Committee for Risk Assessment

RAC

Annex 1

Background document

to the Opinion proposing harmonised classification and labelling at EU level of

sulfur

EC Number: 231-722-6
CAS Number: 7704-34-9

CLH-O-0000007107-77-01/F

The background document is a compilation of information considered relevant by the dossier submitter or by RAC for the proposed classification. It includes the proposal of the dossier submitter and the conclusion of RAC. It is based on the official CLH report submitted to consultation. RAC has not changed the text of this CLH report but inserted text which is specifically marked as 'RAC evaluation'. Only the RAC text reflects the view of RAC.

Adopted

18 March 2022

European Commission

Combined Draft Renewal Assessment Report prepared according to Regulation (EC) N° 1107/2009
and
Proposal for Harmonised Classification and Labelling (CLH Report) according to Regulation (EC) N° 1272/2008

SULPHUR

Volume 1

Rapporteur Member State: France
Co-Rapporteur Member State: Slovenia

Version History

When	What
2020-09	Initial RAR

The RMS is the author of the Assessment Report. The Assessment Report is based on the validation by the RMS, and the verification during the EFSA peer-review process, of the information submitted by the Applicant in the dossier, including the Applicant's assessments provided in the summary dossier. As a consequence, data and information including assessments and conclusions, validated and verified by the RMS experts, may be taken from the applicant's (summary) dossier and included as such or adapted/modified by the RMS in the Assessment Report. For reasons of efficiency, the Assessment Report should include the information validated/verified by the RMS, without detailing which elements have been taken or modified from the Applicant's assessment. As the Applicant's summary dossier is published, the experts, interested parties, and the public may compare both documents for getting details on which elements of the Applicant's dossier have been validated/verified and which ones have been modified by the RMS. Nevertheless, the views and conclusions of the RMS should always be clearly and transparently reported; the conclusions from the applicant should be included as an Applicant's statement for every single study reported at study level; and the RMS should justify the final assessment for each endpoint in all cases, indicating in a clear way the Applicant's assessment and the RMS reasons for supporting or not the view of the Applicant.

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Level 1

SULPHUR

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

1.1.1 Purpose for which the draft assessment report was prepared

This renewal assessment report (RAR) has been prepared in accordance with Commission Regulation (EU) No 844/2012 and Guidance Document SANCO/2012/11251 rev. 4 in order to evaluate the supplementary dossier submitted by the Sulfur Working Group (SWG) and the Sulphur Task Force (STF), and to allow a decision on the renewal of the approval of the active substance Sulphur under Commission Regulation (EC) No 1107/2009.

The harmonised classification and labelling of Sulphur has been considered previously in the EU (ATP01). The existing entry in Annex VI of CLP Regulation (EU) 1272/2008 is: Skin Irrit. 2, H315: Causes skin irritation.
In the framework of the renewal assessment of Sulphur (spelled Sulfur under CLP regulation) under Regulation (EC) 1107/2009, RMS proposed to reconsider the current harmonised classification of the active substance by retaining the current classification and adding Eye Irrit. 2, H319: Causes serious eye irritation and STOT SE 3, H 335: May cause respiratory irritation. Therefore, in this context, a targeted CLH proposal is presented in this document using the common agreed template for DAR/RAR/CLH report.

1.1.2 Arrangements between rapporteur Member State and co-rapporteur Member State

According to Commission Regulation (EU) No 2016/183 France was designated Rapporteur Member State (RMS) and Slovenia assigned as Co-Rapporteur Member State (Co-RMS).

France, as RMS, evaluated the dossier submitted by the applicants and draft the Renewal Assessment Report for all the sections, whereas Slovenia as Co-RMS, conducted a pre-peer review of this report before sending it to the EFSA.
Any deviating views on critical issues between the RMS and the Co-RMS have been reported in Volume 1 Level 3 section 3.1.9.

1.1.3 EU Regulatory history for use in Plant Protection Products

In June 2005, the Sulphur Task Force and the Sulfur Working Group submitted a dossier for the inclusion of the existing active substance Sulphur in Annex I of the Directive 91/414/EEC. France was designated rapporteur Member State (RMS) to carry out the detailed examination of the dossier and report the conclusions to the Commission.

The draft assessment reports (DAR) was submitted to the EFSA on 18 October 2007. In accordance with the provisions of Article 24 of Regulation (EC) No 2229/2004 as last amended by Regulation (EC) 1095/2007, the EFSA organised the consultation on the draft assessment report by all the Member States as well as by Sulphur Task Force and Sulfur Working Group being the data submitters, on 18 February 2008 by making it available.

In accordance with the provisions of Article 24 of Regulation (EC) No 2229/2004 the EFSA sent to the Commission its conclusion on the risk assessment [Conclusions regarding the peer review of the pesticide

risk assessment of the active substance sulphur (finalised 19 December 2008)[1]].

The draft review report was finalised in the Standing Committee on the Food Chain and Animal Health on 13 March 2009. The review report containing the conclusions of the final examination by the Standing Committee was finalised on 22 October 2009 (Sulphur SANCO/2676/08 final, dated on 22 October 2009). Sulphur was listed in Annex I of Directive 91/414/EEC on 1st January 2010 (Commission Directive 2009/70/EC) with the following specific provisions:

- PART A
  Only uses as fungicide and acaricide may be authorised.

- PART B
  For the implementation of the uniform principles of Annex VI, the conclusions of the review report on sulphur, and in particular Appendices I and II thereof, as finalised in the Standing Committee on the Food Chain and Animal Health on 12 March 2009 shall be taken into account.
  In this overall assessment Member States shall pay particular attention to:
  - the protection of birds, mammals, aquatic organisms and non-target arthropods. Conditions of authorisation shall include risk mitigation measures, where appropriate.

  The Member States concerned shall ensure that the notifier submit to the Commission further information to confirm the risk assessment for birds, mammals, sediment dwelling organisms and non-target arthropods. They shall ensure that the notifier at whose request sulphur has been included in this Annex provide such data to the Commission at latest by 30 June 2011.

The original review report of the 22 October 2009 (Sulphur SANCO/2676/08 final, dated on 22 October 2009) containing the conclusions of the final examination by the Standing Committee was updated on 13 July 2012 (Sulphur SANCO/2676/08 final, dated on 13 July 2012) following the assessment of confirmatory data. On 13 July 2012 the Standing Committee on the Food Chain and Animal Health has taken note of the revision of the review report after the assessment of confirmatory data. The assessment was carried out in line with the Guidance document on the procedures for submission and assessment of confirmatory data following inclusion of an active substance in Annex I of Council Directive 91/414/EEC[2]. The Committee agreed that, the risk for the exposed species was acceptable and the conclusions of the original risk assessment was not substantially modified by the evaluation of the submitted confirmatory data. No further review by EFSA has been considered necessary.

By Commission Regulation (EU) 2017/555, the expiry date of approval of Sulphur, initially on 30 December 2019, was extended to 31 December 2020.

According to Regulation (EC) No 459/2010, sulphur is included under Annex IV of Reg. (EC) No 396/2005.

1.1.4 Evaluations carried out under other regulatory contexts

Sulfur was evaluated by US-EPA in 2004 (Docket N° EPA-HQ-OPP-2008-0176).

1.2 APPLICANT INFORMATION

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

- **Sulfur Working Group (SWG)**

BASF SE
APD/RE – LI556

[1] EFSA Scientific Report (2008) n, 1-34.
[2] Doc. SANCO/5634/2009 rev 3, 2.10.2009.

67056 Ludwigshafen, Germany

Syngenta Crop Protection AG
Schwarzwaldallee 215
4002 Basel, Switzerland

Agrostulln GmbH
Werksweg 2
92551 Stulln, Germany

UPL Europe Limited
The Centre, 1st Floor, Birchwood Park
Warrington, Cheshire, WA3 6YN, UK

- **Sulphur Task Force (STF)**

Azufrera y Fertilizantes Pallarés, S.A. (AFEPASA)
Polígono Industrial de Constantí
Avenida Europa, 1-7
E-43120 Constantí (Tarragona), Spain

CEPSA QUÍMICA S.A.
Torre CEPSA
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28046 Madrid, Spain

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37-310 Nowa Sarzyna
woj. Podkarpackie, Poland

Julio Cabrero y Cía, S.L.
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39312 - Requejada (Cantabria), Spain

Petróleos de Portugal (now Petrogal, S.A.)
Rua Tomás da Fonseca, Torre C
1600-209 Lisboa, Portugal

Quimetal Industrial S.A.
Los Yacimentos 1301
Maipù
Santiago 9260062
Región Metropolitana, Chile

Repsol Lubricantes y Especialidades S.A. (now Repsol Lubricants and Specialties, S.A.)
Méndez Álvaro 44
28045 Madrid, Spain

SAPEC Agro S.A. (now ASCENZA Agro S.A.)
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S.T.I. Solfotecnica Italiana S.p.A.
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Sulphur Mills Ltd.
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Western Express Highway
Andheri (E)
Mumbai – 400069, India

Zolfindustria S.r.l.
Via San Cassiano 99
28069 San Martino di Trecate (NO), Italy

Zolfital S.p.A.
Via di Santa Teresa 23
00198 Roma, Italy

1.2.2 Producer or producers of the active substance

- **Sulfur Working Group (SWG)**

BASF SE
APD/RE – LI556
67056 Ludwigshafen, Germany

Syngenta Crop Protection AG
Schwarzwaldallee 215
4002 Basel, Switzerland

Agrostulln GmbH
Werksweg 2
92551 Stulln, Germany

UPL Europe Limited
The Centre, 1st Floor, Birchwood Park
Warrington, Cheshire, WA3 6YN, UK

- **Sulphur Task Force (STF)**

CEPSA QUÍMICA S.A.
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28069 San Martino di Trecate (NO), Italy

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Via di Santa Teresa 23
00198 Roma, Italy

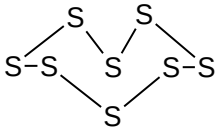
1.2.3 Information relating to the collective provision of dossiers

Two task forces have been formed:
Sulphur Task Force (STF)
Sulfur Working Group (SWG)

The two task forces share the ownership of all non confidential data relative to the active substance (Vol. 3_CA).
Each task force shares between their members all non confidential data relative to their representative formulations, however each task force did not share these data with the other task force (i.e. Vol. 3_CP1 is shared by the members of SWG, and Vol. 3_CP2 is shared by the members of STF).
In addition, each applicant individually submitted confidential data which are not shared, these data are compiled in distinct Vol. 4 (one for each applicant).

1.3 IDENTITY OF THE ACTIVE SUBSTANCE

1.3.1 Common name proposed or ISO-accepted and synonyms	Sulfur Sulphur
1.3.2 Chemical name (IUPAC and CA nomenclature)	
IUPAC	Sulfur
CA	Sulfur
1.3.3 Producer's development code number	Syngenta: SAN 7116 BASF: BASF 175F

1.3.4 CAS, EEC and CIPAC numbers	
CAS	7704-34-9
EEC	231-722-6
CIPAC	18
1.3.5 Molecular and structural formula, molecular mass	
Molecular formula	S_8
Structural formula	
Molecular mass	32.064 g/mol (S) 256.512 g/mol (S_8)
1.3.6 Method of manufacture (synthesis pathway) of the active substance	Confidential information, please refer to Vol. 4
1.3.7 Specification of purity of the active substance in g/kg	990 g/kg
1.3.8 Identity and content of additives (such as stabilisers) and impurities	
1.3.8.1 Additives	Confidential information, please refer to Vol. 4
1.3.8.2 Significant impurities	Confidential information, please refer to Vol. 4
1.3.8.3 Relevant impurities	Mercury: max. 0.1 mg/kg Arsenic: max. 0.1 mg/kg Cadmium: max. 0.1 mg/kg Lead: max. 0.9 mg/kg Nickel: max. 1.2 mg/kg
1.3.9 Analytical profile of batches	Confidential information, please refer to Vol. 4

1.4 INFORMATION ON THE PLANT PROTECTION PRODUCT 1

1.4.1 Applicant	**Sulfur Working Group (SWG)** <u>SWG members</u>: BASF SE APD/RE – LI556 67056 Ludwigshafen, Germany Syngenta Crop Protection AG Schwarzwaldallee 215 4002 Basel, Switzerland Agrostulln GmbH Werksweg 2 92551 Stulln, Germany UPL Europe Limited The Centre, 1st Floor, Birchwood Park Warrington, Cheshire, WA3 6YN, UK

1.4.2 Producer of the plant protection product	**Sulfur Working Group (SWG)** SWG members: BASF SE APD/RE – LI556 67056 Ludwigshafen, Germany Syngenta Crop Protection AG Schwarzwaldallee 215 4002 Basel, Switzerland Agrostulln GmbH Werksweg 2 92551 Stulln, Germany UPL Europe Limited The Centre, 1st Floor, Birchwood Park Warrington, Cheshire, WA3 6YN, UK
1.4.3 Trade name or proposed trade name and producer's development code number of the plant protection product	Name used in core assessment: 'SULFUR 80% WG' Trade names: KUMULUS WG (BASF), Thiovit Jet (Syngenta), Netzschwefel Stulln (Agrostulln), Microthiol Special Disperss (UPL) Code number: BAS 175 01 F (BASF), A8456E (Syngenta), 1001 (Agrostulln), FCG02 (UPL)
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	800 g/kg pure Sulphur
1.4.4.2 Information on the active substances	Sulphur ≥ 99.0% pure
1.4.4.3 Information on safeners, synergists and co-formulants	Confidential (refer to Vol. 4)
1.4.5 Type and code of the plant protection product	WG (water dispersible granules)
1.4.6 Function	Fungicide and acaricide
1.4.7 Field of use envisaged	Agriculture and viticulture
1.4.8 Effects on harmful organisms	Non-systemic, contact and protectant fungicide and acaricide

1.5 INFORMATION ON THE PLANT PROTECTION PRODUCT 2

1.5.1 Applicant	**Sulphur Task Force (STF)** STF members: Azufrera y Fertilizantes Pallarés, S.A. (AFEPASA) Polígono Industrial de Constantí Avenida Europa, 1-7 E-43120 Constantí (Tarragona), Spain CEPSA QUÍMICA S.A. Torre CEPSA Paseo de la Castellana 259A 28046 Madrid, Spain CIECH Sarzyna S.A. ul. Chemików 1 37-310 Nowa Sarzyna woj. Podkarpackie, Poland Julio Cabrero y Cía, S.L. Puerto de Requejada 39312 - Requejada (Cantabria), Spain Petróleos de Portugal (now Petrogal, S.A.) Rua Tomás da Fonseca, Torre C 1600-209 Lisboa, Portugal Quimetal Industrial S.A. Los Yacimentos 1301 Maipù Santiago 9260062 Región Metropolitana, Chile Repsol Lubricantes y Especialidades S.A. (now Repsol Lubricants and Specialties, S.A.) Méndez Álvaro 44 28045 Madrid, Spain SAPEC Agro S.A. (now ASCENZA Agro S.A.) Avenida do Rio Tejo Herdade das Praias 2910-440 Setúbal, Portugal S.T.I. Solfotecnica Italiana S.p.A. Via Matteotti 16 48121 Ravenna (RA), Italy Sulphur Mills Ltd. 604/605, 349 - Business Point, 6th Floor Western Express Highway Andheri (E) Mumbai – 400069, India

	Zolfindustria S.r.l. Via San Cassiano 99 28069 San Martino di Trecate (NO), Italy Zolfital S.p.A. Via di Santa Teresa 23 00198 Roma, Italy
1.5.2 Producer of the plant protection product	SAPEC Agro S.A. (now ASCENZA Agro S.A.) Avenida do Rio Tejo Herdade das Praias 2910-440 Setúbal, Portugal
1.5.3 Trade name or proposed trade name and producer's development code number of the plant protection product	Sulphur Dust Bago de Ouro
1.5.4 Detailed quantitative and qualitative information on the composition of the plant protection product	
1.5.4.1 Composition of the plant protection product	***985 g/kg pure sulphur***
1.5.4.2 Information on the active substances	Sulphur > 99% w/w
1.5.4.3 Information on safeners, synergists and co-formulants	Confidential data, please refer to Vol. 4
1.5.5 Type and code of the plant protection product	DP (Dustable powder)
1.5.6 Function	Fungicide
1.5.7 Field of use envisaged	Viticulture
1.5.8 Effects on harmful organisms	Non-systemic, contact and protectant fungicide

1.6 DETAILED USES OF THE PLANT PROTECTION PRODUCT

1.6.1 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) (m)	Remarks
					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 (l)	Water l/ha min max	Kg a.i./ha min max (l)		
Grapevine (wine and table grapes) (VITVI *Vitis vinifera*)	N-, C-, S-EU	Sulfur 80% WG	F	Powdery mildew [UNCINE *Erysiphe necator* (*Uncinula necator, Oidium tuckeri)]*	WG	800 g/kg	Foliar spray, vehicle-mounted	Post-emergence, crop BBCH 05-81	10	7 days	1-5 kg a.i./hL	200-1000 L/ha	10 kg a.i./ha	28 days	
Grapevine (wine and table grapes) (VITVI *Vitis vinifera*)	N-, C-, S-EU	Sulfur 80% WG	F	Erineum leaf mite ERPHVI *[Colomerus vitis* (*Eriophyes vitis, Phytoptus vitis)]* Rust mite [EPITVI *Calepitrimerus vitis* (*Epitrimerus vitis, Phyllocoptes vitis)]*	WG	800 g/kg	Foliar spray, vehicle-mounted	Post-emergence, crop BBCH 05-81	10	7 days	1-5 kg a.i./hL	200-1000 L/ha	10 kg a.i./ha	28 days	
Cereals (wheat, barley, oat, rye, triticale) (NNNGG)	N-, C-, S-EU	Sulfur 80% WG	F	Powdery mildew ERYSGR *[Blumeria graminis* (*Erysiphe graminis, Oidium monilioides)]*	WG	800 g/kg	broadcast foliage directed boom spray, vehicle-mounted	Post-emergence, crop BBCH 15-69	4	7 days	2-4 kg a.i./hL	200-400 L/ha	8 kg a.i./ha	35 days	

* 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

(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

(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) 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

(k) Indicate the minimum and maximum number of application possible under practical conditions of use

(l) The values should be given in g or kg whatever gives the more manageable number (e.g. 200 kg/ha instead of 200 000 g/ha or 12.5 g/ha instead of 0.0125 kg/ha

(m) PHI - minimum pre-harvest interval

RMS comment: This GAP table format is different from the one provided by the applicant. RMS has updated the table format following EFSA request. EFSA has requested to “update the GAP table using the format available on the EC website, in Volume 1, LoEP and Volumes 3CP_B-3”. The applicant is kindly asked to check if this update is in accordance with its initial GAP table.

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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) (m)	Remarks
					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 (l)	Water l/ha min max	Kg a.i./ha min max (l)		
Grapevine (wine and table grapes) (VITVI *Vitis vinifera*)	C-EU, S-EU	Sulphur Dust	F	Powdery mildew [UNCINE *Erysiphe necator* (*Uncinula necator, Oidium tuckeri)]*	DP	985 g/kg	Foliar dust	Post-emergence, BBCH 15-19: max. 1 application BBCH 20-39: max. 3 applications BBCH 40-89: rest of applications	5	7 days	not applicable	not applicable	29.55 kg a.i./ha	5 days	

* 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
(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
(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) 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
(k) Indicate the minimum and maximum number of application possible under practical conditions of use
(l) The values should be given in g or kg whatever gives the more manageable number (e.g. 200 kg/ha instead of 200 000 g/ha or 12.5 g/ha instead of 0.0125 kg/ha
(m) PHI - minimum pre-harvest interval

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1.6.2 Further information on representative uses

For the representative uses, please refer to tables above (Details of representative uses).

Sulfur 80% WG is to be applied by spraying. Sulphur Dust is to be applied by dusting.

Duration of protection afforded by each application:
The duration of the protection after an application depends on the pest pressure.

Necessary waiting period or other precautions to avoid phytotoxic effects on succeeding crops:
Since sulphur is an essential plant nutrient no harm is expected for succeeding crops. A waiting period and a limitation on choice of succeeding crops are not considered necessary.

Proposed instructions for use:
Label recommendations were not provided by the applicant. Label recommendations should be proposed by the applicant to the concerned Member States in the context of subsequent applications for products authorisation.

1.6.3 Details of other uses applied for to support the setting of MRLs for uses beyond the representative uses

No relevant since no MRLs are set nor needed.

1.6.4 Overview on authorisations in EU Member States

The active substance sulphur was developed for uses such as scab in pome fruits (*Venturia sp*.) and powdery mildews on a range of crops including grapevine (*Erysiphe necator*), pome fruits (*Podosphaera leucotricha*), stone fruits (*e.g. Podosphaera pannosa*), hop (*Podosphaera macularis*), beets (*Erysiphe betae*), cereals (*Blumeria graminis*), vegetables (various species) and ornamentals (various species). It is also known to have acaricidal activity, particularly on eriophyid mites (Eriophyidae).

It has been used for many years in European countries. According to the EU Pesticides database, sulphur is authorised in most of Member States.

Authorisations for a range of different formulations have been achieved in Europe. These include formulations for spraying and for dusting.

