Guidance on pesticides in foods for infants and young children estimates the water consumption of bottle-fed infants as 1.135 L/d (EFSA Journal 2018; 16(6) 5286, 75 pp.). Estimated intakes of CGA325025 from drinking water for the critical consumer group infants are 0.00003 mg/kg bw/day. This is 1.9 % of the toxicology proposed threshold value (TTC CCIII, 0.0015 mg/kg bw/day).

Conclusion

As the estimated intake of CGA325025 from drinking water is ≤ 100 % of the toxicology proposed threshold value (TTC CCIII), and dietary intakes from other sources is not expected, no further consideration is required. In conclusion, CGA325025 contributes 1.9 % of the toxicology proposed threshold value (TTC CCIII). As the estimated intakes of CGA325025 following the proposed use of prosulfuron are below the threshold value (TTC CCIII) of 0.0015 mg/kg bw/day no harmful effect on human health is expected.

SYN547308

Toxicology assessment

SYN547308 is not a rat metabolite. No toxicological studies are available for this metabolite to be able to set a specific ADI. The metabolite has been shown not to be genotoxic. Therefore, the TTC Cramer Class III value (1.5 µg/kg bw/day) is proposed for the consumer risk assessment.

It is noted that the TTC Cramer Class III value has been proposed for the refined risk assessment of CGA325025 and SYN547308, whilst the other metabolites have been assigned specific ADIs. Therefore, the possibility of a combined risk assessment of these two metabolites needs to be considered. HSE notes that although there is structural similarity, this is not striking and a number of functional groups differ between the two compounds. Therefore, a combined risk assessment for the two metabolites assigned the TTC Cramer Class III value is not required.

Residues assessment

The metabolite SYN547308 of prosulfuron could be present in groundwater at levels requiring further consideration. Based upon worst case modelling conducted in the assessment for maize (1 x 20 g a.s./ha, annual application) resulting in worst case PECgw estimation, it is indicated that metabolite SYN547308 is present above the trigger value of 0.1 µg/L in groundwater.

* SYN547308 is not in the plant or animal residue definition for risk assessment; It was not considered in the food during the consumer risk assessment.

* PEC_{gw} calculations after leaching from soil for SYN547308 indicates that the potential exposure to metabolite SYN547308 is < 0.75 µg/L, with maximum PEC_{gw} of 0.220 µg/L.
* In relation to the drinking water contribution, the highest intake is expected for an infant (< 4 months). EFSA Guidance on pesticides in foods for infants and young children estimates the water consumption of bottle-fed infants as 1.135 L/d (EFSA

Journal 2018; 16(6) 5286, 75 pp.). Estimated intakes of SYN547308 from drinking water for the critical consumer group infants are 0.00005 mg/kg bw/day. This is 3.3 % of the toxicology proposed threshold value (TTC CCIII, 0.0015 mg/kg bw/day).

Conclusion

As the estimated intake of SYN547308 from drinking water is ≤ 100 % of the toxicology proposed threshold value (TTC CCIII), and dietary intakes from other sources is not expected, no further consideration is required. In conclusion, SYN547308 contributes 3.3 % of the toxicology proposed threshold value (TTC CCIII). As the estimated intakes of SYN547308 following the proposed use of prosulfuron are below the threshold value (TTC CCIII) of 0.0015 mg/kg bw/day no harmful effect on human health is expected.

2.11.6. Overall conclusion

Toxicology & Residue

CGA150829 (triazine amine), CGA159902, CGA349707, CGA325025 and SYN547308 are not considered relevant at Step 3. Additional in vitro genotoxicity studies on CGA150829 and CGA325025 provided by the applicant showed clear negative results and lack of genotoxic potential. In conclusion, HSE (Toxicology) confirms that newly provided studies address the data gap set by EFSA with regards to genotoxicity of CGA150829 and CGA325025 – overall showing lack of aneugenic and clastogenic potential in vitro and in vivo.

As metabolite CGA349707 is present in groundwater at 0.962 µg/L a refined risk assessment was required at Step 5. The ADI value of 0.001 mg/kg bw/day was proposed to assist with the refined risk assessment of CGA349707. This metabolite is not part of the plant/animal residues definition and estimated intake from drinking water in the critical consumer group does not exceed 100% of the established ADI. No further toxicological consideration is required. Metabolite CGA349707 is therefore non relevant.

As metabolite CGA159902 is present in groundwater at 0.370 µg/L a refined risk assessment was required at Step 5. The ADI value of 0.0013 mg/kg bw/day was

proposed to assist with the refined risk assessment of CGA159902. This metabolite is not part of the plant/animal residues definition and estimated intake from drinking water in the critical consumer group does not exceed 100% of the established ADI. No further toxicological consideration is required. Metabolite CGA159902 is therefore non relevant.