Level 2

SULPHUR

2 SUMMARY OF ACTIVE SUBSTANCE HAZARD AND OF PRODUCT RISK ASSESSMENT

Summary of methodology proposed by the applicant for literature review and for all sections

A literature review was carried out by the applicant for Sulfur and trade names according to Article 8(5) of Regulation (EC) No 1107/2009. This review is in accordance with the EFSA Guidance document as published in EFSA Journal 2011; 9(2):2092.[3]

The detailed process of the search strategy, key words used, analysis of relevance, and results are presented in Volume 3 CA B6, 3 CA B7, 3 CA B8 and 3 CA B9 but a summary is given below.

The search of scientific peer reviewed open literature on side effects of sulfur and plant protection products containing sulfur on humans and non-target organisms (including vertebrates) includes the period between January 2007 and mid of March 2018 (3.5 month before the date of dossier submission in June 2018).

For the active substance sulfur and its products' trade names a total of more than 8000 references (excluding duplicates) were identified and evaluated for potential relevance. Besides references that were clearly out of the scope of the literature review (e.g. publications obviously relating to a completely different topic like information technology or efficacy data), the search results represented the area of toxicology, residues, e-fate and ecotoxicology.

In total 5 references were identified as relevant in the context of side-effects on health (1 article), the environment (3 articles) and on residues in or on treated products, food and feed (1 article). Only supplemental data were found in these publications, confirming the risk assessment. For non-target species, a total of 43 references were retrieved that are potentially relevant. 8 of these provide data for establishing or refining risk assessment parameters. All references found in the literature search which were evaluated for relevance in a detailed assessment of full-text documents are listed in the tables in Appendix 2. The overall results are shown below:

Results of the study selection process for toxicological data

Toxicity (CA 5 / CP 7)	**n**		
	Initial January 2007 - March 2017	**Update** Mid March 2018	**sum**
Total number of *titles* retrieved after all searches of peer-reviewed literature (excluding duplicates)	2585	353	2938
Total number of *titles* excluded from the searches after rapid assessment for relevance	2251 (+166 duplicates)	331 (+22 duplicates)	2528 (+188 duplicates)
Total number of *summary records*(1 to be obtained and screened	168	2 (+1(4))	170 (+1(4))
Total number of *summary records* excluded from the searches after rapid assessment for relevance	147	1	148
Total number of *full-text documents* to be assessed in detail	21(2 (including 16 relating to Ecotoxicity(3))	1	22(2 (including 16 relating to Ecotoxicity(3))
Number of *studies* excluded from further considerations after detailed assessment for relevance	5	0	5
Number of *studies* not excluded for relevance after detailed assessment (i.e. relevant studies and studies of unclear relevance)	0	1	1

(1 Abstract of the publications

[3] European Food Safety Authority; Submission of scientific peer-reviewed open literature for the approval of pesticide active substances under Regulation (EC) No 1107/2009 (OJ L 309, 24.11.2009, p. 1-50). EFSA Journal 2011;9(2):2092. [49 pp.]. doi:10.2903/j.efsa.2011.2092.

(2 3 records are duplicates to the residue section. Publications were evaluated in both, the residues and toxicity part of search, based on the respective requirements.

(3 Publications were evaluated only in the ecotoxicity part of search (for Polioencephalomalacia issue), containing 11 duplicates to Ecotoxicity

(4 Publications were evaluated only in the ecotoxicity part of search (for Polioencephalomalacia issue)

Results of the study selection process for residue data in plants and livestock

Residues (CA 6 / CP 8)	**n**		
	Initial January 2007 - March 2017	**Update** Mid March 2018	**sum**
Total number of *titles* retrieved after all searches of peer-reviewed literature (excluding duplicates)	1631	241	1872
Total number of *titles* excluded from the searches after rapid assessment for relevance	1464 (+52 duplicates)	221 (+20 duplicates)	1685 (+72 duplicates)
Total number of *summary records*(1 to be obtained and screened	115	3	118
Total number of *summary records* excluded from the searches after rapid assessment for relevance	93	3	96
Total number of *full-text documents* to be assessed in detail	22	0	22
Number of *studies* excluded from further considerations after detailed assessment for relevance	20 (+1(2))	0	20
Number of *studies* not excluded for relevance after detailed assessment (i.e. relevant studies and studies of unclear relevance)	1	0	1

(1 Abstract of the publications

(2 Full text of the publication is not available.

Results of the study selection process for environmental fate data

Environmental fate (CA 7 / CP 9)	**n**		
	Initial January 2007 - March 2017	**Update** Mid March 2018	**sum**
Total number of *titles* retrieved after all searches of peer-reviewed literature (excluding duplicates)	1548	333	1881
Total number of *titles* excluded from the searches after rapid assessment for relevance	1461 (+43 duplicates)	311 (+22 duplicates)	1772 (+65 duplicates
Total number of *summary records*(1 to be obtained and screened	44	4 (+2(2))	48 (+2(2))
Total number of *summary records* excluded from the searches after rapid assessment for relevance	23	3	26
Total number of *full-text documents* to be assessed in detail	21	1(+1(3))	23
Number of *studies* excluded from further considerations after detailed assessment for relevance	20	1(+1(3))	22
Number of *studies* not excluded for relevance after detailed assessment (i.e. relevant studies and studies of unclear relevance)	1	2	3

(1 abstract of the publications

(2 two publications were evaluated only in the ecotoxicity part of search.

(3 one publication was not found in the database search but obtained from a cross reference

Results of the study selection process for ecotoxicological data

Ecotoxicity (CA 8 / CP 10)	**n**		
	Initial January 2007 - March 2017	**Update** Mid March 2018	**sum**
Total number of *titles* retrieved after all searches of peer-reviewed literature (excluding duplicates automatically)	1197	173	1370
Total number of *titles* excluded from the searches after rapid assessment for relevance	960 (+56 duplicates)	167 (+6 duplicates)	1127 (62 duplicates)
Total number of *summary records*[1] to be obtained and screened	181	4 (+4[4])	185 (+4[4])
Total number of *summary records* excluded from the searches after rapid assessment for relevance	129	4	133
Total number of *full-text documents* to be assessed in detail	52 (+5[2])	4	56 (+5[2])
Number of *studies* excluded from further considerations after detailed assessment for relevance	19 (+1[3])	4	23 (+1[4])
Number of *studies* not excluded for relevance after detailed assessment (i.e. relevant studies and studies of unclear relevance)	37	2	39 (+ 4[5])

[1] abstract of the publications
[2] These 5 publications contain information for the Polioencephalomalacia issue derived from the Toxicity part of the search
[3] One publication which was considered potentially relevant based on the title was not available as abstract or full-text for assessment.
[4] Publications that were found in the toxicological (n=1), environmental fate (n=2) or tradename (n=1) part of search and have been evaluated only in the ecotoxicity part of search
[5] Addional publications that were found in the tradename (n=4) part of search and have been evaluated only in the ecotoxicity part of search.

The outcomes of the review of scientific open literature are discussed by the RMS in Volumes 3 of the RAR for each section.

2.1 IDENTITY

2.1.1 Summary of identity

Technical sulphur is manufactured with a minimum purity of 990 g/kg. It does not contain additives.
Arsenic (As), Cadmium (Cd), Mercury (Hg), Lead (Pb) and Nickel (Ni) are considered relevant impurities.
The assessment of the data package revealed no issues that need to be included as critical areas of concern with respect to the identity, physical, chemical and technical properties of sulphur or the respective formulation.

The main data regarding the identity of sulphur are given in Vol. 4.

2.2 PHYSICAL AND CHEMICAL PROPERTIES [EQUIVALENT TO SECTION 7 OF THE CLH REPORT TEMPLATE]

2.2.1 Summary of physical and chemical properties of the active substance

Pure sulphur (as well as technical sulphur) is a yellow powder with an odour of sulfur. It has a melting point of 115.8 – 117 °C and a boiling point of >400 °C. It has a relative density of 2.07 at 20°C. Its vapour pressure at 20 °C (9.8×10^{-5} Pa) is rather low indicating that it has a low volatility. It is very slightly soluble in water (16 µg/L) and moderately soluble in organic solvents (from 0.17 g/L in methanol to ~14 g/L in toluene and dichloromethane). It does not dissociate at any pH in the range 4-9.
Sulphur was not found to have flammable, auto-flammable, explosive or oxidising properties.
Under recommended use, no particular problems should be expected due to technical characteristics or physico-chemical properties of the active substance.

2.2.1.1 Evaluation of physical hazards [equivalent to section 8 of the CLH report template]

It should be noted that the substance Sulphur (spelled sulfur under CLP regulation) already has a harmonized classification & labelling approved by the European Union.

The following conclusions are in accordance with this harmonized classification.

2.2.1.1.1 Explosives *[equivalent to section 8.1 of the CLH report template]*

Table 1: Summary table of studies on explosive properties

Method	Results	Remarks	Reference
Statement	Not explosive		Jackson, W. A. (2004), report no.: HT04/289, 30.07.2004 Company report no.: SAN7116/5212 (Syngenta)
EEC A14	Not explosive		Garofani, S. (2005), report no. CH-014/2005

2.2.1.1.1.1 Short summary and overall relevance of the provided information on explosive properties

The substance was exposed to thermal stress, as well as mechanical stress (shock, friction) following EEC A14 test required by Directive 67/548/EEC that was in force in 2005. All tests were negative (Garofani, S. 2005).
In addition, a statement was provided, indicating that the substance is an element and does not contain any bond grouping known to confer explosibility (Jackson, W. A. 2004).

2.2.1.1.1.2 Comparison with the CLP criteria

Test EEC A14 test method is not sufficient on its own to conclude on explosive properties. According to CLP regulation, explosives properties should be tested using UN RTDG Part 1, Section 11 test series. Alternatively, test can be waived when the susbtance does not contain any chemical bond associated with explosive properties. Therefore, the statement Jackson, W. A. 2004 can be considered sufficient.

2.2.1.1.1.3 Conclusion on classification and labelling for explosive properties

Not classified as explosive.

2.2.1.1.6 Flammable solids *[equivalent to section 8.6 of the CLH report template]*

Table 2: Summary table of studies on flammable solids

Method	Results	Remarks	Reference
EEC A9	Flash point: 218 ± 10 °C		Jackson, W. A. (2004), report no.: HT04/289, 30.07.2004 Company report no.:

Method	Results	Remarks	Reference
			SAN7116/5212 (Syngenta)
EEC A10	Not highly flammable (purity 99.9%)		Jackson, W. A. (2004), report no.: HT04/290, 30.07.2004 Company report no.: SAN7116/5211 (Syngenta)
EEC A10	Not highly flammable (purity not reported)		Garofani, S. (2005), report no. CH-011/2005

2.2.1.1.6.1 Short summary and overall relevance of the provided information on flammable solids

The flash point of the substance was measured by using Test Method EEC A9 and flammability was assessed according to Test Method EEC A10. Flash point was measured at 218 °C and the substance is not considered as highly flammable.

2.2.1.1.6.2 Comparison with the CLP criteria

Test N.1 described in UN RTDG Part III Section 31 is required to assess flammability of solids, instead of Test method EEC A9 and A10 that were required by Directive 67/548/EEC. However, as the tests showed that the substance is not highly flammable, no more testing is necessary and the substance should not be classified as flammable solid according to CLP regulation.

2.2.1.1.6.3 Conclusion on classification and labelling for flammable solids

Not classified as flammable solid.

2.2.1.1.7 Self-reactive substances *[equivalent to section 8.7 of the CLH report template]*

Table 3: Summary table of studies on self-reactivity

Method	Results	Remarks	Reference
EEC A2	Not self-reactive		Bee, T. (2017), report no.: GLP3016001516R1V1/2017
UN RTDG Manual of Tests and Criteria, Test N.4	On completion of testing the sample melted and left an orange liquid in the catch tray underneath the sample basket. The test item did not show signs of exothermic activity during the first trial		Bee, T. (2017), report no.: GLP3016001516R1V1/2017

2.2.1.1.7.1 Short summary and overall relevance of the provided information on self-reactive substances

Pure sulphur was heated up to >400 °C and no exothermic reaction was observed.

2.2.1.1.7.2 Comparison with the CLP criteria

Considering the absence of exothermic reaction upon heating, the substance shall not be classified as self-reactive.

2.2.1.1.7.3 Conclusion on classification and labelling for self-reactive substances

Not classified as self-reactive.

2.2.1.1.9 Pyrophoric solids *[equivalent to section 8.9 of the CLH report template]*

Table 4: Summary table of studies on pyrophoric solids

Method	Results	Remarks	Reference

2.2.1.1.9.1 Short summary and overall relevance of the provided information on pyrophoric solids

The substance is slightly soluble in water and the experience shows that it is not pyrophoric.

2.2.1.1.9.2 Comparison with the CLP criteria

No pyrophoric properties was observed experimentally. As experience of handling and manufacturing shows that the substance does not ignite spontaneously in contact with air at normal temperature, waiving tests is acceptable according to CLP regulation.

2.2.1.1.9.3 Conclusion on classification and labelling for pyrophoric solids

Not classified as pyrophoric solid.

2.2.1.1.10 Self-heating substances *[equivalent to section 8.10 of the CLH report template]*

Table 5: Summary table of studies on self-heating substances

Method	Results	Remarks	Reference
Modified EEC A15 (testing material: solid and 5°C temperature increments)	Self-heating: 255 ± 5°C		Jackson , W. A. (2004), report no.: HT04/292, 30.07.2004 Company report no.: SAN7116/5209 (Syngenta)
EEC A16	No ignition below its melting point		Jackson , W. A. (2004), report no.: HT04/293, 30.07.2004 Company report no.: SAN7116/5208 (Syngenta)
UN RTDG Manual of Tests and Criteria, Test N.4	On completion of testing the sample melted and left an orange liquid in the catch tray underneath the sample basket. The test item did not show signs of exothermic activity during the first trial		Bee, T. (2017), report no.: GLP3016001516R1V1/2017

2.2.1.1.10.1 Short summary and overall relevance of the provided information on self-heating substances

The active substance did not ignite nor showed any exothermic activity below its melting point. This was demonstrated by both Test Method EEC A15 and Test N° 4 of UN RTDG Part III Section 33.

2.2.1.1.10.2 Comparison with the CLP criteria

Test N° 4 of UN RTDG is the test recognized to evaluate the self-heating properties of solids according to CLP regulation. As the test was negative, the substance should not be classified for self-heating properties.

2.2.1.1.10.3 Conclusion on classification and labelling for self-heating substances

Not classified as self-heating solid.

2.2.1.1.11 Substances which in contact with water emit flammable gases *[equivalent to section 8.11 of the CLH report template]*

Table 6: Summary table of studies on substances which in contact with water emit flammable gases

Method	Results	Remarks	Reference
Statement	No gas evolved upon dilution into water		

2.2.1.1.11.1 Short summary and overall relevance of the provided information on substances which in contact with water emit flammable gases

Knowledge of the substance and experimental studies show the substance does not emit flammable gases when in contact with water.

2.2.1.1.11.2 Comparison with the CLP criteria

Experimental knowledge on this substance shows that it does not emit flammable gases when in contact with water. Moreover, it is known to form a stable suspension in water and its chemical structure does not contain metals or metalloids. Test is not required according to CLP regulation.

2.2.1.1.11.3 Conclusion on classification and labelling for substances which in contact with water emit flammable gases

Not classified as a substance that emits flammable gas in contact with water.

2.2.1.1.13 Oxidising solids *[equivalent to section 8.13 of the CLH report template]*

Table 7: Summary table of studies on oxidising solids

Method	Results	Remarks	Reference
EEC A17	Sulfur is oxidising according to DSD regulation		Garofani, S. (2005), report no. CH-012/2005
UN RTDG Manual of Tests and Criteria, Test O.1	The burning rate or burning intensity of the test substance was not increased in comparison to that of the reference material		Bee, T. (2017), report no.: GLP3016001516R1V1/2017

2.2.1.1.13.1 Short summary and overall relevance of the provided information on oxidising solids

Based on the experimental test O.1 of UN RTDG Part I Section 34, the substance has no oxidising properties according to CLP.

2.2.1.1.13.2 Comparison with the CLP criteria

Test O.1 of UN RTDG is the recommended test to evaluate oxidising properties of solids according to CLP regulation. Experimental study showed that the substance has no oxidising properties

2.2.1.1.13.3 Conclusion on classification and labelling for oxidising solids

Not classified for oxidising properties.

2.2.1.1.14 Organic peroxides *[equivalent to section 8.14 of the CLH report template]*

Table 8: Summary table of studies on organic peroxides

Method	Results	Remarks	Reference

2.2.1.1.14.1 Short summary and overall relevance of the provided information on organic peroxides

Not applicable as the substance does not contain peroxides.

2.2.1.1.14.2 Comparison with the CLP criteria

Not applicable.

2.2.1.1.14.3 Conclusion on classification and labelling for organic peroxides

Not classified as organic peroxides.

2.2.1.1.15 Corrosive to metals *[equivalent to section 8.15 of the CLH report template]*

Table 9: Summary table of studies on the hazard class corrosive to metals

Method	Results	Remarks	Reference

2.2.1.1.15.1 Short summary and overall relevance of the provided information on the hazard class corrosive to metals

Considering its chemical structure, the substance is not corrosive to metals. Moreover, the substance is a solid with a melting point above 55 °C.

2.2.1.1.15.2 Comparison with the CLP criteria

No corrosiveness to metals is expected for this susbstance. As the substance is a solid that cannot become liquid up to 55 °C, the experimental test can be waived and the substance should not be considered for classification as corrosive to metals.

2.2.1.1.15.3 Conclusion on classification and labelling for corrosive to metals

Not classified as corrosive to metals.

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

KUMULUS WG

The preparation KUMULUS WG is a formulation of type wettable granules (WG). It presents as grey brown fine solid granules of average diameter around 250 µm, with a moderate odour of sulphur and contains 800 g/kg of Sulphur. It is not explosive, does not have oxidising properties and is not flammable nor auto-flammable. This formulation is essentially non dusty. It is not highly flammable, and not auto-flammable. Its bulk density is from 0.862 (loose) to 0.953 g/mL (tapped). When dispersed at 1% in water, it has a pH between 7.5 and 9.4. Its resistance to attrition is 100%, its wettability is immediate and no material remains on a 75 µm screen during a wet sieve test. It is not foaming and has acceptable suspensibility and spontaneity of dispersion from 0.2 to 8.4 % v/v in water. Its technical characteristics as well as the content in Sulphur are not changed after storage for 2 weeks at 54 °C or 2 years at ambient temperature, and a shelf life of 2 years is therefore considered acceptable.
Under recommended use, no particular problems should be expected due to technical characteristics or physical and chemical properties.

THIOVIT JET

The preparation THIOVIT JET is a formulation of type wettable granules (WG). It presents as dark brown granules with an unpleasant odour of sulphur and contains 800 g/kg of Sulphur. This formulation is nearly dust-free. It does not present explosive and oxidising properties. It is not flammable and not auto-flammable up to 140°C. Its bulk density is 1.026 g/ml when tapped. When dispersed at 1% in water, it has a pH of 9.9. There is no effect of high temperature on the stability of the formulation, since after 14 days at 54°C, neither the active ingredient content nor the technical properties were changed. Only 0.01% of material remains on a 75 µm screen during a wet sieve test. The preparation has a wettability of 8 second. The spontaneity of the dispersion is 93%. After 1 minute, less than 60 mL of foam remains at 2% v/v or below, but reaches 70 mL at 12.5% v/v dispersion. The attrition resistance is 97%. The content of active substance is unchanged by 8 weeks storage at 40 °C or 2 years storage at ambient temperature, demonstrating an acceptable 2 year shelf life for the product.
The formulation should be stored at a temperature below 40 °C.
No information on the size of granules has been provided and is required.
Under recommended use, no particular problems should be expected due to its technical characteristics or physico-chemical properties.

NETZSCHWEFEL STULLN

The preparation NETZSCHWEFEL STULLN is a formulation of type wettable granules (WG). It presents as dark brown solid granules with an average diameter in the 180-250 µm range, with a characteristic odour of Sulphur, and contains 800 g/kg of Sulphur. This formulation is nearly dust-free, and only 0.49% of material remains on a 75 µm screen during a wet sieve test. It does not present explosive and oxidising properties. It is not highly flammable, and not auto-flammable up to 420°C. Its bulk density is 0.874 g/mL when tapped. Its resistance to attrition is 99%. When dispersed at 1% in water, it has a pH of 4.9. The stability studies after 14 days storage at 54°C and after 2 years at ambient temperature show no significant change in the technical properties nor in the content of active substance, demonstrating that a shelf life of 2 years is acceptable.
Under recommended use, no particular problems should be expected due to technical characteristics or physico-chemical properties.

MICROTHIOL SPECIAL DISPERSS

The preparation MICROTHIOL SPECIAL DISPERSS is a formulation of type wettable granules (WG). It presents as light brown granules, with an average diameter in the 106~180 µm range, with a woody odour, and it contains 800 g/kg of Sulphur. This formulation is nearly dust-free. It does not present explosive and oxidising properties. It is not highly flammable, and not auto-flammable up to 229 °C. Its bulk density is between 0.8 (loose) and 0.9 g/mL (tapped). When dispersed at 1% in water, it has a pH of 9.9. Less than 0.1% of material remains on a 75 µm screen during a wet sieve test. Suspensibility was above 80%. After 1 minute, 53 mL of foam remains (for a 10% concentration), persistent foam test has not been performed after storage although it is required. The attrition resistance is 99%.
Neither the technical characteristics nor the content of active sulphur were changed after storage of 2 years at ambient temperature, demonstrating that a shelf life of 2 years is acceptable. However, a storage at 54 °C for 2 weeks showed significant and detrimental effects on wettability, suspensibility and spontaneity of dispersion. As a consequence, the formulation should be stored at ambient temperature.
Under recommended use, no particular problems should be expected due to technical characteristics or physico-chemical properties.

SULPHUR DUST

The preparation SULPHUR DUST is a dustable powder (DP). It is an odourless, light yellow solid powder, containing 985 g/kg of Sulphur. This formulation does not present explosive nor oxidising properties. It is not highly flammable, and is not auto-flammable up to 221°C. Its tap density is ranging from 0.84 to 1.03 g/mL. When dispersed at 1% in water, it has a pH of 6.75. 10% of the particles are smaller than 5.65

µm, and >50% have a diameter below 50 µm. Moreover, it is considered as dusty, therefore the risks after inhalation shall be evaluated. The technical properties and the content of active substance is unchanged by 2 years storage at ambient temperature demonstrating an acceptable shelf life of 2 years for the product. Under recommended use, no particular problems should be expected due to its technical characteristics or its physical and chemical properties.

RAC evaluation of physical hazards

Summary of the Dossier Submitter's proposal

The Dossier Submitter (DS) proposed no classification for all physical hazards, based on test results and the results of the screening procedure relevant for each hazard class. Sulfur does not contain any molecular structures associated with self-reactive properties and no peroxide or acidic moieties and has a melting point above 55°C. Thus, it does not fulfil criteria for self-reactive substances, organic peroxides, or corrosive to metals. According to a UN RTDG N.4 test, sulfur is not a self-heating substance. Based on long-term handling experience, sulfur is not a pyrophoric solid, it doesn't emit flammable gases upon contact and does not react with water. According to a UN RTDG O.1 test, sulfur does not fulfil the criteria for an oxidising solid.

Comments received during consultation

No comments were received during the consultation.

Assessment and comparison with the classification criteria

Sulfur is a solid, hence hazard classes for gases and liquids do not apply. A test according to EEC method A.14 showed sulfur not to be explosive, in addition the DS stated that the substance does not contain structural features indicative of explosive properties as per table A6.1 of Annex 6 of the UN RTDG. A negative EEC method A.10 was included in the dossier. When negative, this test is equivalent to UN RTDG N.1 test.

RAC agrees with the assessment of the DS on the physical hazards and proposes **no classification.**

2.3 DATA ON APPLICATION AND EFFICACY

2.3.1 Summary of effectiveness

Sulfur 80%WG and Sulphur Dust are currently registered on the representative uses in some MS. Sulphur has been used in agriculture and viticulture for a long time and sulphur effectiveness is well-known.

More detailed consideration will be fully assessed in the context of subsequent applications for products authorisation.

2.3.2 Summary of information on the development of resistance

Sulphur as fungicide

According to the FRAC (Fungicide Resistance Action Committee), sulphur is in the mode of action group M02, *i.e.* inorganic chemicals with multi-site mode of action.

No resistance case to sulphur was reported for fungal diseases (FRAC, 2020[4] and R4P, the Research and Reflection Ring on Pesticide Resistance, 2018[5]).

It is unlikely that sulphur resistance could occur for fungal diseases due to the inorganic nature and multi-site action of the compound.
FRAC has classified sulphur as a low risk fungicide regarding resistance development (FRAC, 2020[6]).

Sulphur as acaricide

According to the IRAC (Insecticide Resistance Action Committee), sulphur is in the mode of action group UN, *i.e.* Compounds of unknown or uncertain Mode of Action.

A resistance case to sulphur was reported for the western predatory mite (*Metaseiulus occidentalis*) in 1981 in a vineyard in the United States of America (Arthropod Pesticide Resistance Database, 2020[7]).
However, no resistance case to sulphur was reported for harmful mites (APRD, 2020 and R4P, 2018).

Considering this information, sulphur can be considered as a low risk acaricide regarding resistance development.

2.3.3 Summary of adverse effects on treated crops

More detailed consideration will be fully assessed in the context of subsequent applications for products authorisation.

2.3.4 Summary of observations on other undesirable or unintended side-effects

More detailed consideration will be fully assessed in the context of subsequent applications for products authorisation.

2.4 FURTHER INFORMATION

2.4.1 Summary of methods and precautions concerning handling, storage, transport or fire

Refer to Vol. 3CA_B4, Vol. 3CP1_B4 and Vol. 3CP2_B4.

2.4.2 Summary of procedures for destruction or decontamination

Refer to Vol. 3CA_B4, Vol. 3CP1_B4 and Vol. 3CP2_B4.

2.4.3 Summary of emergency measures in case of an accident

Refer to Vol. 3CA_B4, Vol. 3CP1_B4 and Vol. 3CP2_B4.

[4] Anonymous (2020): FRAC – List of first confirmed cases of plant pathogenic organisms resistant to disease control agents, revised May 2020, available online: https://www.frac.info/knowledge-database/downloads
[5] Anonymous (2018): R4P - List of cases of resistance to plant protection products detected in France, February 2018, available online: https://www.r4p-inra.fr/en/resistance-status-in-france/
[6] Anonymous (2020): FRAC - Fungal control agents sorted by cross resistance pattern and mode of action (including FRAC Code numbering), available online: https://www.frac.info/knowledge-database/downloads
[7] Anonymous (2020): APRD, available online: https://www.pesticideresistance.org/

2.5 METHODS OF ANALYSIS

2.5.1 Methods used for the generation of pre-authorisation data

Refer to Vol. 3CA_B5, Vol. 3CP1_B5 and Vol. 3CP2_B5.

2.5.2 Methods for post control and monitoring purposes

Refer to Vol. 3CA_B5, Vol. 3CP1_B5 and Vol. 3CP2_B5.

2.6 EFFECTS ON HUMAN AND ANIMAL HEALTH

2.6.1 Summary of absorption, distribution, metabolism and excretion in mammals *[equivalent to section 9 of the CLH report template]*

Table 10: Summary table of toxicokinetic studies

Method	Results	Remarks	Reference
No relevant study			

2.6.1.1 Short summary and overall relevance of the provided toxicokinetic information on the proposed classification(s)

No absorption, distribution, metabolism and excretion studies were conducted on sulfur.
As agreed for the first approval of the active substance (EFSA, 2008), it was considered unnecessary to require toxicokinetics studies with sulfur.
Sulfur is a naturally occurring element that is essential to the human body and needed at relatively high levels. The average human body contains approximately 175 g of sulfur incorporated into sulfates, proteins, keratin, enzymes, etc.
It is generally regarded as safe for human exposure given the wide range of background exposure, since it is naturally present and abundant in food, where it can be found in the form of sulfate, free amino acids, proteins and vitamins.
By oral route, there are indications that elemental sulfur is transformed into hydrogen sulphide by the intestinal microflora which is then absorbed by intestinal mucosa. Absorbed hydrogen sulfide is then oxidised to sulfate which enters the normal sulfate body-pool. Other sulfur-containing ions may also possibly be formed. No potential for accumulation was reported.
Regarding absorption of sulfur as sulfates, absorption of sulfates from the gastrointestinal tract depends upon the amount of sulfate ingested as absorption of the sulfate ion occurs by active transport. After absorption, sulfates are freely distributed in blood and does not accumulate in tissues. Sulfates are usually eliminated by renal excretion however at high doses, sulfates are also excreted in faeces.
Overall, sufficient data on the absorption, distribution, metabolism and excretion of sulfur in mammals and humans are available indicating a similar metabolic profile of sulfur after absorption. Thus, and considering that sulfur is an essential element for all living organisms, comparative *in vitro* metabolism studies or any other additional toxicokinetics studies were not performed or required.

2.6.2 Summary of acute toxicity

Studies on acute toxicity of sulfur were conducted with sulfur technical and/or ‘Sulphur Dust’ as a surrogate for technical sulfur since the minimum content of the active substance in this representative product is specified as 985 g/kg and the only co-formulant is an inert carrier.

2.6.2.1 Acute toxicity - oral route [equivalent to section 10.1 of the CLH report template]

Table 11: Summary table of animal studies on acute oral toxicity

Method, guideline, deviations[1] if any	Species, strain, sex, no/group	Test substance	Dose levels, duration of exposure	Value LD_{50}	Reference
Guideline: OECD 401 (1987) GLP: Yes Acceptable	Rat Wistar Males and females 5/sex	Sulfur technical Batch No.: 1089 DLD Purity: 100.2% w/w Vehicle: corn oil	2000 mg/kg bw Single-dose oral gavage	> 2000 mg/kg bw for both males and females *Clinical signs*: laboured	Terlouw, G. et al., 1994 I 93/160 (TDS BS4194)

Method, guideline, deviations[1] if any	Species, strain, sex, no/group	Test substance	Dose levels, duration of exposure	Value LD_{50}	Reference
				respiration (5 f, 5 m), rales (1 m), nose staining (1 f, 2 m), piloerection (5 f, 5 m), vocalization (1 f, 2 m)	
Guideline: OECD 423 (2001) GLP: Yes Acceptable	Rat Wistar Females 3/treatment step	Sulphur Dust Batch No.: I-GLA Purity: 98.5% w/w Vehicle: groundnut oil	2000 mg/kg bw Single-dose oral gavage	> 2000 mg/kg bw *Clinical signs*: none	Mohan Kumar, S.B., 2005 4257/05
Guideline: OECD 425 (2002) modified GLP: Yes Acceptable	Rat Wistar 3 females	Sulphur Dust Batch No.: L-BPA Purity: 98.6% w/w Vehicle: peanut oil	35000 mg/kg bw Oral gavage – 5000 mg/kg bw given 7 times during 24 hours	> 35000 mg/kg bw *Clinical signs*: none	Patani, K., 2009 8390

Table 12: Summary table of human data on acute oral toxicity

Type of data/report	Test substance	Relevant information about the study (as applicable)	Observations	Reference
No relevant human data				

Table 13: Summary table of other studies relevant for acute oral toxicity

Type of study/data	Test substance	Relevant information about the study (as applicable)	Observations	Reference
No relevant study				

2.6.2.1.1 Short summary and overall relevance of the provided information on acute oral toxicity

The acute oral toxicity (LD_{50}) of sulfur technical and 'Sulphur Dust' in rats is above 2000 mg/kg bw. In a further acute oral toxicity study in rats with 'Sulphur Dust' conducted for the purpose of refined ecotoxicological risk assessment, even no effects were noted at the highest tested rate of 35000 mg/kg bw (5000 mg/kg bw given 7 times during 24 hours) and the median lethal dose was set above this test level.

2.6.2.1.2 Comparison with the CLP criteria regarding acute oral toxicity

The oral LD_{50} of sulfur in rats is above the cut-off value of 2000 mg/kg bw for classification for acute toxicity by oral route according to CLP.

2.6.2.1.3 Conclusion on classification and labelling for acute oral toxicity

According to CLP criteria, no classification for acute oral toxicity is warranted for sulfur.

2.6.2.2 Acute toxicity - dermal route [equivalent to section 10.2 of the CLH report template]

Table 14: Summary table of animal studies on acute dermal toxicity

Method, guideline, deviations[1] if any	Species, strain, sex, no/group	Test substance	Dose levels, duration of exposure	Value LD_{50}	Reference
Guideline: OECD 402 (1981) GLP: Yes Acceptable	Rat Wistar Males and females 5/sex	Sulfur technical Batch No.: 1089 DLD Purity: 100.2% w/w Vehicle: corn oil	2000 mg/kg bw 24-h application	> 2000 mg/kg bw for both males and females *Clinical signs*: erythema and/or scaling (3 f, 5 m)	Terlouw, G. et al., 1994 I 93/157 (TDS BS4188)
Guideline: OECD 402 (1981) GLP: Yes Acceptable	Rat Wistar Males and females 5/sex	Sulphur Dust Batch No.: I-GLA Purity: 98.5% w/w Vehicle: deionised water	2000 mg/kg bw 24-h application	> 2000 mg/kg bw for both males and females *Clinical signs*: none	Mohan Kumar, S.B., 2005 4258/05

Table 15: Summary table of human data on acute dermal toxicity

Type of data/report	Test substance	Relevant information about the study (as applicable)	Observations	Reference
No relevant human data				

Table 16: Summary table of other studies relevant for acute dermal toxicity

Type of study/data	Test substance	Relevant information about the study (as applicable)	Observations	Reference
No relevant study				

2.6.2.2.1 Short summary and overall relevance of the provided information on acute dermal toxicity

The acute dermal toxicity on rats was tested with sulfur technical and 'Sulphur Dust' and the LD50 was above 2000 mg/kg bw in both studies.

2.6.2.2.2 Comparison with the CLP criteria regarding acute dermal toxicity

The dermal LD_{50} of sulfur in rats is above the cut-off value of 2000 mg/kg bw for classification for acute toxicity by dermal route according to CLP.

2.6.2.2.3 Conclusion on classification and labelling for acute dermal toxicity

According to CLP criteria, no classification for acute dermal toxicity is warranted for sulfur.

2.6.2.3 Acute toxicity - inhalation route [equivalent to section 10.3 of the CLH report template]

Table 17: Summary table of animal studies on acute inhalation toxicity

Method, guideline, deviations[1] if any	**Species, strain, sex, no/group**	**Test substance, form and particle size (MMAD)**	**Dose levels, duration of exposure**	**Value LC_{50}**	**Reference**
Guideline: OECD 403 (1981) GLP: Yes Acceptable	Rat Wistar Males and females 5/sex	Sulfur technical Batch No.: 1089 DLD Purity: 100.2% w/w MMAD/GSD: 3.8 µm/1.3	5.43 mg/L/4-h Nose-only exposure	> 5.43 mg/L/4-h for both males and females *Mortality*: males 2/5, females 0/5 *Clinical signs*: All rats during exposure: decreased breathing frequency, irregular breathing, chocking breathing, partly closed eyes; Post-exposure period: general pale appearance, blepharospasms, nasal encrustations and dirty fur	Groten I., 1994 V94.137 (TDS BS4470)
Guideline: OECD 403 (1981) GLP: Yes Acceptable	Rat Wistar Males and females 5/sex	Sulphur Dust Batch No.: I-GLA Purity: 98.5% w/w MMAD/GSD: 4.2 µm/3.1	4.5 mg/L/4-h Nose-only exposure	> 4.5 mg/L/4-h for both males and females (highest achievable aerosol concentration) *Mortality*: none *Clinical signs*: none	Müller, P.Y., 2005 A23512

Table 18: Summary table of human data on acute inhalation toxicity

Type of data/report	**Test substance**	**Relevant information about the study (as applicable)**	**Observations**	**Reference**
No relevant human data				

Table 19: Summary table of other studies relevant for acute inhalation toxicity

Type of study/data	**Test substance**	**Relevant information about the study (as applicable)**	**Observations**	**Reference**
No relevant study				

2.6.2.3.1 Short summary and overall relevance of the provided information on acute inhalation toxicity

In two acute inhalation toxicity studies, rats were exposed for 4 hours (nose only) to sulfur technical and ‘Sulphur Dust’. The median lethal concentration (LC50) was established to be above 5.45 mg/L and 4.5 mg/L air, respectively, the highest achievable air concentrations in both test systems.

2.6.2.3.2 Comparison with the CLP criteria regarding acute inhalation toxicity

The LC_{50} of sulfur in rat is greater than the maximum attainable concentrations obtained in two acute inhalation studies where rats were exposed for 4-hour (nose-only).

2.6.2.3.3 Conclusion on classification and labelling for acute inhalation toxicity

According to CLP criteria, no classification for acute toxicity by inhalation is warranted for sulfur.

RAC evaluation of acute toxicity

ORAL ROUTE

Summary of the Dossier Submitter's proposal

Three GLP and OECD test guideline compliant acute oral toxicity studies conducted in rats with Sulphur Dust or technical sulfur were included in the dossier. No mortalities were observed in any study, thus the oral LD_{50} for sulfur was concluded to be over 2000 mg/kg bw. In a limit dose LD_{50} test from 1994 using 2000 mg/kg bw technical grade sulphur in corn oil administered to female and male rats, clinical signs including laboured breathing and piloerection were noted in all animals, and nose staining and vocalisation were reported in one female and 2 males. No toxicological effects were noted in either of two studies conducted in 2005 and 2009, respectively, with Sulphur Dust, using peanut oil as vehicle. In first study, one dose of 2000 mg/kg bw was administered to 3 female rats, whilst the most recent study used an extreme regime of 7 administrations of 5000 mg/kg bw within 24 hours to 3 female rats. Based on the available data, the DS proposed not to classify the substance for acute oral toxicity.

Comments received during consultation

One MSCA supported the proposal for no classification. The commenter pointed to a published case of a man surviving ingestion of 60 g sulfur as supporting evidence. No further details were provided in the reference.

Assessment and comparison with the classification criteria

The criteria for classification for acute oral toxicity in category 4 was not met, as the LD_{50} values reported were all above 2000 mg/kg bw/day.

In agreement with the DS, RAC concludes that **sulphur does not warrant classification for acute oral toxicity.**

DERMAL ROUTE

Summary of the Dossier Submitter's proposal

Acute dermal toxicity data were from two GLP and OECD test guideline compliant studies published in 1994 and 2005, respectively, conducted in rats with sulfur technical and

Sulphur Dust, respectively. No mortalities were observed in either study. In the first study that used technical grade sulfur in corn oil, erythema and/or scaling was reported in 3 females and 5 males. No clinical signs were seen in the second study using deionised water as the vehicle. As the LD_{50} values were above 2000 mg/kg bw in the available studies, no classification for acute dermal toxicity was proposed by the DS.

Comments received during consultation

One MSCA supported the proposal for no classification for acute dermal toxicity.

Assessment and comparison with the classification criteria

The LD_{50} values reported were above 2000 mg/kg bw/day, thus above the criteria for classification for acute dermal toxicity in category 4. RAC noted that the use of water as the vehicle in the second study may have impacted on the reliability of this study, as sufficient contact with the skin may not have been ensured as specified in OECD TG 402.

However, based on the study using corn oil as vehicle, RAC concludes, in agreement with the DS, that **sulfur does not warrant classification for acute dermal toxicity.**

INHALATION ROUTE

Summary of the Dossier Submitter's proposal

Two GLP and OECD TG 403 compliant studies on acute inhalation toxicity in rats were available.

The first study (report published 1994), used sulfur technical applied by nose-only application as particles with a MMAD of 3.8 µm at a mean measured concentration of 5.43 mg/L. Two males out of five died whilst all females survived. Clinical signs were recorded in all animals and included affected breathing and partly closed eyes during exposure, and blepharospasms, nasal encrustations and dirty fur post-exposure.

The second study (report published 2005) used Sulphur Dust as a dust aerosol at 4.5 mg/L, the highest aerosol concentration achievable, using nose-only application. The MMAD was 4.2 µm. No mortalities or clinical signs were reported.

The DS proposed not to classify for acute inhalation toxicity.

Comments received during consultation

One MSCA supported the proposal for no classification.

Assessment and comparison with the classification criteria

In the acute inhalation toxicity studies sulfur was tested up to the highest concentration achievable, 5.43 and 4.5 mg/L, respectively. The mortality rate was below 50% of the animals in the first study, whilst the second study did not cause any mortality at 4.5 mg/L. Thus, the classification criteria for acute inhalation toxicity for dusts and mists (5 mg/L)are not met in either study.

Based on these data, RAC concludes that **sulfur does not warrant classification for acute inhalation toxicity.**

2.6.2.4 Skin corrosion/irritation [equivalent to section 10.4 of the CLH report template]

Table 20: Summary table of animal studies on skin corrosion/irritation

Method, guideline, deviations[1] if any	**Species, strain, sex, no/group**	**Test substance**	**Dose levels, duration of exposure**	**Results** **- Observations and time point of onset[2]** **- Mean scores/animal** **- Reversibility**	**Reference**
Guideline: OECD 404 (1992) GLP: Yes Acceptable	Rabbit NZW 6 (males or females)	Sulfur technical Batch No.: 1089 DLD Purity: 100.2% w/w Vehicle: vaseline	0.5 g, 4 hours	Irritant to the skin Average score per rabbit (24-72h): Erythema and eschar: 2.3; 2.3; 3; 2.3; 3; 3 Oedema: 1; 1; 2; 1.3; 2; 2 Reversibility: 7 days	Prinsen M.K. (1994). V94.064 (TDS BS4369)
Guideline: OECD 404 (2002) GLP: Yes Acceptable	Rabbit NZW 3 (males)	Sulphur Dust Batch No.: I-GLA Purity: 98.5% w/w Vehicle: deionised water	0.5 g, 4 hours	Non-irritant to the skin Average score per rabbit (24-72h): Erythema and eschar: 0; 0; 0 Oedema: 0; 0; 0	Yogeesh B.S. (2005). 4260/05

Table 21: Summary table of human data on skin corrosion/irritation

Type of data/report	**Test substance**	**Relevant information about the study (as applicable)**	**Observations**	**Reference**
Please refer to 2.6.9 Summary of medical data and information: Signs of skin irritation were observed in people who handle the pesticide or come into contact with foliage during field work (US-EPA RED 1991), were reported in human incident databases (US-EPA 2009) and in the French Toxicovigilance Programme "Mutualité Sociale Agricole", and were mentioned as side-effects related to the therapeutical use of sulfur as a keratolytic (The Extra Pharmacopoeia, Martindale, 31st edition 1996). Several cases of skin irritation due to incidental exposure during handling were reported by the Occupational Medical and Health Protection department of a sulfur formulation site.				