As metabolite CGA150829 (triazine amine) is present in groundwater at 0.234 µg/L a refined risk assessment was required at Step 5. The ADI of 0.0007 mg/kg bw/day was proposed to assist with the refined risk assessment of CGA150829. This metabolite is not part of the plant/animal residues definition and estimated intake from drinking water in the critical consumer group does not exceed 100% of the established ADI. No further toxicological consideration is required. Metabolite CGA150829 is therefore non relevant.

For the remaining metabolites, CGA325025 and SYN547308, a refined risk assessment was required at Step 5. The estimated intake of CGA325025 and SYN547308 from drinking water in the critical consumer group (infants) as calculated does not exceed 100% of the TTC Cramer Class III value of 1.5 µg/kg bw/day. No further toxicological consideration is required. Metabolites CGA325025 and SYN547308 are therefore non relevant.

Two new toxicological studies have been submitted to address data gaps identified by EFSA for groundwater metabolites CGA150829 and CGA325025, their potential genotoxicity and impact on the relevance assessment. Both studies ([redacted], 2020 and [redacted], 2021) provided clear negative results and with the rest of the available studies allow conclusion that both metabolites have no genotoxic activity. Additionally, none of the groundwater metabolites has been shown to exceed their relevant ADIs, as confirmed by the refined consumer risk assessment and are considered non relevant.

The above information allows HSE to conclude that the restriction limiting the use of prosulfuron to one application every three years can be lifted. However parent prosulfuron still breaches the 0.1 µg/L limit following annual applications at 20 g/ha in 2 out of 4 GB relevant FOCUS scenarios. On this basis, consideration will be required at product level to demonstrate acceptable groundwater scenario for all GB

relevant scenarios, product restriction may be required to protect groundwater resources.

Level 3

Prosulfuron

3. PROPOSED DECISION WITH RESPECT TO THE APPLICATION

3.1. BACKGROUND TO THE PROPOSED DECISION

3.1.1. Proposal on acceptability against the decision making criteria – Article 4 and annex II of Regulation (EC) No 1107/2009

- It is considered that Article 4 of the Retained Regulation (EC) No 1107/2009 is complied with and the data considered supports the proposed lifting of the restriction.

- It is considered that in the absence of a full dossier, the relevant information has been presented for the approval conditions of the active substance to be amended. There is no need to re-evaluate elements of the approval which are unaffected.

- It is considered that in line with Article 6 of Retained Regulation (EC) No 1107/2009 approval should continue to be subject to the conditions and restrictions as stated in the original approval, except for the removal of the restriction on application rates.

- It is confirmed that (where relevant) an ADI 0.02 mg/kg bw/d, AOEL 0.06 mg/kg bw/d and ARfD 0.1 mg/kg bw can be established with an appropriate safety margin of at least 100 taking into account the type and severity of effects and the vulnerability of specific groups of the population.

- Prosulfuron is currently approved in GB as a candidate for substitution since the active substance fulfils the criteria as persistent (P) and toxic (T) in accordance with the criteria provided for in points 3.7.2.1 and 3.7.2.3 of Annex II to Regulation (EC) No. 1107/2009 respectively. Prosulfuron still meets the conditions of indent 2 of point 4 of Annex II (it meets two of the criteria to be considered as a PBT substance) and therefore shall be approved pursuant to Article 24 of Regulation (EC) No 1107/2009 as a candidate for substitution. No change is required based on this amendment application.

3.1.2. List of studies to be generated, still ongoing or available but not peer reviewed

There are no studies which are still to be generated or on-going in relation to this Article 7 amendment application.

3.1.3. Issues that could not be finalised

An issue is listed as an issue that could not be finalised where there is not enough information available to perform an assessment, even at the lowest tier level, for the representative uses in line with the Uniform Principles, as laid out in Commission Regulation (EU) No 546/2011, and where the issue is of such importance that it could, when finalised, become a concern (which would also be listed as a critical area of concern if it is of relevance to all representative uses).

Area of the risk assessment that could not be finalised on the basis of the available data	Relevance in relation to representative use(s)
None.	