Table 22: Summary table of other studies relevant for skin corrosion/irritation

Sulphur **Volume 1 – Level 2**

Type of study/data	Test substance	Relevant information about the study (as applicable)	Observations	Reference
No relevant study				

2.6.2.4.1 Short summary and overall relevance of the provided information on skin corrosion/irritation

Two skin irritation studies were performed in rabbits, one with sulfur technical and one with Sulphur Dust. Although no skin irritation was noted in the study with Sulphur Dust made into paste by adding a sufficient volume of de-ionised water, skin irritation was noted in the study conducted on sulfur technical mixed with vaseline.

Furthermore, data are available in humans. Signs of skin irritation were consistently observed when using sulfur:
- in people who handle the pesticide or come into contact with foliage during field work (US-EPA RED 1991),
- in human incident databases (US-EPA 2009),
- in the French Toxicovigilance Programme "Mutualité Sociale Agricole", where cases of moderate to severe skin irritation with subsequent scaling were reported,
- as side-effects related to the therapeutic use of sulfur as a keratolytic agent (The Extra Pharmacopoeia, Martindale, 31st edition 1996),
- in people incidentally exposed during handling reported by the Occupational Medical and Health Protection department of a sulfur formulation site (refer to Volume 4 - BASF).

Moreover, in the acute dermal toxicity study conducted on sulfur technical at the limit dose of 2000 mg/kg bw in 5 male and female rats, minimal erythema at the application site was observed and persisted during days 2-5 for 3 female and 4 male rats. Mild skin scaling was seen at the application site in 2/5 females and 5/5 males between days 2-6 and appeared fully reversible.

2.6.2.4.2 Comparison with the CLP criteria regarding skin corrosion/irritation

Substances are classified as irritant to the skin (Category 2) if:
(1) Mean value of ≥ 2,3 - ≤ 4,0 for erythema/eschar or for oedema in at least 2 of 3 tested animals from gradings at 24, 48 and 72 hours after patch removal or, if reactions are delayed, from grades on 3 consecutive days after the onset of skin reactions; or
(2) Inflammation that persists to the end of the observation period normally 14 days in at least 2 animals, particularly taking into account alopecia (limited area), hyperkeratosis, hyperplasia, and scaling; or
(3) In some cases where there is pronounced variability of response among animals, with very definite positive effects related to chemical exposure in a single animal but less than the criteria above.

Furthermore, according to CLP criteria, the weight of evidence determination using expert judgment shall be applied, and specifically, human data should be considered: "*A weight of evidence determination means that all available information bearing on the determination of hazard is considered together, such as the results of suitable in vitro tests, relevant animal data, information from the application of the category approach (grouping, read-across), (Q)SAR results,* ***human experience such as occupational data and data from accident databases, epidemiological and clinical studies and well documented case reports and observations***".
"*For the purpose of classification for health hazards (Part 3) established hazardous effects seen in appropriate animal studies or from human experience that are consistent with the criteria for classification shall normally justify classification. Where evidence is available from both humans and animals and there is a conflict between the findings, the quality and reliability of the evidence from both sources shall be evaluated in order to resolve the question of classification.* ***Generally, adequate, reliable and representative data on humans*** *(including epidemiological studies, scientifically valid case studies*

as specified in this Annex or statistically backed experience) ***shall have precedence over other data****."*

In the skin irritation study conducted on sulfur technical mixed with vaseline (Prinsen 1994), mean scores met the criteria for classification. On the contrary, in the skin irritation study conducted on Sulphur Dust made into paste by adding a sufficient volume of de-ionised water, no irritation was observed.

Moreover, signs of skin irritation were consistently observed when using sulfur following occupational exposure, from incident databases and from the use as a medication.

2.6.2.4.3 Conclusion on classification and labelling for skin corrosion/irritation

According to CLP criteria, based on a weight evidence approach considering animal and human data, classification for skin irritation Cat. 2 H315 is warranted for sulfur.

This is in line with the harmonised classification and labelling of sulfur (Regulation (EC) No 790/2009).

RAC evaluation of skin corrosion/irritation

Summary of the Dossier Submitter's proposal

Two skin irritation studies in rabbits as well as reports from human experience are presented in the dossier.

The animal studies from 1994 and 2005, respectively, were conducted according to OECD test guidelines and GLP and were deemed acceptable by the DS.

In the first study, application of technical sulfur mixed with vaseline for 4 hours led to mean erythema scores of 2.3 in 3 animals, and 3 in another 3 animals over 24, 48 and 72 hours, and oedema scores of between 1 and 2 in the 6 animals. The effects were reversible by 7 days in all animals.

In the second study, Sulphur Dust was applied as a paste with deionized water and did not lead to erythema, eschar or oedema of the skin up to 72 hrs after a 4 hour-application.

Further, the acute dermal toxicity study performed on the technical grade substance as described above (section on acute toxicity) reported minimal to mild and reversible irritation in some of the animals for 2-6 days.

In humans, skin and eye irritation in field workers in contact with sulfur dust or treated foliage were reported in the US-EPA RED[8] in 1991.

A publication from the Californian Department of Food and Agriculture reporting several symptoms, including itching in six Californian vineyard field workers exposed from helicopter application of sulfur.

Medical surveillance of French farmers by the governmental toxicovigilance body "Mutualité Sociale Agricole" in the period 1997-2012 identified 24 cases of various irritative symptoms from exposure to sulfur with no concomitant exposure. Skin findings observed were moderate to severe skin irritation in 14 workers out of 15 workers exposed to sulfur as wettable powder and in 4 out of 9 workers exposure to dust formulations.

[8] US-EPA RED: US-EPA RE-registration Eligibility Document

No adverse findings were reported in most reports of occupational medical surveillance of factories, but several cases of eye and skin irritation and malaise were reported at one sulfur formulation site.

Also, incidences of skin irritation from the medical use of sulfur as a keratolytic agent were reported in a pharmacopeia (Reynolds, 1996).

The DS proposed to retain the existing classification for sulfur as Skin irritant Category 2 H315 based on a weight of evidence approach based on the animal and human data available.

Comments received during consultation

One MSCA provided the study report for the 1994 study and supported the classification proposal as Skin irritant Category 2 H315 based on the findings of that study and the available human evidence.

Additional key elements

In an annex to the US EPA pesticide review from 2009 mentioned above, a table from OPP lists ten incidents related to sulfur exposure from 2000 to 2006, one of which reported skin irritation in five of 12 female fieldworkers exposed to sulfur that was applied aerially to the vineyard in which they worked. The pesticide review further included information from the Association of American Poison Control Center (AAPCC) compiling incidents of poisonings, mostly in a residential setting. The database has registered 1.5 million incidences of adverse health effects over the period 1993-2005, 958 (0.06%) of these involving sulfur. Skin irritation was reported in 17% of the cases. The annex further quotes data from NIOSH SENSOR Pesticides (Calvert *et al*., 2004) from surveillance in 1998 and 1999 where skin irritation was reported in 58% of 78 cases.

Details provided by the DS on the French toxicovigilance programme data from 1997-2012 confirmed that the 24 reported cases included in the classification proposal were related to exposure to sulfur products alone, with no concomitant exposure to other pesticides. Furthermore, the French background report also included 86 reports on health incidents related to occupational exposure in different tasks to sulfur alone or in association with other pesticides were reported in the period 1997-2012. Skin irritation occurred in 59.6% of the cases, 44.0% related to wettable formulations and 15.6 to powdered formulations.

A handbook reference notes sulfur to have low toxicity and be an irritant to the skin, eye, and respiratory tract, with no further details provided (Gosselin *et al.* 1976).

Assessment and comparison with the classification criteria

The CLP criteria for classification as a skin irritant includes reference to animal data as well as human evidence to be considered in a weight of evidence approach.

The results of the skin irritation study in rabbits from 1994 using technical sulfur in vaseline meet the criteria for classification as skin irritant in category 2, as all 6 animals showed mean skin erythema score ≥2.3 and ≤4.0. The DS points to the possible influence

of the use of vaseline as a vehicle on the positive results of one of the animal tests. RAC considers that the possible enhancing irritative effect of vaseline on the response seen in rabbits cannot be qualified or quantified based on the presented data, and thus considers that the study from 1994 should be included in the weight of evidence evaluation of the endpoint for classification purposes.

The second rabbit study did not cause any skin reaction and thus did not indicate a need for classification. However, the use of water as a moistening agent gives uncertainty as to the validity of this study.

The CLP criteria stipulate that human data should also be considered in the weight of evidence approach of all available data. Thus, occupational data should also be considered when deemed adequate and reliable. RAC considers that the reports of skin irritation from occupational exposure to sulfur from American and French governmental occupational health databases as well as information from one Industrial health and safety department constitute a robust and consistent evidence of the skin irritation potential of sulfur.

Based on the animal and human data available, RAC concludes that **the current classification of sulfur as Skin irritant Category 2 H315: Causes skin irritation should be maintained**.

2.6.2.5 Serious eye damage/eye irritation [equivalent to section 10.5 of the CLH report template]

Table 23: Summary table of animal studies on serious eye damage/eye irritation

Method, guideline, deviations[1] if any	**Species, strain, sex, no/group**	**Test substance**	**Dose levels duration of exposure**	**Results** **- Observations and time point of onset[2]** **- Mean scores/animal** **- Reversibility**	**Reference**
Guideline: OECD 405 (1987) GLP: Yes Acceptable	Rabbit NZW 6 (males or females)	Sulfur technical Batch No.: 1089 DLD Purity: 100.2% w/w Vehicle: none	0.1 g	Non-irritant to the eye Average score per rabbit (24-72h): Cornea: 0; 0; 0; 0; 0; 0 Iris: 0; 0; 0; 0; 0; 0 Conjunctiva- redness: 1; 0; 0.7; 0.7; 1; 0.3 Conjunctiva – chemosis: 0; 0; 0; 0; 0.3; 0 Reversibility: 1 to 7 days	Prinsen M.K. (1994). V94.063 (TDS BS4368)
Guideline: OECD 405 (2002) GLP: Yes Acceptable	Rabbit NZW 3 (males)	Sulphur Dust Batch No.: I-GLA Purity: 98.5% w/w Vehicle: none	0.1 ml	Non-irritant to the eye Average score per rabbit (24-72h): Cornea: 0; 0; 0 Iris: 0; 0; 0 Conjunctiva- redness: 1; 0.7; 1 Conjunctiva – chemosis: 0.7; 0.3; 0.7 Reversibility: 2 to 3 days	Ravi G.S. (2005). 4261/05

Table 24: Summary table of human data on serious eye damage/eye irritation

Type of data/report	**Test substance**	**Relevant information about the study (as applicable)**	**Observations**	**Reference**

Please refer to 2.6.9 Summary of medical data and information:

Signs of eye irritation were observed in people who handle the pesticide or come into contact with foliage during field work (US-EPA RED 1991), in workers occasionally exposed to sulfur in California during an application by helicopter (Maddy & Edmiston 1998), were reported in human incident databases (US-EPA 2009) and in the French Toxicovigilance Programme "Mutualité Sociale Agricole".
Several cases of eye irritation due to incidental exposure during handling were reported by the Occupational Medical and Health Protection department of a sulfur formulation site.

Table 25: Summary table of other studies relevant for serious eye damage/eye irritation

Type of study/data	Test substance	Relevant information about the study (as applicable)	Observations	Reference
No relevant study				

2.6.2.5.1 Short summary and overall relevance of the provided information on serious eye damage/eye irritation

After eye instillation of sulfur technical (Prinsen 1994) or Sulphur Dust (Ravi, 2005) to male and female rabbits, slight to moderate redness and slight swelling of the conjunctivae were observed in all animals; these effects had cleared after day 7 at the latest.

Data are available in humans. Signs of eye irritation were consistently observed when using sulfur:
- in people who handle the pesticide or come into contact with foliage during field work (US-EPA RED 1991),
- in human incident databases (US-EPA 2009),
- in workers occasionally exposed to sulfur in California during an application by helicopter (Maddy & Edmiston 1998)
- in the French Toxicovigilance Programme "Mutualité Sociale Agricole", where cases of conjunctival irritation/erythema, corneal ulceration and lacrimation were reported,
- in people incidentally exposed during handling reported by the Occupational Medical and Health Protection department of a sulfur formulation site (refer to Volume 4 - BASF).

Moreover, elemental sulfur is used as a keratolytic agent and it is recommended to avoid contact with the eyes and other mucous membranes (The Extra Pharmacopoeia, Martindale, 31st edition 1996).

2.6.2.5.2 Comparison with the CLP criteria regarding serious eye damage/eye irritation

Substances are classified as irritating to eyes (Category 2) if, when applied to the eye of an animal, it produces at least in 2 of 3 tested animals, a positive response of:
– corneal opacity ≥ 1 and/or
– iritis ≥ 1, and/or
– conjunctival redness ≥ 2 and/or
– conjunctival oedema (chemosis) ≥ 2
calculated as the mean scores following grading at 24, 48 and 72 hours after installation of the test material, and which fully reverses within an observation period of 21 days.

Furthermore, according to CLP criteria, the weight of evidence determination using expert judgment shall be applied, and specifically, human data should be considered: "*A weight of evidence determination means that all available information bearing on the determination of hazard is considered together, such as the results of suitable in vitro tests, relevant animal data, information from the application of the category approach (grouping, read-across), (Q)SAR results,* ***human experience such as occupational data and data from accident databases, epidemiological and clinical studies and well documented case***

reports and observations".

"*For the purpose of classification for health hazards (Part 3) established hazardous effects seen in appropriate animal studies or from human experience that are consistent with the criteria for classification shall normally justify classification. Where evidence is available from both humans and animals and there is a conflict between the findings, the quality and reliability of the evidence from both sources shall be evaluated in order to resolve the question of classification.* ***Generally, adequate, reliable and representative data on humans*** *(including epidemiological studies, scientifically valid case studies as specified in this Annex or statistically backed experience)* ***shall have precedence over other data****."*

In the available *in vivo* studies with either sulfur technical or Sulphur Dust, although signs of irritation were noted in almost all animals, mean scores did not meet the criteria for classification and reversibility of the findings were observed from Day 1 to 7.

Nevertheless, signs of eye irritation were consistently observed when using sulfur following occupational exposure or from incident databases. Moreover, elemental sulfur is used as a keratolytic agent.

Therefore, although the available eye irritation studies showed slight to moderate eye irritation with mean scores not sufficient to classify sulfur as an eye irritant, taking into account the therapeutical use of elemental sulfur as a keratolytic as well as the recommendation of avoiding contact with the eyes, mouth, and other mucous membranes, in addition to the many cases of eye irritation collected in the occupational setting and from the incident databases after sulfur exposure, the RMS considers that sulfur should be considered as an eye irritant and classification as eye irritant Category 2 H319 is warranted.

2.6.2.5.3 Conclusion on classification and labelling for serious eye damage/eye irritation

According to CLP criteria, based on a weight of evidence approach considering animal and human data, classification for eye irritation Cat. 2 H319 is warranted for sulfur.

RAC evaluation of serious eye damage/irritation

Summary of the Dossier Submitter's proposal

Two OECD TG 405 and GLP compliant studies in rabbits included in the dossier resulted in slight to moderate eye irritation from sulfur application. In the first study, from 1994, instillation of 100 mg technical sulfur (powder) to the eye of 6 rabbits led to mean scores of 0 for corneal opacity, iritis and conjunctival chemosis, and scores of a maximum of 1 (one out of 6 animals) for redness of the conjunctiva. All effects were reversible within one to seven days.

A second study from 2005, used 0.1 mL (84g) grounded Sulphur Dust. The eyes were rinsed with deionised water after 24 hrs. Two out of the 3 animals reacted with mean conjunctiva redness scores of 1, whilst one animal had a score of 0.7. Chemosis scores were all less than one, whilst corneal opacity and iritis scores were 0 in all animals. Reversibility occurred within two or three days.

Eye irritation was reported by the US-EPA RED in field workers (incidences not available in the dossier) after handling sulfur pesticide or sulfur treated foliage.

The Californian Department of Food and Agriculture also reported eye irritation in six vineyard field workers exposed after helicopter application of sulfur.

In US-EPA (2009[9]), results from a number of American incidence databases on residential and occupational cases from the mid 1990's up to around 2006 related to exposure to sulfur confirmed the dermal ocular and respiratory irritative properties of sulfur. The incidence numbers generally were low, and most of them were of low severity, but also cases of moderate and a few cases of high severity were reported.

Medical surveillance of French farmers by the governmental toxicovigilance body "Mutualité Sociale Agricole" in the period 1997-2012 identified 24 cases of various irritative symptoms from exposure to sulfur with no concomitant exposure. Eye irritation was reported in 7 out of 15 workers exposed to sulfur as wettable formulations and in 6 out of 9 workers exposure to dust formulations. The severity of the effects varied from conjunctival irritation to corneal ulceration.

Medical surveillance at one industrial formulation site also reported cases of eye and skin irritation, whilst the other applicant's factories did not report any cases.

In a pharmacopeia (Reynolds, 1996), it is recommended to avoid contact with eyes and mucous membranes when using sulfur in pharmaceutical applications due to the keratolytic effect of sulfur.

Based on the consistent information from databases on occupational and residential exposure that sulfur causes irritation to the eyes in humans, supported by the animal data showing effects meeting the classification criteria and the caution recommendation for using sulfur as a pharmaceutical agent, the DS proposes to classify sulfur as an Eye irritant in Category 2 H319.

Comments received during consultation

One MSCA supported the proposed classification as eye irritant, stressing the consistent reporting of effects in humans ranging from conjunctival effects to corneal ulceration.

An industry group supported by an expert statement disputed that the eye irritant effects in humans are sufficient for classification. Further, they stressed that the results from the animal data did not meet the classification criteria. The DS maintained that the human data showed eye irritancy and their conclusion to classify with H319.

Additional key elements

The US EPA RED[10] on sulfur (1991) included a short summary of an eye irritation study conducted in the rabbit with 98% pure sulfur. The study caused "conjunctival redness and discharge" and led the US EPA to the conclusion that sulfur was a US category III eye irritant. This category is defined by eye irritation reversible within 7 days or irritation with no corneal involvement.

In the annex to the US EPA pesticide review from 2009 mentioned above, ten incidents related to sulfur from 2000 to 2006 were listed from OPP, one including 21 workers re-entering a treated field experiencing amongst others watery eyes. From the AAPCC[11] 1.5 million incidences of adverse health effects from chemicals exposure were reported over

[9] US-EPA (2009) Sulfur. Human Health Risk Scoping Document in Support of Registration Review - Addendum
[10] RED: Re Eligibility Document
[11] AAPCC: Association of American Poison Control Center

the period 1993-2005, 958 (0.06%) involving sulfur, 21% of these included ocular symptoms.

The background report on the French toxicovigilance programme confirmed that the 24 reported cases over the period of 1997-2012 included in the classification proposal were related to exposure to sulfur products alone, with no concomitant exposure to other pesticides. The report further provided background information that overall 39.5% of 86 reliable exposure cases during that period had led to ocular symptoms.

A handbook reference notes sulfur to have low toxicity and be an irritant to the skin, eye, and respiratory tract, with no further details provided (Gosselin *et al.* 1976).

Assessment and comparison with the classification criteria

The effects reported of the two animal studies in the classification proposal as well as the additional study from the US registration process were insufficient for classification as an eye irritant in category 2, as no effects were reported to the cornea or iris, and the conjunctiva scores were below 2 in all studies, and the effects are reversible.

Incidents of eye irritation in workers and residents from exposure to sulfur in governmental databases in the US and in France an incident in an industrial formulation site and handbook information point to potential for transient eye irritation. However, the numbers reported are low when considering the extensive use of sulfur over several decades, and the effects are reversible.

Therefore, RAC concludes that based on the available data **sulfur does not fulfil the criteria for classification for serious eye damage/irritation**.

2.6.2.6 Respiratory sensitisation [equivalent to section 10.6 of the CLH report template]

Table 26: Summary table of animal studies on respiratory sensitisation

Method, guideline, deviations[1] if any	Species, strain, sex, no/group	Test substance	Dose levels, duration of exposure	Results	Reference
No relevant study					

Table 27: Summary table of human data on respiratory sensitisation

Type of data/report	Test substance	Relevant information about the study (as applicable)	Observations	Reference
No human data				

Table 28: Summary table of other studies relevant for respiratory sensitisation

Type of study/data	Test substance	Relevant information about the study (as applicable)	Observations	Reference
No relevant study				

2.6.2.6.1 Short summary and overall relevance of the provided information on respiratory sensitisation

No formally recognized and validated animal tests currently exist for respiratory sensitisation. There was no evidence of respiratory irritation in single dose inhalation study in rats and there was no indication of sensitisation.