3.1.4. Critical areas of concern

An issue is listed as a critical area of concern:

(a) where the substance does not satisfy the criteria set out in points 3.6.3, 3.6.4, 3.6.5 or 3.8.2 of Annex II of Retained Regulation (EC) No 1107/2009 and the applicant has not provided detailed evidence that the active substance is necessary to control a serious danger to plant health which cannot be contained by other available means including non-chemical methods, taking into account risk mitigation measures to ensure that exposure of humans and the environment is minimised, or

(b) where there is enough information available to perform an assessment for the representative uses in line with the Uniform Principles, as laid out in Commission Regulation (EU) 546/2011, and where this assessment does not permit to conclude that for at least one of the representative uses it may be expected that a plant protection product containing the active substance will not have any harmful effect on human or animal health or on groundwater or any unacceptable influence on the environment.

An issue is also listed as a critical area of concern where the assessment at a higher tier level could not be finalised due to a lack of information, and where the assessment performed at the lower tier level does not permit to conclude that for at least one of the representative uses it may be expected that a plant protection product containing the active substance will not have any harmful effect on human or animal health or on groundwater or any unacceptable influence on the environment.

Critical area of concern identified	Relevance in relation to representative use(s)
None.	

3.1.5. Overview table of the concerns identified for each representative use considered

None.

3.1.6. Area(s) where expert consultation is considered necessary

It is recommended to organise a consultation of experts on the following parts of the assessment report:

Area(s) where expert consultation is considered necessary	Justification
None.	

3.2. PROPOSED DECISION

It is proposed that:

Under the Retained Regulation (EC) No 1107/2009 the approval of the active substance Prosulfuron can be amended to remove the following restriction:

Use shall be limited to one application every three years on the same field at a maximum dose of 20 g active substance per hectare.

It is proposed that the following be specified as areas requiring particular attention when evaluating applications for product authorisation(s):

- The protection of groundwater, when the substance is applied in regions with vulnerable soil and/or climatic conditions.
- The risk to non-target terrestrial and aquatic plants.

The list of data gaps identified during the peer review process for the renewal of prosulfuron, presented in the EFSA Conclusion (2014) are still applicable to GB where relevant.

3.3. RATIONAL FOR THE CONDITIONS AND RESTRICTIONS TO BE ASSOCIATED WITH THE APPROVAL OR AUTHORISATION(S), AS APPROPRIATE

3.3.1. Particular conditions proposed to be taken into account to manage the risks identified within this Article 7 amendment application

Proposed condition/risk mitigation measure	Relevance in relation to representative use(s)
None.	

3.4. APPENDICES

GUIDANCE DOCUMENTS USED IN THIS ASSESSMENT

Section Toxicology

EFSA Panel on Plant Protection Products and their Residues (PPR); Guidance on Dermal Absorption. EFSA Journal 2012;10(4):2665. [30 pp.] doi:10.2903/j.efsa.2012.2665

Guidance of EFSA: Submission of scientific peer-reviewed open literature for the approval of pesticide active substances under Regulation (EC) No 1107/2009: EFSA Journal 2011;9(2):2092.

Guidance on the application of the CLP criteria; guidance to Regulation (EC) No 1272/2008 on classification, labelling and packaging (CLP) of substances and mixtures Version 4.0 June 2015.

European Commission, 2011. Guidance Document on the Assessment of the Equivalence of Technical Materials of Substances Regulated under Regulation (EC) No 1107/2009. SANCO/10597/2003 – rev. 9, 17 June 2011.

Section Residues

EC (European Commission), 1996. Appendix G. Livestock Feeding Studies. 7031/VI/95 rev.4

EC (European Commission), 1997a. Appendix A. Metabolism and distribution in plants. 7028/IV/95-rev.3.

EC (European Commission), 1997b. Appendix B. General recommendations for the design, preparation and realization of residue trials. Annex 2. Classification of (minor) crops not listed in the Appendix of Council Directive 90/642/EEC. 7029/VI/95-rev.6.

EC (European Commission), 1997c. Appendix C. Testing of plant protection products in rotational crops. 7524/VI/95-rev.2.

EC (European Commission), 1997d. Appendix E. Processing studies. 7035/VI/95-rev.5.

EC (European Commission), 1997e. Appendix F. Metabolism and distribution in domestic animals. 7030/VI/95-rev.3

EC (European Commission), 1997f. Appendix H. Storage stability of residue samples. 7032/VI/95-rev.5.

EC (European Commission), 1997g. Appendix I. Calculation of maximum residue level and safety intervals. 7039/VI/95. As amended by the document: classes to be used for the setting of EU pesticide maximum residue levels (MRLs). SANCO 10634/2010.

EC (European Commission), 2000. Residue analytical methods. For pre-registration data requirement for Annex II (part A, section 4) and Annex III (part A, section 5 of Directive 91/414. SANCO/3029/99-rev.4.