2.6.2.6.2 Comparison with the CLP criteria regarding respiratory sensitisation

As there are no animal and human data, classification is not possible.

2.6.2.6.3 Conclusion on classification and labelling for respiratory sensitisation

According to CLP criteria, no classification for respiratory sensitisation is warranted for sulfur.

2.6.2.7 Skin sensitisation [equivalent to section 10.7 of the CLH report template]

Table 29: Summary table of animal studies on skin sensitisation

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance	Dose levels duration of exposure	Results	Reference
Maximisation test Guideline: OECD 406 (1992) GLP: Yes Acceptable with limitations (intradermal induction caused very strong skin reactions in control and treated groups)	Guinea pig 10 animals in the control group, 20 in the test group	Sulfur technical Batch No.: 1089 DLD Purity: 100.2% w/w	**Intradermal induction**: 1% test substance diluted with paraffin oil and FCA/physiological saline. **Topical induction**: 25% test substance in ethanol or vaseline *(uncertainty in the study report).* **Topical Challenge**: *First challenge*: 25% and 15% test substance in vaseline *Second challenge*: 25%, 15% and 10% test substance in vaseline	**First challenge**: - 25% in vaseline: 18/19 and 5/19 positive responses at 24- and 48-hour respectively - 15% in vaseline: 16/19 and 2/19 positive responses at 24- and 48-h respectively **Second challenge**: - 25% in vaseline: 9/19 and 11/19 positive responses at 24- and 48-hour respectively - 15% in vaseline: 6/19 and 8/19 positive responses at 24- and 48-h respectively - 10% in vaseline: 2/19 and 5/19 positive responses at 24- and 48-h respectively	Arcelin G. (1994) TDS BS4515
Buehler test Guideline: OECD 406 (1992) GLP: Yes	Guinea pig 10 animals in the control group, 20	Sulfur technical Batch No.: 1089 DLD Purity:	**Topical induction**: 25% test substance in vaseline	**First challenge**: - 25% in vaseline: 8/20 and 4/20 positive responses at 24- and 48-hour respectively	Arcelin G. (1994) TDS BS4516

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance	Dose levels duration of exposure	Results	Reference
Acceptable with limitations (concentrations used for the challenges not appropriate as shown to be irritant)	in the test group	100.2% w/w	**Topical Challenge**: *First challenge*: 25% and 15% test substance in vaseline *Second challenge*: 25% and 15% test substance in vaseline 15% Thiovit in vaseline 15% Thiovit in bi-distilled water	- 15% in vaseline: 9/20 and 9/20 positive responses at 24- and 48-h respectively **Second challenge**: - 25% in vaseline: 8/20 and 8/20 positive responses at 24- and 48-hour respectively - 15% in vaseline: 6/20 and 6/20 positive responses at 24- and 48-h respectively - 15% Thiovit in vaseline: 10/20 and 9/20 positive responses at 24- and 48-h respectively - 15% Thiovit in bi-distilled water: 0/20 and 0/20 positive responses at 24- and 48-h respectively	
Maximisation test Guideline: OECD 406 (1992) GLP: Yes Acceptable	Guinea pig 10 animals in the control group, 20 in the test group	Sulphur Dust Batch No.: I-GLA Purity: 98.5% w/w	**Intradermal induction**: 1% test substance diluted with paraffin oil and FCA/physiological saline. **Topical induction**: 100% test substance (0.5g as paste in deionised water) **Topical Challenge**: 100% test substance (0.5g as paste in deionised water)	**After challenge**: 0/20 and 0/20 positive responses at 24- and 48-hour respectively	Venugopala Rao K. (2005) 4262/05

Table 30: Summary table of human data on skin sensitisation

Type of data/report	Test substance	Relevant information about the study (as applicable)	Observations	Reference
Please refer to 2.6.9 Summary of medical data and information: Skin sensitisation was not observed in the available human data.				

Table 31: Summary table of other studies relevant for skin sensitisation

Type of study/data	Test substance	Relevant information about the study (as applicable)	Observations	Reference
Please refer to Volume 3CP B6 – Sulfur 80%WG				

2.6.2.7.1 Short summary and overall relevance of the provided information on skin sensitisation

Three skin sensitisation studies are available on sulfur. Two of them (Maximisation and Buehler test methods) were conducted on sulfur technical in vaselin and the third one (Maximisation test) was conducted on Sulphur Dust moistened in water.
Sulfur is clearly not a skin sensitizer in the maximisation test when applied to 100% incorporated in water (Venugopala Rao, 2005), whereas an inconclusive result was observed in a Maximisation test (Arcelin, 1994) and in a Buehler test (Arcelin, 1994) that used Vaseline as vehicle when testing lower concentrations of up to 25% of sulfur.
The two assays performed on sulfur technical are considered acceptable with limitations. In the Maximisation test (Arcelin, 1994), very strong skin irritation was observed in control and treated groups after intradermal induction: the area around the injection site was erythematous and oedematous from test day 2 to 5, became necrotic from test day 6 to 8; encrustation and exfoliation of encrustation were noted from test day 10 to 18 and 19 to termination of test, respectively. In the Buehler assay (Arcelin 1994), the concentrations used for the challenges were found to be irritant in the pre-test assay. Since, according to OECD TG 406, highest non-irritant concentrations should be used, these concentrations were not appropriate in this assay. Furthermore, in both assays, vaseline was used as a vehicle. Nevertheless, according to the results of skin irritation studies, it was shown that Sulfur technical mixed with vaseline was irritant whereas Sulphur Dust moistened with deionised water was non-irritant to the skin of rabbits. Therefore, vaseline could have an influence on the irritation of the skin by the test chemical. As a consequence, the positive results observed in these assays could be more consistent with a non-specific irritation than with a sensitisation reaction. This is supported by the discrepancies noted in the Buehler assay after the second challenge conducted with Thiovit either in vaseline or in bi-distilled water: a negative response was observed with Thiovit in bi-distilled water whereas a positive response was noted with Thiovit in vaseline.
Therefore, given the limitations of the maximisation and Buehler assays performed on Sulfur technical, related to the very strong skin reactions observed after intradermal induction or to the choice of the challenge concentrations respectively, as well as the use of vaseline which could have an impact on the skin irritation potential of the test substance, no firm conclusion on the skin sensitising potential of sulfur can be drawn from these studies.
Overall, only the skin sensitisation study using Sulphur Dust in water (maximisation test of Venugopala Rao, K., 2005) is fully acceptable and the data are considered appropriate to use for the classification of sulfur. Under the conditions of this maximisation test, Sulphur Dust, applied to 100% incorporated in water to form a paste, did not induce skin sensitisation in guinea pigs.

The conclusion is supported by the results of the skin sensitisation studies with the plant protection product ‘Sulfur 80% WG’ evaluated in Volume 3CP B6. Overall, five out of six studies including two maximisation tests and three Buehler tests can be considered reliable with or without restrictions and are considered appropriate for classification purposes.

Furthermore, human skin sensitisation was not retrieved in a recent literature search, occupational medical surveillance, epidemiological studies and/or case reports.

2.6.2.7.2 Comparison with the CLP criteria regarding skin sensitisation

Substances shall be classified as skin sensitisers (Category 1) in accordance with the following criteria:
(i) if there is evidence in humans that the substance can lead to sensitisation by skin contact in a substantial number of persons, or
(ii) if there are positive results from an appropriate animal test.
When an adjuvant type test method for skin sensitisation is used, a response of at least 30 % of the animals is considered as positive. For a non-adjuvant Guinea pig test method a response of at least 15 % of the animals is considered positive.
Sub-category 1A applies for substances showing a high frequency of occurrence in humans and/or a high potency in animals can be presumed to have the potential to produce significant sensitisation in humans. Severity of reaction may also be considered.
Sub-category 1B applies for substances showing a low to moderate frequency of occurrence in humans and/or a low to moderate potency in animals can be presumed to have the potential to produce sensitisation

in humans. Severity of reaction may also be considered.

Based on the maximisation assay (Arcelin, 1994) and Buehler test (Arcelin, 1994) conducted on sulfur technical in vaseline, criteria for skin sensitisation classification were met since positive responses in more than 30% and 15% of the animals, respectively, were noted. Nevertheless, as explained above (Section 2.6.2.7.1), given the limitations of these assays, related to the very strong skin reactions observed after intradermal induction or to the choice of the challenge concentrations respectively, as well as the use of vaseline which could have an impact on the skin irritation potential of the test substance, no firm conclusion on the skin sensitising potential of sulfur can be drawn from these studies, which are considered as acceptable with limitations.

Overall, only the skin sensitisation study using Sulphur Dust in water (maximisation test of Venugopala Rao, K., 2005) is fully acceptable and the data are considered appropriate to use for the classification of sulfur. Under the conditions of this maximisation test, Sulphur Dust, applied to 100% incorporated in water to form a paste, did not induce skin sensitisation in guinea pigs (0% positive result).

The conclusion is supported by the results of the skin sensitisation studies with the plant protection product 'Sulfur 80% WG' evaluated in Volume 3CP B6. Overall, five out of six studies including two maximisation tests and three Buehler tests can be considered reliable with or without restrictions and showed negative results.

Furthermore, human skin sensitisation was not retrieved in a recent literature search, occupational medical surveillance, human incident databases, epidemiological studies and/or case reports.

2.6.2.7.3 Conclusion on classification and labelling for skin sensitisation

According to CLP criteria, based on a weight of evidence approach considering animals studies on the active substance and the products containing 80% of sulfur, as well as human data, classification for skin sensitisation is not warranted for sulfur.

RAC evaluation of skin sensitisation

Summary of the Dossier Submitter's proposal

Three Guinea pig studies with sulfur were included by the DS. All studies were stated to be GLP and OECD 406 compliant, and were therefore accepted in the pesticides dossier. However, the conduct and results of the Guineapig Maximisation Test (GPMT) and the Buehler test from 1994 were concluded to be of low reliability.

A GPMT from 2005 using Sulphur Dust was considered to be reliable by the DS. The study was conducted at concentrations of 1% Sulphur Dust in paraffin oil for intradermal induction and 100% of the substance, moistened with water, for topical induction and topical challenge. None of the 20 animals reacted at 24 hr or 48 hr after challenge.

The GPMT from 1994 conducted with sulfur technical used 1% test substance in paraffin oil and FCA for the intradermal induction phase. Strong skin reactions (oedema, then necrosis, encrustations) were seen after the intradermal induction with FCA/saline in control and treated groups. Reactions to epidermal induction were seen after use of SLS in paraffin oil of 25% sulfur in vaseline. First challenge concentrations of 15 and 25% sulfur in vaseline resulted in positive reactions in respectively 16 and 18 out of 19 animals, dropping to 2 and 5 animals at 48 hrs. After the second challenge, 2, 6 and 9 animals

reacted to 10, 15 and 25% vaseline at 24 hrs, respectively. At 48 hrs, 5, 8 and 11 treated animals showed "signs of allergic skin reactions". Scar formation was reported in 5, 2 and 6 animals, in the 10, 15 and 25% sulfur treated groups at this time point and necrotic skin was reported in one animal of the 10% group at both time points. No positive reactions were observed in animals challenged with vaseline alone. The DS pointed to the limitations of the study due to the strong skin reactions to intradermal induction and the possible enhancing effect of vaseline to conclude that this GPMT study is therefore not suited for classification purposes.

A Buehler test from 1994 with technical sulfur was also available. Induction was conducted with 25% sulfur in vaseline. Skin irritation was reported in 3/20, 15/20 and 16/20 animals at the first, second and third topical induction treatments. The dossier submitter noted that 15 and 25% sulfur in vaseline had shown to be skin irritating in a preliminary test. The challenge and rechallenge used 15 or 25% sulfur in vaseline. The study also included application of 15% of an 80% sulfur formulation using water and vaseline at the rechallenge phase. Positive responses after the first and second challenge to 15% or 25% sulfur in vaseline were seen in 4/20 to 9/20 animals. No reactions were recorded with the formulation containing 12% sulfur (15% of 80%) using water as the vehicle, whilst 10 respectively 9 out of 10 animals reacted to at 24 respectively 48 hrs after challenge in the group treated with the formulation when using vaseline as vehicle. Therefore, the DS also regards this Buehler test as being inconclusive, and considered the skin reactions to instead reflect irritative properties of sulfur in vaseline.

Further animal studies conducted with sulfur pesticide products containing up to 80% sulfur using water as moistening agent were considered reliable. None of them resulted in skin sensitisation.

In humans, there are no reports of skin sensitising effects of sulfur.

Based on the above data, the DS proposed not to classify of skin sensitisation.

Comments received during consultation

One MSCA supported the proposal of no classification and pointed to the limitations and unclarities in the Buehler and the GPMT with sulfur technical from 1994.

Assessment and comparison with the classification criteria

Classification for skin sensitisation can be based on results from animal studies and or human evidence. With respect to animal data, the classification criteria specifically refer to the GPMT, Buehler test and/or LLNA test.

The OECD TG 406 on the GPMT gives no specific recommendations for topical application (induction or challenge). For insoluble substances, in guidance given in that part of the TG, 80% ethanol/water is preferred for induction and acetone for challenge in the TG for the Buehler test.

The results from skin sensitising studies with sulfur technical using vaseline as the vehicle were regarded to be equivocal as the vehicle may have enhanced the skin irritation reactions. Also, reactions declined at rechallenge, supporting the conclusion that the effects were due to skin irritation rather than to sensitisation. Therefore, RAC considers that the GPMT and the Buehler test conducted with sulfur (from 1994) were equivocal.

Furthermore, severe skin effects are seen with the use of FCA in the GPMT test with sulfur technical, further compromising the validity of that study.

In the most recent GPMT, using water as the vehicle, RAC considers that sufficient contact with the skin was not obtained and the study is therefore not regarded to be adequate.

Therefore, RAC concludes that **classification for skin sensitisation is not warranted due to inconclusive data**.

2.6.2.8 Phototoxicity

Table 32: Summary table of studies on phototoxicity

Method, guideline, deviations if any	Test substance	Dose levels duration of exposure	Results	Reference
In vitro 3T3 NRU phototoxicity study OECD 432 (2004) Acceptable	Sulphur Dust Batch No.: E-GZB Purity: 98.5% w/w	Balb/3T3 c31 cells were treated with the test substance at concentrations of 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5 and 5.0 µg/mL in the absence and presence of irradiation.	Not phototoxic.	Duschl R. (2017) 1787901

Table 33: Summary table of human data on phototoxicity

Type of data/report	Test substance	Relevant information about the study (as applicable)	Observations	Reference
No relevant human data				

Table 34: Summary table of other studies relevant for phototoxicity

Type of study/data	Test substance	Relevant information about the study (as applicable)	Observations	Reference
No relevant study				

In an *in vitro* phototoxicity study, sulfur showed no phototoxicity potential in BALB/c 3T3 cells.

2.6.2.9 Aspiration hazard [equivalent to section 10.13 of the CLH report template]

Table 35: Summary table of evidence for aspiration hazard

Sulphur **Volume 1 – Level 2**

Type of study/data	Test substance	Relevant information about the study (as applicable)	Observations	Reference
Not applicable, sulfur is a solid				

2.6.2.9.1 Short summary and overall relevance of the provided information on aspiration hazard

Not applicable

2.6.2.9.2 Comparison with the CLP criteria regarding aspiration hazard

Not applicable

2.6.2.9.3 Conclusion on classification and labelling for aspiration hazard

According to CLP criteria, no classification for aspiration hazard is warranted for sulfur.

2.6.2.10 Specific target organ toxicity-single exposure (STOT SE) [equivalent to section 10.11 of the CLH report template]

Table 36: Summary table of animal studies on STOT SE (specific target organ toxicity-single exposure)

Method, guideline, deviations[1] if any, species, strain, sex, no/group	Test substance, route of exposure, dose levels, duration of exposure	Results - NOAEL/LOAEL - target tissue/organ - critical effects at the LOAEL	Reference
Please refer to 2.6.2.1, 2.6.2.2 and 2.6.2.3			

Table 37: Summary table of human data on STOT SE (specific target organ toxicity-single exposure)

Type of data/report	Test substance	Route of exposure Relevant information about the study (as applicable)	Observations	Reference
Please refer to 2.6.9 Summary of medical data and information: Signs of respiratory tract irritation were observed in workers occasionally exposed to sulfur in California during an application by helicopter (Maddy & Edmiston 1998) and were reported in human incident databases (US-EPA 2009) and in the French Toxicovigilance Programme “Mutualité Sociale Agricole”.				

Table 38: Summary table of other studies relevant for STOT SE (specific target organ toxicity-single exposure)

Type of study/data	Test substance	Relevant information about the study (as applicable)	Observations	Reference
No relevant study				

2.6.2.10.1 Short summary and overall relevance of the provided information on specific target organ toxicity – single exposure (STOT SE)

In the acute oral and dermal toxicity studies (refer to 2.6.2), there was no evidence of specific target organ toxicity.

Whereas in the acute inhalation toxicity study conducted on Sulphur Dust (Müller, 2005), no evidence of clinical signs was observed, clinical signs were reported in the acute inhalation toxicity conducted on sulfur technical (Groten, 1994). A decrease in breathing frequency was noted in all rats starting from the second hour of exposure. Irregular breathing was observed in all rats during the last two hours of exposure. In the first hour after exposure, all rats showed choking breathing and the eyes were partly closed.

In humans, signs of respiratory tract irritation were observed when using sulfur:
- in human incident databases (US-EPA 2009), where it is stated that respiratory symptoms/health effects were reflective of the known irritating properties of sulfur,
- in the French Toxicovigilance Programme "Mutualité Sociale Agricole", where cough, upper airway irritation, rhinitis, epistaxis and oropharyngeal irritation were reported,
- in workers occasionally exposed to sulfur in California during an application by helicopter (Maddy & Edmiston 1998) who experienced runny noses, throat irritation and cough.

2.6.2.10.2 Comparison with the CLP criteria regarding STOT SE (specific target organ toxicity-single exposure)

Specific target organ toxicity (single exposure) is defined as specific, non-lethal target organ toxicity arising from a single exposure to a substance. All significant health effects that can impair function, reversible and irreversible, immediate and/or delayed effects are considered.
STOT-SE categories 1 and 2 are assigned on the basis of clear evidence of significant or severe toxicity to a specific target organ arising from a single exposure to a substance. STOT-SE category 3 is assigned for the transient effects of respiratory tract irritation and narcotic effects.

There is no evidence from single or repeated dose studies of any clinical signs or other adverse effects indicative of specific target organ toxicity following single exposures to sulfur at non-lethal doses meeting the classification criteria for specific target-organ toxicity category 1 or 2.
Also, no evidence of narcotic effects was observed in the available studies.

However, as described in 2.6.2.10.1., evidence of transient effects of respiratory tract irritation was reported in one of the acute inhalation toxicity study, as well as in human data.

According to CLP regulation, *the criteria for classifying substances as Category 3 for respiratory tract irritation are:*
(a) respiratory irritant effects (characterised by localised redness, oedema, pruritis and/or pain) that impair function with symptoms such as cough, pain, choking, and breathing difficulties are included. This evaluation will be based primarily on human data;
(…)
(d) there are currently no validated animal tests that deal specifically with RTI, however, useful information may be obtained from the single and repeated inhalation toxicity tests. For example, animal studies may provide useful information in terms of clinical signs of toxicity (dyspnoea, rhinitis etc) and

histopathology (e.g. hyperemia, edema, minimal inflammation, thickened mucous layer) which are reversible and may be reflective of the characteristic clinical symptoms described above. Such animal studies can be used as part of weight of evidence evaluation;

The effects observed in the acute inhalation toxicity study (decrease in breathing frequency, irregular breathing and choking breathing observed shortly after the start of the exposure and demonstrated to be reversible) and in humans (cough, upper airway irritation, rhinitis, epistaxis, oropharyngeal irritation, runny noses, throat irritation) are considered to meet the criteria for STOT SE 3 classification.

2.6.2.10.3 Conclusion on classification and labelling for STOT SE (specific target organ toxicity-single exposure)

According to CLP criteria, based on a weight evidence approach considering animal and human data, classification for STOT SE Category 3 for respiratory tract irritation (H335) is considered warranted for sulfur.

RAC evaluation of specific target organ toxicity – single exposure (STOT SE)

Summary of the Dossier Submitter's proposal

The acute toxicity animal data described for oral and dermal routes showed no evidence of specific target organ toxicity. With respect to the inhalation route, an acute inhalation study in rats reported choking breathing from the first hour and decreased breathing frequency in all rats from the second hour of the 4-hour exposure to 5.43 mg/L technical sulfur. No clinical signs were reported in the acute inhalation toxicity study conducted with Sulphur Dust at 4.55 mg/L air.

A number of reports from epidemiological studies and toxicovigilance programmes show respiratory tract effects and chronic bronchitis.

The US-EPA RED (1991) concluded in their summary that handling of Sulphur Dust can cause eye and skin irritation in handling the pesticides or when in contact with treated foliage.

In 1996, the California Department of Food and agriculture reported an incident from 1986 in six vineyards workers exposed to sulfur dust applied by aerial spraying leading to signs of irritation to the respiratory tract amongst other throat irritation and cough in the workers.

Incidences in different American databases reviewed in the US EPA pesticide review of sulfur in 2009 showed that the effects related to exposure to sulfur were mostly related to the irritant properties of the substance to the eyes, the skin and the respiratory tract whilst toxicity of sulfur was low.

The DS further referred to the French governmental toxicovigilance programme of farmers that reported 13 cases of slight to severe irritation to skin, eyes and respiratory tract between 1997 and 2006, excluding cases of concomitant exposure to other pesticides. One worker with a medical history of asthma had bronchospasm requiring hospital admission. Amongst 24 cases reported from 1997 to 2012, there were 13 cases of respiratory findings, 5 of which were caused by wettable formulations and 8 were due to

exposure to a dust formulation of sulfur. Findings of nasal irritation symptoms occurred in 6 workers exposed to dust formulations and 2 exposed to wettable formulations.

The dosser submitter proposed classification as STOT SE in category 3; H335 based on the irritation effects to the respiratory tract reported consistently in occupational exposure to sulfur, supported by the effect in one animal study.

Comments received during consultation

An industrial organisation disputed in a comment and an attached expert statement that the severity of the effects reported in humans are insufficient to support classification, and stressed that there were both animal and human data not showing irritation to the respiratory tract. In their response, the DS referred to their analysis on the animal and human data, which in a weight of evidence approach led to the conclusion that sulfur should be classified for respiratory tract irritation.

One MSCA supported classification as STOT SE, category 3; H335, pointing to the decreased breathing frequency seen in rats exposed to 5.43 mg/L and the signs of respiratory tract irritation reported in incident databases from occupational exposure to sulfur.

Additional key elements

In the US EPA pesticide review from 2009 mentioned above, an annex referring to incident databases included a table from US EPA's Office of Pesticide Programs (OPP) listing ten incidents related to sulfur exposure, from 2000 to 2006, three of them reporting respiratory effects, which amongst others included the following: Twenty-one field workers entered a vineyard about 6 hours after the field was treated with a sulfur dust product. The crew worked in the vineyard for about an hour. After it was discovered that the reentry interval for the product had not expired the workers were ordered out of the field. The workers reported teary and watery eyes, sore throats, nose irritation, headaches, and tingling in the tongue and mouth. One woman reported vomiting. The pesticide review further included information from the Association of American Poison Control Center (AAPCC) compiling incidents of poisonings, mostly in residential setting. The database has registered 1.5 million incidences of adverse health effects over the period 1993-2005, 958 (0.06%) involving sulfur.

Details provided by the DS on the French toxicovigilance programme showed that a total of 126 reports on health incidents related to occupational exposure in different tasks to sulfur alone or in association with other pesticides were reported in the period 1997-2012, 86 of which were evaluated to be reliable. The French background report showed that handling of foliage upon re-entry into a treated field accounted for 43.6% of the reported cases. The detailed document further confirmed that the 24 reported cases included in the classification proposal were related to exposure to sulfur products alone, with no concomitant exposure to other pesticides. The number of cases with respiratory symptoms was confirmed to be 13, 5 of which occurring from wettable formulations.

A handbook reference notes sulfur to have low toxicity and be an irritant to the skin, eye, and respiratory tract, with no further details (Gosselin *et al.*, 1976).

In "The extra pharmacopeia" (Reynolds, 1996), sulfur is described to be keratolytic. Precautions include avoiding contact with eyes, mouth and other mucous membranes.

Assessment and comparison with the classification criteria

Substances should be classified for STOT SE in categories 1 respectively 2 if they produce significant toxicity or can be presumed to be harmful to humans from a single exposure. Guidance values for classification on the basis of animal data are specified in the classification criteria.

Classification as STOT SE in Category 3 is attributed to substances causing narcotic effects or causing respiratory tract irritation after single exposure.

Sulfur did not show signs of significant target organ toxicity in animals exposed to concentrations within the guidance values for classification in category 2 from either route of exposure. The available human data do not report significant organ toxicity from a single exposure. Thus, classification in categories 1 and 2 are not relevant.

Results from American and French human reports from incidences of exposure of workers show varying degrees of respiratory tract irritation including rhinitis, cough, and breathing difficulties. The US EPA refers to irritation as a well-known irritating property of sulfur. Symptoms of respiratory tract irritation (irregular and chocking breathing) were also seen in a study of acute inhalation toxicity in rats at a concentration 5.43 mg/L.

The DS considered the reports of respiratory tract irritation in humans exposed to sulfur, supported by the effects seen in one animal study in their proposal for classification for respiratory tract irritation STOT SE Category 3; H335.

RAC assessed that the effects on the respiratory tract reported in the acute inhalation study should not be considered for classification for STOT SE, as they occurred at a dose also leading to death in two animals, and therefore these findings are regarded as unspecific, sublethal toxicity reaction.

RAC notes the human cases of respiratory tract effects from exposure to sulfur from American and French databases. However, the reports include few details on the severity of the effects. Considering the extensive use of sulfur through several decades, the number of cases reported are low. RAC concludes that the severity of the effects on the respiratory tract are low and outside the scope of classification for respiratory irritation.

Based on the available animal and human data, RAC concludes, contrary to the proposal from the DS, that **classification for STOT SE is not warranted for sulfur**.

2.6.3 Summary of repeated dose toxicity (short-term and long-term toxicity) [section 10.12 of the CLH report]

2.6.3.1 Specific target organ toxicity-repeated exposure (STOT RE) [equivalent to section 10.12 of the CLH report template]

Table 39: Summary table of animal studies on repeated dose toxicity (short-term and long-term toxicity) STOT RE (specific target organ toxicity - repeated exposure)

Sulphur **Volume 1 – Level 2**

Method, guideline, deviations if any, species, strain, sex, no/group	**Test substance, route of exposure, dose levels, duration of exposure**	**Results** **- NOAEL/LOAEL** **- target tissue/organ** **- critical effects at the LOAEL**	**Reference**
28-day, oral (gavage) rat study OECD 407 (1995) Wistar rat 6/sex/group Acceptable Deviations from current guideline (2008): Organ weight of prostate (incl. seminal vesicles with coagulating gland) and historical control data for organ weights were missing. Vagina, cervix and skeletal muscle were not histopathologically examined.	Sulphur Dust Batch No.: I-GLA Purity: 98.5% w/w Oral (gavage) 0, 100, 400 and 1000 mg/kg bw/d Recovery groups (14 days following the treatment period): 0 and 1000 mg/kg bw/d	**NOAEL = 1000 mg/kg bw/d** No adverse effect ***Effects considered not treatment-related and not adverse:*** *- Changes in haematological and clinical chemistry parameters in treated groups: not dose-related and/or of small magnitude and/or within the expected range of background values, not associated with other corresponding findings*	Ramesh E. (2005) 4264/05
90-day, oral (gavage) rat study OECD 408 (1998) Wistar rat 10/sex/group Acceptable Deviations from current guideline (2018): HDL and LDL were not measured in clinical chemistry and serum total T4, T3 and TSH were not quantified. At necropsy the female oestrus cycle was not determined. Organ weights for prostate (incl. seminal vesicle with coagulating gland) and pituitary gland were not recorded and cervix, vagina, mammary gland in males and skeletal muscle were not histopathologically examined. No historical control data were included.	Sulphur technical Batch No.: SML/RD/T/S-191 Purity: 99.6% w/w Oral (gavage) 0, 100, 400 and 1000 mg/kg bw/d Recovery groups (28 days following the treatment period): 0 and 1000 mg/kg bw/d	**NOAEL = 1000 mg/kg bw/d** No adverse effect ***Effects considered not treatment-related and not adverse:*** *- Changes in haematological and clinical chemistry parameters in treated groups: not dose-related and/or of small magnitude, not associated with other corresponding findings*	Malleshappa H.N. (2006) 4191/05

90-day, oral (gavage) rat study OECD 408 (1998) Wistar rat 10/sex/group Acceptable Deviations from current guideline (2018): Urea, HDL, LDL were not measured in clinical chemistry. Serum total T4, T3 and TSH were not quantified and at necropsy the female oestrus cycle was not determined. Organ weights for prostate (incl. seminal vesicle with coagulating gland) and pituitary gland were not recorded and cervix, mammary gland in males, coagulating glands and skeletal muscle were not histopathologically examined. No historical control data included.	Sulphur Dust Batch No.: L-BPA Purity: 98.0% w/w Oral (gavage) 0, 100, 400 and 1000 mg/kg bw/d Recovery groups (28 days following the treatment period): 0 and 1000 mg/kg bw/d	**NOAEL = 400 mg/kg bw/d** **Critical effects at the LOAEL of 1000 mg/kg bw/d:** in males: decreased body weight (-7% at the end of the treatment period, -10% during recovery), body weight gain (-12%) and food consumption (-7%) ***Effects considered not treatment-related and not adverse:*** *- Changes in haematological and clinical chemistry parameters in treated groups: not dose-related and/or of small magnitude, not associated with other corresponding findings* *- Increased relative testis and epididymides weight: at 1000 mg/kg bw/d only in the recovery group (not in the main group), no histopathological findings, likely related to the decreased body weight*	Zimmermann M.F. (2009) RF-5764.307.031.08
28-day, dermal rat study OECD 410 (1981) Wistar rat 5/sex/group Acceptable	Sulphur technical Batch No.: SML/RD/T/S-191 Purity: 99.6% w/w Dermal, 6 hours/day, 5 days/week 0, 100, 400 and 1000 mg/kg bw/d Recovery groups (14 days following the treatment period): 0 and 1000 mg/kg bw/d	**1/ Local NOAEL = 400 mg/kg bw/d in males and females** Local LOAEL = 1000 mg/kg bw/d **Critical local effects at the LOAEL of 1000 mg/kg bw/d:** Microscopically skin findings (hyperkeratosis of the treated skin in both sexes, hyperkeratosis of the untreated skin in females) **2/ Systemic NOAEL= 1000 mg/kg bw/d** No adverse systemic effect ***Effects considered not treatment-related and not adverse:*** *- Decreased body weight gain and body weight in males at 1000 mg/kg bw/d, in the recovery group only (not in the main group), likely due to the high body weight values in the recovery control group* *- Changes in haematological and clinical chemistry parameters in treated groups: not dose-related and/or of small magnitude and/or within expected range of background values, not associated with other corresponding findings*	Malleshappa H.N. (2006) 4190/05

28-day, dermal rat study OECD 410 (1981) Wistar rat 5/sex/group Acceptable Deviations: The test substance was not moistened before application on skin as recommended in the guideline, but the dry, solid powder was applied on the skin and then covered with a porous gauze moistened with corn oil.	Sulphur Dust Batch No.: L-BPA Purity: 98.0% w/w Dermal, 6 hours/day, 5 days/week 0, 100, 400 and 1000 mg/kg bw/d Recovery groups (14 days following the treatment period): 0 and 1000 mg/kg bw/d	**1/ Local NOAEL = 1000 mg/kg bw/d** No adverse local effect **2/ Systemic NOAEL= 1000 mg/kg bw/d** No adverse systemic effect	Zimmermann M.F. (2009) RF-5764.327.002.08

Table 40: Summary table of human data on repeated dose toxicity STOT RE (specific target organ toxicity-repeated exposure)

Type of data/report	**Test substance**	**Route of exposure Relevant information about the study (as applicable)**	**Observations**	**Reference**
No relevant human data				

Table 41: Summary table of other studies relevant for repeated dose toxicity STOT RE (specific target organ toxicity-repeated exposure)

Type of study/data	**Test substance**	**Relevant information about the study (as applicable)**	**Observations**	**Reference**
No relevant study				

2.6.3.1.1 Short summary and overall relevance of the provided information on specific target organ toxicity – repeated exposure (short-term and long-term toxicity)

Studies on short-term toxicity of sulfur were conducted with sulfur technical and/or 'Sulphur Dust' as a surrogate for technical sulfur since the minimum content of the active substance in this representative product is specified as 985 g/kg and the only co-formulant is an inert carrier.
One 28-day oral rat toxicity study, two 90-day oral rat toxicity studies and two 28-day dermal rat toxicity studies were available.

<u>28-day oral toxicity study</u>

In a 28-day oral toxicity study (Ramesh, 2005), administration of 'Sulphur Dust' (as a surrogate for technical sulfur) to Wistar rats at 100, 400 and 1000 mg/kg bw/d had no effects on general health. There were no clinical/toxic signs or pre-terminal deaths. There were no effects on functional neurological observations, growth, food consumption, haematological and biochemical parameters, organ weights and their ratios in either sex. There were also no gross or histopathological changes. Under the conditions of this study, Sulphur Dust administered orally by gavage at dose levels up to 1000 mg/kg bw/d did not show adverse effects in Wistar rats.

90-day oral toxicity studies

In a 90-day oral toxicity study (Malleshappa, 2006), administration of sulfur technical to Wistar rats at 100, 400 and 1000 mg/kg bw/d did not cause any changes of toxicological significance, the NOAEL being set at 1000 mg/kg bw/d, the highest dose tested. In a newly generated 90-day oral toxicity study with 'Sulphur Dust' administered to Wistar rats at the same dose levels (Zimmermann, 2009), effects on body weight parameters and food consumption were observed at the highest dose level of 1000 mg/kg bw/d. Therefore, in this study, the NOAEL is set at 400 mg/kg bw/day.

28-day dermal toxicity studies

A repeated dose (28-day) dermal toxicity study was carried out with sulfur technical in Wistar rats at doses of 0, 100, 400 and 1000 mg/kg bw/d (Malleshappa, 2006). There were no clinical toxic signs, pre-terminal deaths, local skin reactions by visual inspection, changes in skin/fur, growth or food consumption. There were no treatment-related changes in haematological and biochemical parameters, organ weights and their ratios in either sex. In the absence of systemic adverse effects, the systemic NOAEL is set at 1000 mg/kg bw/d, the highest tested dose. Microscopically skin findings (hyperkeratosis of the treated skin in both sexes, hyperkeratosis of the untreated skin in females) were observed with a higher incidence at the high dose level of 1000 mg/kg bw/d. Therefore, a local NOAEL is proposed to be set at 400 mg/kg bw/d.
In a newly generated 28-day dermal toxicity study with 'Sulphur Dust' applied to Wistar rats at the same dose levels (Zimmermann, 2009), no systemic or local adverse effects were reported. The systemic and local NOAEL of this study are therefore set at 1000 mg/kg bw/d, the highest tested dose.

Table 42: Extrapolation of equivalent effective dose for toxicity studies of greater or lesser duration than 90 days

Study reference	**Effective dose (mg/kg/day)**	**Length of exposure**	**Extrapolated effective dose when extrapolated to 90-day exposure**	**Classification supported by the study**
Dermal toxicity rat study Malleshappa 2006	1000	28-day	333	No

Inhalation toxicity

No repeated-dose inhalation toxicity study is available on sulfur.

In accordance with the data requirements for active substances (Commission Regulation (EU) No 283/2013), short-term toxicity studies via the inhalation route shall be considered where the vapour pressure exceeds 10^{-2} Pascals, which is not the case for sulfur (vapour pressure 9.8×10^{-5} Pa at 20 °C).

It is noteworthy that some adverse effects occurring after long-term inhalation exposure were reported in humans (please refer to Vol 3CA B.6.9). Nevertheless, chronic findings were only reported when sulfur was not the only active substance used and/or on isolated cases. Chronic bronchitis, chronic sinusal effects and respiratory disturbances were observed in mine workers who were exposed to Sulfur dust but also to sulfur dioxide during their lifetime (US EPA, 1991). In the French Toxicovigilance Programme "Mutualité Sociale Agricole", only one case of severe bronchospasm requiring hospital admission occurred in a farmer with a medical history of asthma over the period 1997-2012. The observed adverse effects on the respiratory tract were reflective of the irritating properties of sulfur and were linked to acute exposures.

The major concern arise from the epidemiological study conducted in California (Raanan *et al*., 2017) which evaluated associations between residential proximity to elemental sulfur applications and

respiratory symptoms and spirometry of children living in an agricultural community (please refer to Vol 3CA B.6.9.4). The authors demonstrated that poorer lung function (spirometry measurements) and higher odds of reported respiratory symptoms and asthma medication use were found in 7-year old children living within 0.5 km and 1 km of elemental sulfur applications during the previous week, month and year. Overall, the RMS considered that, although some limitations were noted in this paper, this epidemiological study is sufficiently robust to be considered as a signal. In agreement with the study authors, it is considered that further studies would be beneficial in order to confirm or infirm these results in other study populations.

Based on screening data in companies manufacturing sulfur or sulfur formulations provided in the confidential parts of the dossier (please refer to Vol 4), the occupational medical surveillance of factory workers revealed no evidence of any adverse findings, except cases of eye and/or skin irritations. Thus, in no case are any adverse respiratory effects noted despite many years of handling the technical and formulated material.

In rodents, two acute inhalation toxicity studies are available. From these studies (see table below and Vol 3CA B.6.2.3), sulfur is not considered toxic by the inhalation route. The studies were guideline compliant in terms of concentrations tested and particle size of material. Clinical observations were noted only in the study with sulfur technical and these were noted mainly during the exposure period. The LC_{50} is greater than 5 mg/L, the maximum dose for this study type. In surviving animals, no adverse macropathological effects were noted post-mortem.

Acute inhalation studies conducted with sulfur:

Test compound (purity of sulfur)	**Dose level**	**MMAD (GSD) [µm]**	**Results**	**Reference**
Sulfur technical (100.2% pure)	5.43 mg/L/4-h Nose-only exposure	3.8 (1.3)	Deaths: males 2/5; females 0/5 Clinical signs: during exposure: slight to moderate decreased breathing frequency, slight irregular breathing; post exposure: slight choking, partial eye closure, general pale appearance, blepharospasms, nasal encrustations, dirty fur LC_{50} > 5 mg/m^3	Groten, I., 1994
'Sulphur dust' (98.5% purity)	4.552 mg/L/4-h Nose-only exposure	4.22 (3.05) 4.25 (3.11)	Deaths: males 0/5; females 0/5 Clinical signs: none LC_{50} > 4.5 mg/L air [highest achievable concentration]	Müller, P.Y., 2005

MMAD = mean mass median aerodynamic diameter
GSD = Geometric standard deviation

From a regulatory point of view, as sulfur is not a volatile substance (vapour pressure does not exceed 10^{-2} Pascals), a short-term toxicity study via the inhalation route is not mandatory as a first instance.
Nevertheless, taking into account the results of the newly submitted epidemiological study, the RMS considered that this could be a justification for conducting a repeat dose inhalation study with sulfur. The need for a subchronic toxicity study by inhalation route is proposed to be discussed between Member States during the expert meeting.

It is also noteworthy that many of the plant protection products are in the form of a very fine powder (90% of particles <53µm; 10% of the particles < 5.7µm) applied as powder/dust, which could raise concern related to non-dietary exposure. Furthermore, it was demonstrated from the exposure study (Garofani S., 2010a) that inhalation represents the major part of systemic exposure of bystander/resident, particularly in children (please refer to Volume 3CP Sulphur Dust B6).

<u>Lack of a short-term oral toxicity study in a second non-rodent species</u>

No short-term oral toxicity study was performed on a non-rodent species. Nevertheless, given that a similar metabolic profile of sulfur after absorption is likely in different species, inter-species difference is not expected for sulfur. Moreover, sulfur is generally regarded as safe for human exposure given the wide range of background exposure, its low acute and short-term toxicity and its non-genotoxic potential. In addition, it is an essential element needed at a high dose level. Therefore, it was considered unnecessary to require a short-term oral toxicity in a non-rodent species with sulfur.

2.6.3.1.2 Comparison with the CLP criteria regarding STOT RE (specific target organ toxicity-repeated exposure)

Substances are classified as specific target organ toxicants following repeated exposure on the basis of "significant" or "severe" toxicity. In this context "significant" means changes which clearly indicate functional disturbance or morphological changes which are toxicologically relevant. "Severe" effects are generally more profound or serious than "significant" effects and are of a considerably adverse nature which significantly impact on health.
In accordance with the guidance on the application of the CLP criteria, the following effects might be indicative of significant or severe toxicity and thus merit classification for STOT-RE.

a) Morbidity or death resulting from repeated or long-term exposure.

b) Significant functional changes in the central or peripheral nervous systems or other organ systems

c) Any consistent and significant adverse change in clinical biochemistry, haematology or urinalysis parameters

d) Significant organ damage noted at necropsy and/or subsequently seen or confirmed at microscopic examination

e) Multi-focal or diffuse necrosis, fibrosis or granuloma formation in vital organs with regenerative capacity

f) Morphological changes that are potentially reversible but provide clear evidence of marked organ dysfunction (e.g., severe fatty change in liver)

In order to help reach a decision about whether a substance shall be classified or not, and to what degree it
shall be classified (Category 1 or Category 2), dose/concentration 'guidance values' are provided for consideration of the dose/concentration which has been shown to produce significant health effects.