EC (European Commission), 2004. Residue analytical methods. For post-registration control. SANCO/825/00-rev.7.

EC (European Commission), 2010. Classes to be used for the setting of EU pesticide Maximum Residue Levels (MRLs). SANCO 10634/2010 Rev. 0, finalized in the Standing Committee on the Food Chain and Animal Health at its meeting of 23-24 March 2010.

EC (European Commission), 2011. Appendix D. Guidelines on comparability, extrapolation, group tolerances and data requirements for setting MRLs. 7525/VI/95-rev.9.

Section fate and behaviour in the environment

FOCUS (2006) “Guidance Document on Estimating Persistence and Degradation Kinetics from Environmental Fate Studies on Pesticides in EU Registration” Report of the FOCUS Work Group on Degradation Kinetics, EC Document Reference Sanco/10058/2005 version 2.0, 434 pp

EFSA (2014) European Food Safety Authority, 2014. EFSA Guidance Document for evaluating laboratory and field dissipation studies to obtain DegT50 values of active substances of plant protection products and transformation products of these active substances in soil. EFSA Journal 2014;12(5):3662, 37 pp., doi:10.2903/j.efsa.2014.3662

FOCUS. (1996). Soil Persistence Models and EU Registration, European Commission Document No. 7617/VI/96.

FOCUS. (2000). FOCUS Groundwater Scenarios in the EU Review of Active Substances. Report of the FOCUS Groundwater Scenarios Workgroup. EC Document Reference Sanco/321/2000 rev.2, 202 pp.

FOCUS. (2002). Generic Guidance for FOCUS groundwater scenarios. Version 1.1

FOCUS. (2009). Assessing Potential for Movement of Active Substances and their Metabolites to Ground Water in the EU. Report of the FOCUS Ground Water Work Group, EC Document Reference Sanco/13144/2010 version 1, 604 pp.

FOCUS. (2011). Generic Guidance for Tier 1 FOCUS Ground Water Assessments. Version 2.0.

Sanco/221/2000 rev.10. 25 February 2003. Guidance document on the assessment of the relevance of metabolites in Groundwater of substance regulated under Council Directive 91/4141/EEC

3.5. REFERENCE LIST

Section toxicology

Commission Implementing Regulation (EU) No 2017/375 of 02 March 2017 renewing the approval of the active substance prosulfuron, as a candidate for substitution, in accordance with Regulation (EC) No 1107/2009 of the European Parliament and of the Council concerning the placing of plant protection products on the market, and amending the Annex to Commission Implementing Regulation (EU) No 540/2011 (OJ L 58, 4.3.2017, p. 6).

Commission Implementing Regulation (EU) 2021/574 of 30 March 2021 amending Implementing Regulations (EU) 2017/375 and (EU) No 540/2011 as regards the conditions of approval of the active substance prosulfuron (OJ L 120, 8.4.2021, p. 9–12).

Conclusion on the peer review of the pesticide risk assessment of the active substance prosulfuron, EFSA, 2014. Available: https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2014.3815

EFSA (European Food Safety Authority), Anastassiadou, M, Arena, M, Auteri, D, Brancato, A, Bura, L, Carrasco Cabrera, L, Chaideftou, E, Chiusolo, A, Crivellente, F, De Lentdecker, C, Egsmose, M, Fait, G, Greco, L, Ippolito, A, Istace, F, Jarrah, S, Kardassi, D, Leuschner, R, Lostia, A, Lythgo, C, Magrans, O, Mangas, I, Miron, I, Molnar, T, Padovani, L, Parra Morte, JM, Pedersen, R, Reich, H, Santos, M, Sharp, R, Stanek, A, Sturma, J, Szentes, C, Terron, A, Tiramani, M, Vagenende, B and Villamar-Bouza, L, 2020. Conclusion on the peer review of the pesticide risk assessment of the active substance prosulfuron. EFSA Journal 2020;18(7):6181, 20 pp.

Further revisions to the revised Renewal Assessment Report (RAR) on prosulfuron prepared by the Rapporteur Member State France in the framework of Regulation (EC) No 1107/2009, February 2019.

Section residues

EC (European Commission), 2001. Review report for the active substance prosulfuron. Finalised in the Standing Committee on the Food Chain and Animal Health at its meeting on 26 February 2002 in view of the inclusion of prosulfuron in Annex I of Directive 91/414/EEC. SANCO/3055/99-FINAL, 2 July 2002.

France,1998. Draft assessment report on the active substance prosulfuron prepared by the rapporteur Member State France in the framework of Council Directive 91/414/EEC, December 1998.