The only systemic adverse effect observed in the repeated-dose toxicity studies conducted on sulfur up to 1000 mg/kg bw/d were an effect on body weight and food consumption parameters (approx. 10% decrease compared to the control group) in one of the two available 90-day studies at the dose level of 1000 mg/kg bw/d. Such effects are not considered indicative of significant or severe toxicity, occurred at a dose level above the guidance values for classification (90-day oral rat studies: 10 mg/kg bw/d for Category 1, 100 mg/kg bw/d for Category 2) and therefore do not trigger STOT-RE classification.
Also, microscopic skin findings were noted at the dose level of 1000 mg/kg bw/d in the 28-day dermal toxicity study conducted on sulfur technical. This local finding is not considered as 'significant' or 'severe', and occurred at a dose level above the guidance values for classification (28-day dermal rat studies: 60 mg/kg bw/d for Category 1, 600 mg/kg bw/d for Category 2).
Therefore, no classification as STOT-RE is warranted for sulfur.

2.6.3.1.3 Conclusion on classification and labelling for STOT RE (specific target organ toxicity-repeated exposure)

According to CLP criteria, no classification for STOT RE is warranted for sulfur.

RAC evaluation of specific target organ toxicity – repeated exposure (STOT RE)

Summary of the Dossier Submitter's proposal

The evidence available on the potential repeated dose toxicity of sulfur to specific organs included animal studies and human data. The available animal studies included one 28-day and two 90-day studies in rats by the oral route and two 28-day dermal toxicity studies in rats, all conducted according to OECD TG between 2005 and 2009, using either technical sulfur or Sulphur Dust as the test substance.

In a 90-day study with Sulphur Dust, where animals were dosed with 0, 100, 400 and 1000 mg/kg bw by gavage, decreased body weights were seen in males at the high dose (7%, increasing to 10% in the subsequent 28-day recovery period). Increased relative testis and epididymides weights in the high dose group were reported in the recovery period but were considered to be due to decreased body weights in that dose group. Small changes in haematological and biochemistry parameters were not considered treatment-related. Small, non dose-related changes in haematology and clinical chemistry were also reported in the 28-day oral gavage study with Sulphur Dust using the same dose levels.

In the 90-day oral toxicity-study conducted with technical sulfur, the only effects reported were changes in haematological and biochemistry parameters with no other corresponding findings.

In the dermal 28-day study with no recovery period, doses of 0, 100, 400 and 1000 mg/kg bw/day technical sulfur caused no systemic effect, but hyperkeratosis was reported at the high dose at the treated sites in both sexes and in females also at untreated sites.

With Sulphur Dust applied under a gauze patch moistened with corn oil using the same doses, no local or systemic effects were reported at any dose level.

In the US-EPA databases, occupational cases of chronic bronchitis, chronic sinusal effects and respiratory effects were reported following exposure to sulfur, but in co-exposure to other pesticides. In the French Toxicological Programme, one case of bronchospasm occurred in a farmer with a medical history of asthma.

An epidemiological study of respiratory symptoms and spirometry was performed in 237 7-year old children living in the Salinas Valley in California, within 0.5 km and 1 km of agricultural areas treated with sulfur at one week, month and year after the applications. The study reported higher odds ratios for respiratory symptoms and asthma medication and poorer lung function in the children, the symptoms decreasing with time. The study had some limitations e.g. the reliability of the questionnaire used for symptoms and medication recording, uncertainty in the determination of exposure levels to sulfur, possible co-exposure to other pesticides and/or to smoke, difficulties of performing spirometry in young age children. The DS assessed the study to constitute a "signal" and encouraged further studies to potentially confirm the findings.

The DS proposed no classification for STOT RE for any routes of exposure.

Comments received during consultation

An MSCA supported the DS proposal to not classify for STOT RE based on the available information. With respect to repeated dose by inhalation, the MSCA pointed to two publication on human experience provided in the dossier, commented on the requirement for an additional animal study and noted that testing requirements are not relevant under CLP.

A group of industrial companies disputed the need for requiring an additional sub-chronic inhalation study, pointing to the already existing database not supporting an effect of sulfur following repeated exposure.

The DS in their response maintained that the lack of animal data on toxicity to inhalation following repeated exposure led to the conclusion that data are inconclusive for classification for STOT RE.

In their specific response to this comment, RAC confirmed that classification is to be performed with the available data. Whilst agreeing with the DS that further information would strengthen the evaluation of this end-point, RAC emphasised that discussion of requirements for further data is not relevant under CLP.

Assessment and comparison with the classification criteria

The criteria for classification as STOT RE require significant functional disturbance or morphological changes or severe effects with a serious adverse impact on health. Guidance values are provided to placing substances in category 1 or 2 or to decide to not classify when evaluating animal data.

Effects on body weights reported in one 28-day study in rats at the highest dose of 1000 mg/kg/day was not considered to be of sufficient severity to warrant classification. The slight effects on clinical biochemistry and haematology of rats reported in the oral studies are insufficient for classification as they lack a dose-response relationship and statistical significance.

Therefore, no classification was warranted for STOT RE by the oral route.

In the dermal 28-day repeated dose toxicity study, hyperkeratosis occurred in the high dose group of 1000 mg/kg bw/day only. The findings were considered borderline with respect to their severity. When extrapolated to a 90-day duration, the dose-level corresponds to 333 mg/kg bw, which is above the guidance value for classification as STOT RE 2 of 200 mg/kg bw/day, and no classification for STOT RE by the dermal route is proposed.

No repeated or long-term inhalation toxicity studies in animals are available. In humans the restricted number of reports from occupational settings of chronic effects by the inhalation route related to sulfur exposure also reported co-exposure to other pesticides. One epidemiological study of 7-year old children residing near fields treated with sulfur raised concern. However, RAC concludes that the study is not sufficiently robust due to a number of uncertainties in its conduct to support classification on its own.

Therefore, RAC agrees with the DS that no classification for STOT RE can be applied due to inconclusive data.

2.6.4 Summary of genotoxicity / germ cell mutagenicity [equivalent to section 10.8 of the CLH report template]

Table 43: Summary table of genotoxicity/germ cell mutagenicity tests *in vitro*

Method, guideline, deviations[1] if any	Test substance	Relevant information about the study including rationale for dose selection (as applicable)	Observations /Results	Reference
Bacterial reverse mutation test OECD 471 (1997) Acceptable Deviations: Precipitation was evaluated in a separate precipitation test.	Sulphur Dust Batch No.: I-GLA Purity: 98.5% w/w	*Salmonella typhimurium* (TA 1535, TA 1537, TA 98 and TA 100) *Escherichia coli* WP2 *uvrA* All strains treated up to 5000 µg/plate with and without metabolic activation	Negative (+/- S9)	Shivaran S. (2005) 4265/05
Chromosome aberration assay OECD 473 (1997) Acceptable Deviations from current guideline (2016): Lower number of evaluated cells. Cytotoxicity determined by viable cell counts at the end of the treatment period. Precipitation was only assessed in separate precipitation test.	Sulphur Dust Batch No.: I-GLA Purity: 98.5% w/w	Chinese hamster ovary cell line CHO-K1 The maximum test item concentration based on cytotoxicity. 3h treatment – S9: 4, 8, 16, 32 and 64 µg/mL 3h treatment + S9: 4, 8, 16, 32 and 64 µg/mL 19h35min treatment –S9: 2, 4, 8, 16, 32 and 64 µg/mL	Negative (+/- S9)	Indrani B.K. (2005) 4266/05

Table 44: Summary table of genotoxicity/mutagenicity tests in mammalian somatic or germ cells *in vivo*

Method, guideline, deviations[1] if any	Test substance	Relevant information about the study (as applicable)	Observations/Results	Reference
Mammalian Erythrocyte Micronucleus test in Swiss albino mice OECD 474 (1997) Acceptable Deviations from current guideline (2016): Bone marrow exposure was not demonstrated. Number of evaluated cells lower than required by the current test guideline	Sulphur technical Batch No.: SML/RD/T/S-191 Purity: 99.6% w/w	2000 mg/kg bw (limit dose) administered twice by gavage with a 24-h interval to male and female Swiss albino mice. 5 mice/sex/group Sampling 23-24h after the second treatment	Negative No mortality, no clinical abnormalities No effects on the PCE/total RBC ratio. No direct proof of bone marrow exposure. Therefore, reliability of the negative result is questionable.	Geetha Rao G. (2005) 4192/05

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Method, guideline, deviations[1] if any	Test substance	Relevant information about the study (as applicable)	Observations/Results	Reference
Mammalian Erythrocyte Micronucleus test in Swiss albino mice OECD 474 (1997) Acceptable Deviations from current guideline (2016): Bone marrow exposure was not demonstrated. IP injection generally not recommended. Number of evaluated cells lower than required by the current test guideline.	Sulphur Dust Batch No.: L-BPA Purity: 98.05% w/w	2000 mg/kg bw (limit dose) administered twice by IP injections with a 24-h interval to male and female Swiss albino mice (based on an initial toxicity test). 5 mice/sex/group Sampling 24h after the second injection	Negative One mortality in the male treated group (treatment-relationship not proven). No effects on the PCE/NCE ratio. No direct proof of bone marrow exposure. Therefore, reliability of the negative result is questionable.	Grigoli M.B. (2009) RF-5764.402.496.08

Table 45: Summary table of human data relevant for genotoxicity / germ cell mutagenicity

Type of data/report	Test substance	Relevant information about the study (as applicable)	Observations	Reference
No relevant human data				

2.6.4.1 Short summary and overall relevance of the provided information on genotoxicity / germ cell mutagenicity

Studies on genotoxicity of sulfur were conducted with sulfur technical and/or 'Sulphur Dust' as a surrogate for technical sulfur since the minimum content of the active substance in this representative product is specified as 985 g/kg and the only co-formulant is an inert carrier.

Sulfur showed negative results in an Ames assay and in an *in vitro* chromosomal aberration test. In addition, an *in vitro* mammalian cell gene mutation test is scheduled to complete the *in vitro* genotoxicity testing series required by Regulation (EU) 283/2013. The applicant informed the RMS that the expected finalisation date of this study would be October 2020.

Two *in vivo* micronucleus assays are available on sulfur: one with sulfur technical by oral route and one with Sulphur Dust by intraperitoneal injection. They were both performed under GLP according to OECD TG 474. Although some deviations according to current OECD TG 474 (2016) were noted, the studies were compliant with OECD TG 474 (1997) and could be considered acceptable. Under the conditions of these studies, no statistically significant increase in the number of micronuclei was noted at the limit dose of 2000 mg/kg bw. Nevertheless, the reliability of the negative results were questionable as the bone marrow was not demonstrated to be exposed in these studies. In the absence of ADME studies and of systemic toxicity observed in the toxicity studies available on sulfur, lines of evidence of bone marrow exposure could not be gathered. Nevertheless, as sulfur is an essential element of low toxicity needed at a high dose level and retrieved in dietary items/food consumptions, as no genotoxicity concern was raised for sulfur despite its long history of use (including pharmaceutical uses) and as the available genotoxicity assays showed negative results (pending results of the *in vitro* mammalian cell gene mutation assay to be

submitted later), the RMS considered that the concern on genotoxicity is very low and that further data are not required.

Overall, sulfur can be considered as devoid of genotoxic potential (provided that the ongoing *in vitro* mammalian cell gene mutation test would confirm this conclusion).

Co-RMS agreed that repeated micronucleus assay in mouse bone marrow should not be required due to questionable exposure of target tissue. However, in order to demonstrate the lack of genotoxic potential of sulfur *in vivo*, they considered that an *in vivo* genotoxicity study at site of first contact would be the most appropriate.

Sulfur shows no phototoxic properties in the *in vitro* 3T3 NRU phototoxicity test. Thus, there is no evidence of photosensitivity of active substance and any further study on photomutagenicity is not considered necessary.

2.6.4.2 Comparison with the CLP criteria regarding genotoxicity / germ cell mutagenicity

The classification criteria for germ cell mutagenicity takes into account test results from mutagenicity or genotoxicity tests *in vitro* and from studies with mammalian somatic and germ cells *in vivo*. Overall, sulfur can be considered as devoid of genotoxic potential (provided that the ongoing *in vitro* mammalian cell gene mutation test confirms this conclusion).
Based on the CLP criteria, sulfur does not require classification and labelling for germ cell mutagenicity.

2.6.4.3 Conclusion on classification and labelling for genotoxicity / germ cell mutagenicity

According to CLP criteria, no classification for genotoxicity/germ cell mutagenicity is warranted for sulfur.

RAC evaluation of germ cell mutagenicity

Summary of the Dossier Submitter's proposal

The CLH dossier included reference to two *in vitro* tests: an Ames assay and an *in vitro* chromosome aberration assay, both from 2005, conducted with Sulphur Dust. Both tests followed OECD TG applicable at the time and they were deemed acceptable by the DS. The Ames test included 4 *salmonella typhimurium* strains and one *E.coli* strain and used up to 5000 µg/plate. The results were negative with and without S9 metabolic activation in all 5 bacterial strains. The chromosomal aberration test that used Chinese hamster ovary cells up to 64 µg/mL, the maximal possible concentration due to cytotoxicity, also yielded negative results with and without S9 metabolic activation.

Furthermore, the dossier mentioned that an *in vitro* mammalian gene mutation assay is expected in October 2020. The study report was provided during the consultation of the CLH report (see below).

The DS also included in the dossier two negative GLP and OECD TG 474 compliant *in vivo* micronucleus assays conducted in mice: one with sulfur technical by the oral route and one with Sulphur Dust by intraperitoneal injection. Neither of the studies showed increased numbers of micronuclei at the limit dose of 2000 mg/kg bw. The DS pointed to the fact that it was not demonstrated that the substance had indeed reached the bone

marrow, as no systemic toxicity was reported. Furthermore, no information on the toxicokinetics of sulfur was available in the application. The results of the *in vivo* tests were therefore questionable.

Based on the available negative *in vitro* data, although still pending the results of the *in vitro* mammalian cell gene mutation assay, on the low systemic toxicity of sulfur, on the lack of reports of genotoxicity from the use of the substance in food and as a pharmaceutical agent and on the exposure to the substances due to its nature as an essential element the DS concludes the genotoxic potential of sulfur is very low.

The DS quotes the co-RMS in the DAR that they were of the view that the genotoxicity at the first site of contact could not be totally excluded as no confirmatory *in vivo* test was available.

The DS concluded that the available data do not support classification for mutagenicity.

Comments received during consultation

One comment from a group of industrial companies supplied the report of the announced *in vitro* gene mutation test in Chinese Hamster V79 cells conducted according to OECD TG 476 with Sulphur 98.5 DP (dustable powder formulation). The comment and a separate document from an expert on the assessment of the genotoxicity of sulfur further argued that no further testing is necessary to confirm the lack of genotoxicity of sulfur at a site of contact. The DS responded that the new study is valid and that the negative result with and without metabolic activation confirmed the conclusion that sulfur is not mutagenic.

Another comment, from an MSCA, supported the proposal to not classify sulfur for mutagenicity, and proposed to include three publicly available reports of mutagenicity testing in the overall evaluation of mutagenicity. The DS noted that one of the studies was not considered acceptable by the DS, and although some limitations were identified in the OECD TG compliant studies, they are sufficient to conclude on the endpoint.

Additional key elements

In addition to the negative *in vitro* tests available in the dossier (Ames test and chromosomal aberration test) with and without metabolic activation, the newly submitted *in vitro* gene mutation test in Chinese Hamster V79 cells showed no mutagenic effects of sulfur.

RAC considered that the negative results of the two available *in vivo* chromosome aberration tests, one by the oral route and one by intraperitoneal injection, were not reliable and cannot be used for classification purposes, as it not demonstrated that the bone marrow was reach in either study.

General information on the local action of sulfur and its low systemic toxicity points to a low potential for systemic – let alone germ cell targeted - mutagenicity.

The potential for site of contact genotoxic effect also appears to be low, as effects were not reported in the *in vitro* tests concentrations up to those causing cytogenicity or precipitation.

Finally, it is noted that sulfur is an essential element, that it is used in several applications leading to high exposure, albeit with no reporting of genotoxic effects from humans.

Assessment and comparison with the classification criteria

Considering that the *in vitro* mammalian cell gene mutation test confirmed the negative results from the other *in vitro* tests and having regard to the knowledge on the low systemic toxicity of the substance, the DS concluded that sulfur does not have a genotoxic potential and thus should not be classified.

RAC agrees the with the DS conclusion not to classify sulfur for Germ cell mutagenicity.

RAC agrees that sulfur is unlikely to have a systemic mutagenic effect given its nature as an essential element, and as its widespread use in pharmaceutical products and in food has not led to reporting of concern for genotoxic effects, and given that the *in vitro* assays were negative. RAC notes that the negative *in vivo* micronucleus tests are unreliable as none of them were demonstrated to have reached the bone marrow, and no other organs were investigated. RAC considers that a slight potential for sulfur to be capable of inducing a site-of contact genotoxic effect exists, but that this potential is low, given the consistently negative results of the *in vitro* studies.

Therefore, RAC concludes that based on the data available, including the recent *in vitro* mammalian cell gene mutation test, **sulfur does not warrant classification for Germ cell mutagenicity**.

2.6.5 Summary of long-term toxicity and carcinogenicity [equivalent to section 10.9 of the CLH report template]

Table 46: Summary table of animal studies on long-term toxicity and carcinogenicity

Method, guideline, deviations[1] if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results - NOAEL/LOAEL - target tissue/organ - critical effects at the LOAEL	Reference
No relevant study			

Table 47: Summary table of human data on long-term toxicity and carcinogenicity

Type of data/report	Test substance	Relevant information about the study (as applicable)	Observations	Reference
No relevant human data				

Table 48: Summary table of other studies relevant for long-term toxicity and carcinogenicity

Type of study/data	Test substance	Relevant information about the study (as applicable)	Observations	Reference
No relevant study				

2.6.5.1 Short summary and overall relevance of the provided information on long-term toxicity and carcinogenicity

No long-term toxicity and carcinogenesis studies were conducted on sulfur.

A comprehensive search of scientific peer reviewed open literature on side effects of sulfur and plant protection products containing sulfur on humans was conducted in accordance with Article (8) of Regulation 1107/2009. To identify publications containing such information on side effects, the relevance and reliability of the literature published between January 2007 (more than 10 years before the date of the dossier submission) and mid of March 2018 (3.5 months before the date of dossier submission in June 2018) was assessed. No essential data relevant to health hazards of sulfur to humans were found in the open literature.

As agreed for the first approval of the active substance (EFSA, 2008), sulfur is generally regarded as safe for human exposure given the wide range of background exposure, its low acute and short-term toxicity and its non-genotoxic potential. In addition, it is an essential element needed at a high dose level. Therefore, it was considered unnecessary to require long-term and carcinogenicity studies with sulfur.

2.6.5.2 Comparison with the CLP criteria regarding carcinogenicity

Table 49: Compilation of factors to be taken into consideration in the hazard assessment

Species and strain	Tumour type and background incidence	Multi-site responses	Progression of lesions to malignancy	Reduced tumour latency	Responses in single or both sexes	Confounding effect by excessive toxicity?	Route of exposure	MoA and relevance to humans
Not applicable								

In the absence of long-term and carcinogenesis study, comparison with CLP criteria is not applicable.

2.6.5.3 Conclusion on classification and labelling for carcinogenicity

In accordance to the summary provided in 2.6.5.1, classification for carcinogenicity is not warranted for sulfur.

RAC evaluation of carcinogenicity

Summary of the Dossier Submitter's proposal

No information from animal studies or human data were available on this endpoint for sulfur, and no classification is therefore proposed.

Comments received during consultation

One MSCA supported the proposal not to classify sulfur for carcinogenicity, as no data were available.

Assessment and comparison with the classification criteria

No classification is warranted based on a complete lack of information in the dossier[12].

2.6.6 Summary of reproductive toxicity [equivalent to section 10.10 of the CLH report template]

2.6.6.1 Adverse effects on sexual function and fertility – generational studies [equivalent to section 10.10.1 of the CLH report template]

Table 50: Summary table of animal studies on adverse effects on sexual function and fertility – generational studies

Method, guideline, deviations[1] if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results - NOAEL/LOAEL (for sexual function and fertility, parents) - target tissue/organ - critical effects at the LOAEL	Reference
No relevant study			

Table 51: Summary table of human data on adverse effects on sexual function and fertility

Type of data/report	Test substance	Relevant information about the study (as applicable)	Observations	Reference
No relevant human data				

Table 52: Summary table of other studies relevant for toxicity on sexual function and fertility

Type of study/data	Test substance	Relevant information about the study (as applicable)	Observations	Reference
No relevant study				

2.6.6.1.1 Short summary and overall relevance of the provided information on adverse effects on sexual function and fertility – generational studies

No reproductive toxicity studies were conducted on sulfur.

[12] As agreed for the first approval of the active substance (EFSA, 2008), sulfur is generally regarded as safe for human exposure given the wide range of background exposure, its low acute and short-term toxicity and its non-genotoxic potential. In addition, it is an essential element needed at a high dose level. Therefore, it was considered unnecessary to require long-term and carcinogenicity studies with sulfur.

A comprehensive search of scientific peer reviewed open literature on side effects of sulfur and plant protection products containing sulfur on humans was conducted in accordance with Article (8) of Regulation 1107/2009. To identify publications containing such information on side effects, the relevance and reliability of the literature published between January 2007 (more than 10 years before the date of the dossier submission) and mid of March 2018 (3.5 months before the date of dossier submission in June 2018) was assessed. No essential data relevant to health hazards of sulfur to humans were found in the open literature.

As agreed for the first approval of the active substance (EFSA, 2008), sulfur is generally regarded as safe for human exposure given the wide range of background exposure, its low acute and short-term toxicity and its non-genotoxic potential. In addition, it is an essential element needed at a high dose level. Therefore, it was considered unnecessary to require reproductive toxicity studies with sulfur.

2.6.6.1.2 Comparison with the CLP criteria regarding adverse effects on sexual function and fertility

In the absence of reproductive toxicity study, comparison with CLP criteria is not applicable.

2.6.6.2 Adverse effects on development [equivalent to section 10.10.4 of the CLH report template]

Table 53: Summary table of animal studies on adverse effects on development

Method, guideline, deviations[1] if any, species, strain, sex, no/group	**Test substance, dose levels duration of exposure**	**Results** **- NOAEL/LOAEL (for parent, offspring and for developmental effects)** **- target tissue/organ** **- critical effects at the LOAEL**	**Reference**
No relevant study			

Table 54: Summary table of human data on adverse effects on development

Type of data/report	**Test substance**	**Relevant information about the study (as applicable)**	**Observations**	**Reference**
No relevant human data				

Table 55: Summary table of other studies relevant for developmental toxicity

Type of study/data	**Test substance**	**Relevant information about the study (as applicable)**	**Observations**	**Reference**
No relevant study				

2.6.6.2.1 Short summary and overall relevance of the provided information on adverse effects on development

Please refer to 2.6.6.1.1.

2.6.6.2.2 Comparison with the CLP criteria regarding adverse effects on development

Please refer to 2.6.6.1.2.

2.6.6.3 Adverse effects on or via lactation [equivalent to section 10.10.7 of the CLH report template]

Table 56: Summary table of animal studies on effects on or via lactation

Method, guideline, deviations[1] if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results - NOAEL/LOAEL - target tissue/organ - critical effects at the LOAEL	Reference
No relevant study			

Table 57: Summary table of human data on effects on or via lactation

Type of data/report	Test substance	Relevant information about the study (as applicable)	Observations	Reference
No relevant human data				

Table 58: Summary table of other studies relevant for effects on or via lactation

Type of study/data	Test substance	Relevant information about the study (as applicable)	Observations	Reference
No relevant study				

2.6.6.3.1 Short summary and overall relevance of the provided information on effects on or via lactation

Please refer to 2.6.6.1.1.

2.6.6.3.2 Comparison with the CLP criteria regarding effects on or via lactation

Please refer to 2.6.6.1.2.

2.6.6.4 Conclusion on classification and labelling for reproductive toxicity

In accordance to the summary provided in 2.6.6.1.1, classification for reproductive toxicity is not warranted for sulfur.

RAC evaluation of reproductive toxicity

Summary of the Dossier Submitter's proposal

No animal studies providing information on sexual function and fertility, developmental toxicity or lactation were available. There was also no information in the open literature

on human health effects of sulfur. Therefore, no classification is proposed for the endpoints related to reproductive toxicity.

Comments received during consultation

One MSCA supported the proposal not to classify for endpoints under reproductive toxicity due to lack of data.

Assessment and comparison with the classification criteria

RAC agrees with the DS that no classification should be applied to sulfur for sexual function and fertility, developmental toxicity or effect on or via lactation **based on a complete lack of information in the dossier[13].**

2.6.7 Summary of neurotoxicity

Table 59: Summary table of animal studies on neurotoxicity

Method, guideline, deviations if any, species, strain, sex, no/group	**Test substance, dose levels duration of exposure**	**Results: - NOAEL/LOAEL - target tissue/organ -critical effect at LOAEL**	**Reference**
No relevant study			

No neurotoxicity study was provided and is not required for the same reasons as described above (please refer to 2.6.5.1 and 2.6.6.1.1). Further, sulfur does not belong to chemical groups known to induce neurotoxicity and no concern was raised from any toxicity study.
In addition, no essential data relevant to health hazards including neurotoxic effects of sulfur to humans were found in a comprehensive search of scientific peer reviewed open literature according to Article (8) of Regulation 1107/2009.

2.6.8 Summary of other toxicological studies

2.6.8.1 Toxicity studies of metabolites and impurities

No study is available.

2.6.8.2 Supplementary studies on the active substance

No study is available.

[13] As agreed for the first approval of the active substance (EFSA, 2008), sulfur is generally regarded as safe for human exposure given the wide range of background exposure, its low acute and short-term toxicity and its non-genotoxic potential. In addition, it is an essential element needed at a high dose level. Therefore, it was considered unnecessary to require reproductive toxicity studies with sulfur.

2.6.9 Summary of medical data and information

Occupational medical surveillance of factory workers revealed no evidence of adverse effects, except several cases of eye and/or skin irritation and several cases of malaise due to incidental exposure during handling reported by the Occupational Medical and Health Protection department of a sulfur formulation site.

According to US-EPA Re-registration Eligibility Document (RED – 1991), eye and skin irritations were reported in people who handle 'Sulphur Dust' or come into contact with foliage during field work.
During an incident reported by the California Department of Food and agriculture, signs and symptoms experiences in six field workers who were exposed when a helicopter applied dusting sulfur to the vineyards in which they were working included eye irritation, runny noses, nausea, headache, throat irritation, cough and itching (Maddy & Edmiston 1988).
An US-EPA document (2009) reported incident information linked to the use of sulfur available in several human incident databases: the OPP Incident Data System (IDS), the American Association of Poison Control Centers (AAPCC) database, the California Pesticide Illness Surveillance Program (PISP) Incident Data and the National Institute for Occupational Safety and Health Sentinel Event Notification System for Occupational Risks (NIOSH SENSOR). The overall conclusion drawn by US-EPA was that, based on review of incident data from these databases, the risk posed to human health by sulfur appears low. Across the databases, the relative number of reported incidents was low, the severity of reported health effects was low, and for most databases the dermal, ocular and respiratory symptoms/health effects were reflective of the known irritating properties of sulfur.
The toxicovigilance programme of the French « Mutualité Sociale Agricole » which is the government body in charge of the social security and occupational surveillance of farmers reported 24 cases of health adverse effects related to sulfur exposure over the period 1997-2012, excluding all cases with concomittent exposure to other pesticides. Skin irritation (moderate to severe skin irritation with subsequent scaling), eye irritation (conjunctival irritation, corneal ulceration, lacrimation) and respiratory tract irritation (cough and upper airway irritation) were most frequently reported. Severe bronchospasm requiring hospital admission occurred in a farmer with a medical history of asthma. No skin sensitisation reactions were observed. Amongst the 24 reported cases, 15 were linked to exposure to wettable formulations (WG, WP) and 9 were linked to dust formulations (DP). Although the number of cases was low, it is noteworthy that skin findings were most predominantly observed with wettable formulations (n=14 out of 15) whereas respiratory findings were most predominantly reported for dust powder formulations (n=8 out of 9). Moreover, dust formulations were responsible of more ORL and ocular findings than wettable formulations.

No biological exposure indices have been validated for monitoring sulfur exposure in the occupational setting.

In relation to the use of sulfur as medication (keratolytic and mild antiseptic widely employed in the form of lotions in the treatment of acnea and superficial fungal infections), the reported side-effects included skin irritation as well as dermatitis following repeated application. Contact with the eyes, mouth, and other mucous membranes should be avoided (Reynolds *et al*., The Extra Pharmacopoeia, Martindale, 31st edition 1996).

Some reports of high, non-fatal ingested doses of sulfur can be found in the literature, resulting in metabolic acidosis and intoxication from excessive release of hydrogen sulfide. A man survived the ingestion of 60 g sulfur over 24 hours (Gosselin, et al., 1976) and a woman with kidney disease who ingested 250 g sublimed sulfur over 6 days survived, but developed lethargy, confusion and metabolic acidosis (Blum and Coe, 1977). No overt symptoms were reported by 6 healthy volunteers given 500 – 700 mg/day of colloidal sulfur for 10 days (Greengard and Woolley, 1940).

In one reference (Raanan *et al*., 2017) associations between residential proximity to elemental sulfur applications and respiratory symptoms and spirometry of children living in an agricultural community are examined. Poorer lung function (spirometry measurements) and higher odds of reported respiratory

symptoms and asthma medication use were found in 7-year old children living within 0.5 km and 1 km of elemental sulfur applications during the previous week, month and year. The RMS considers that, although some limitations were noted, this epidemiological study is sufficiently robust to be considered as a signal. In agreement with the study authors, it is considered that further studies would be beneficial in order to confirm or infirm these results in other study populations.

2.6.10 Toxicological end points for risk assessment (reference values)

Table 60: Overview of relevant studies for derivation of reference values for risk assessment

Species	Study (method/type, length, route of exposure)	Test substance	Critical effect	NOAEL	LOAEL	Cross reference
Wistar rat	28-day Oral gavage	Sulphur Dust	No adverse effect	1000 mg/kg bw/d	>1000 mg/kg bw/d	Ramesh E. (2005) 4264/05
Wistar rat	90-day Oral gavage	Sulfur technical	No adverse effect	1000 mg/kg bw/d	>1000 mg/kg bw/d	Malleshappa H.N. (2006) 4191/05
Wistar rat	90-day Oral gavage	Sulphur Dust	No adverse effect	400 mg/kg bw/d	1000 mg/kg bw/d	Zimmermann M.F. (2009) RF-5764.307. 031.08
Wistar rat	28-day Dermal	Sulfur technical	No adverse systemic effect Microscopically skin findings	1000 mg/kg bw/d 400 mg/kg bw/d	>1000 mg/kg bw/d 1000 mg/kg bw/d	Malleshappa H.N. (2006) 4190/05
Wistar rat	28-day Dermal	Sulphur Dust	No adverse systemic effect No adverse local effect	1000 mg/kg bw/d 1000 mg/kg bw/d	>1000 mg/kg bw/d >1000 mg/kg bw/d	Zimmermann M.F. (2009) RF-5764.327. 002.08

As agreed during the first peer review of the active substance (EFSA, 2008), sulfur is generally regarded as safe for human given the wide range of background exposure and its low acute and short term toxicity as well as its lack of genotoxicity. At the same time, sulfur is an essential element required at high dose levels.

Overall, considering that sulfur is an essential element needed at high dose levels, the wide background exposure levels of sulfur, the low additional burden originating from crop protection uses of sulfur as well as the toxicological properties of sulfur, setting of an ADI or other toxicological reference values is not required. This is in agreement with the results of the 1st EU review (EFSA, 2008) and evaluations of other competent authorities. The RED issued by the US-EPA states that "*as sulphur is generally recognized as safe, no dietary risk assessment was performed*" (US-EPA, 1991a[14]). In addition, the European Agency for the Evaluation of Medicinal Products, Veterinary Medicines and Inspections issued in 2003 a safety assessment for sulfur used as a medicine in food producing animals and stated that "*the allocation of an ADI for sulphur is considered inappropriate*"[15] [EMEA, 2003].

For the same reasons and considering the low acute toxicity of sulfur, an acute reference dose (ARfD) is also not required.

[14] US-EPA, 1991a: Re-registration Eligibility Document (RED), Office of Pesticide Programs, PB92-114453 (540/RS-92-161, May 1991)

[15] EMEA, 2003. www.emea.eu.int

The same applies to the acceptable operator exposure level (AOEL) and the Acute Acceptable Operator Exposure Level (AAOEL). Instead, as proposed during the first EU peer review, exposure might be assessed against the average sulfur background level (24 mg/kg bw/day) (see below). Any assessment of acute exposure levels is not required due to the low acute toxicity of sulfur.

Therefore, it is proposed to maintain the conclusion of the first EU review on the toxicological reference values summarised in the EFSA Scientific Report (2008) and confirmed in the EC review report (SANCO/2676/08-final, 2012) *i.e.* not to set an ADI, ARfD and AOEL for sulfur. The same applies to the AAOEL, a new endpoint requested by Regulation (EC) No 1107/2009. For an essential element as sulfur, exposure is evaluated against background levels.

2.6.10.1 Toxicological end point for assessment of risk following long-term dietary exposure – ADI (acceptable daily intake)

As agreed during the first EU review (EFSA, 2008), considering that sulfur is an essential element needed at high dose levels, the wide background exposure levels of sulfur, the low additional burden originating from crop protection uses of sulfur as well as the low toxicity profile of sulfur (low acute and short term toxicity as well as lack of genotoxicity), setting of an ADI is not required.

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

As agreed during the first EU review (EFSA, 2008), considering that sulfur is an essential element needed at high dose levels, the wide background exposure levels of sulfur, the low additional burden originating from crop protection uses of sulfur as well as the low toxicity profile of sulfur (low acute and short term toxicity as well as lack of genotoxicity), setting of an ARfD is not required.

2.6.10.3 Toxicological end point for assessment of occupational, bystander and residents risks – AOEL (acceptable operator exposure level)

As agreed during the first EU review (EFSA, 2008), considering that sulfur is an essential element needed at high dose levels, the wide background exposure levels of sulfur, as well as the low toxicity profile of sulfur (low acute and short term toxicity as well as lack of genotoxicity), setting of an AOEL is not required.

Instead, as proposed during the first EU peer review, exposure might be assessed against the average sulfur background level.

Sulfur is naturally present and abundant in food where it can be found in the form of sulfates, free amino-acids (cysteine and methionine, the latter one is essential for human organisms), proteins and vitamins (i.e. vitamin B1 – thiamine, vitamin B7 - biotin). When applied to plants or when ingested by animals, elemental sulfur is transformed mainly into sulfate and proteins.

As evaluated in the Residues section, different values of estimated intake of sulfur through food consumption (diet and drinking water) could be proposed and are summarised in the following table.

Table 61: Summary of dietary intake data

Source	Intake expressed as “total sulfur” (mg/kg bw/d)
U.S, National Academy of Medicine, 2005	18.1 to 30.6, mean of 24
Expert Group on Vitamins and Minerals, 2003	167
Ingenbleek, Y. 2003	18 (without drinking water)
PRIMo Rev 3.1 and Ingenbleek, 2003	3.12 to 48.1 (without drinking water) 56.13 max (with drinking water)

1/ US National Academy of Medicine, 2005

According to the US National Academy of Medicine (2005), the daily consumer intake of sulfur via diet and drinking water can be estimated to be between 3.25 and 5.5 g per person and day (expressed as sulfate equivalent) with an average sulfate intake of 4.4 g/pers/d. Adjusting this value by the molecular weights (MW) of sulfate (96.1 g/mol) and sulfur (32.1 g/mol), this average intake of sulfate equivalents corresponds to an average intake of total sulfur of:

- 4.4 g/pers/day x (32.1 [MW_{sulfur}] / 96.1 [$MW_{sulfate}$]) = 1.4697 g/pers/day;
  rounded to two significant figures = **1.5 g/pers/day of sulfur**
- *converted to a body weight of 60 kg*
  (1.4697 x 1000 mg/pers/day) / 60 kg bw = 24.495 mg/kg bw/d;
  rounded to two significant figures = **24 mg/kg bw of sulfur**

It is noted that 1.6 g/pers/day and 26 mg/kg bw/d were set in the 1st EU review, probably due to minor rounding errors.

The US National Academy of Medicine provides an estimate for nearly all relevant dietary sulfur sources, *i.e.* (i) dietary organic sulfur containing compounds (includes methionine and cysteine) (ii) sulfate in drinking water and beverages and (iii) inorganic sulfate in food. The estimated total intake of sulfur expressed as sulfate equivalent is between 3.25 and 5.5 g per person and day corresponding to a sulfur intake of **18.1 – 30.6 mg sulfur/kg bw/d** for a 60 kg model person.

Table 62: Estimated total daily intake of sulfate equivalents and total sulfur of an adult (US National Academy of Medicine, 2005)

Source	**Concentration in source**	**Daily intake of sulfate equivalents from source**	**Daily intake of**	
			Sulfate equivalents (g per pers./d)	**Total sulfur (mg/kg bw/d)[b]**
Dietary organic sulfur containing compounds (includes methionine and cysteine)	0.7 g per g of sulfur amino acids	Average protein intake is ≈ 100 g/d which provides ≈ 4 g of sulfur amino acids	2.8	16
Sulfate in drinking water and beverages	0.1–0.5 g/L of fluid	2.6 L[a]	0.26 – 1.3 Average = 0.78	1.4 – 7.2 4.3
Inorganic sulfate in food	Varies	2-3 kg	0.2 – 1.5 Average = 0.85	1.1 – 8.4 4.7
Estimated total sulfate			3.25 – 5.55 Average = 4.40	18 – 31 24

[a] Estimated intake of drinking water and beverages for men and women

[b] Calculated with the data for sulfate equivalents in consideration of a body weight of 60 kg and using the equation: Total sulfur (mg/kg bw/d) = Sulfate equivalents (g per pers./d) x 32.1/96.1 ($MW_{sulfate}/MW_{sulfur}$) x 1000/60 (kg bw); results rounded to two significant figures

2/ Expert Group on Vitamins and Minerals, 2003

In a statement of the Expert Group on Vitamins and Minerals, 2003, the sulfur intake via food was estimated to be 10 g sulfur per day which corresponds to 167 mg/kg bw/d for an adult of 60 kg body weight.

3/ Published paper Ingenbleek, 2006

Ingenbleek 2006 calculated the sulfur contents in a range of plant and animal foodstuff as the sum methionine and cysteine content. Based on these data, a dietary intake of 1.1 g sulfur per person and day from the consumption of the sulfur amino acids in food corresponding to 18.3 mg sulfur/kg bw/d for a model person of 60 kg bodyweight was deduced as a rough estimate, however without considering sulfur (as sulfate) in drinking water or inorganic sulfate in food.

4/ PRIMo calculations

Databases of UK and Australian composition of foods (updated respectively in 2014 and in 2019) were used with PRIMo rev.3.1 model in order to estimate the natural exposition to sulfur through food. Data coming from paper of Ingenbleek, Y. 2003 were also considered, in particular for cereal grains. Estimated intakes of sulfur ranges from 3.12 mg/kg bw/d for PL general to maximum of 48.1 mg/kg bw/d for NL toddler with the highest contribution of milk. It is noted that sea food, which is known for high sulfur content, was not considered. Thus, the true amount of total sulfur taken up with food will be considerably higher than these estimated levels. It is noted that exposure via drinking water is not considered in the model. Based on data about sulfur content given in the paper of Ingenbleek, Y. 2003, the mean intake calculated for drinking water is 1.78 mg/kg bw/d for adult, 5.35 mg/kg bw/d for children and 8.03 mg/kg bw/d for infant. Therefore, taking into account all data and calculations presented above, the maximum intake calculated for sulfur is 56.13 mg/kg bw/ d for NL toddler.

Overall, the intake of total sulfur estimated by the US National Academy of Medicine (2005) is in good agreement with the results of the PRIMo dietary exposure calculations and the data of Ingenbleek (2006), however worst case for use as reference background compared to the estimate of the Expert Group on Vitamins and Minerals (2003). Since the US National Academy of Medicine (2005) paper provides estimates for nearly all relevant dietary sulfur sources including drinking water, this reference is considered as key report for sulfur dietary background level.

Considering the wide range of natural dietary sulfur exposure with maximum estimated levels of 167 mg/kg bw/d, the low toxicity of sulfur and the fact that sulfur is an element essential for human health, the use of an average background level of 24 mg sulfur/kg bw/d as surrogate reference value is sufficiently protective. Any additional safety margins, such as the use of minimum dietary exposure levels, is not warranted.

It is noted that the same database was used to set the background level of sulfur during the 1st EU review, resulting in a value of 26 mg/kg bw/d, probably due to minor rounding errors.

2.6.10.4 Toxicological end point for assessment of occupational, bystander and residents risks – AAOEL (acute acceptable operator exposure level)

As proposed for the AOEL, considering that sulfur is an essential element needed at high dose levels, the wide background exposure levels of sulfur, as well as the low toxicity profile of sulfur (low acute and short term toxicity as well as lack of genotoxicity), setting of an AAOEL is not required.

Furthermore, any assessment of acute exposure levels is not required due to the low acute toxicity of sulfur.

2.6.11 Summary of product exposure and risk assessment

Non-dietary exposure and risk assessments were performed for all population groups likely to be exposed as a result of the application of ‘Sulfur 80% WG’ and ‘Sulphur Dust’ according to the critical GAP uses of these products intended for the renewal approval application.

As already concluded in the first EU review of sulfur and confirmed by the evaluations of this supplementary dossier, setting of an AOEL or other toxicological reference values (see above) is not required. For an essential element like sulfur, it is more appropriate to assess non-dietary and dietary exposure of humans against background levels.
As such, exposure for risk assessment is compared to sulfur background level of 24 mg/kg/day (see Section 2.6.10.3) established based on consumer diet and drinking water

All exposure estimates were performed according to EFSA Guidance (2014)[16]. Acute non-dietary exposures assessments were not conducted since not required.

General input parameters for the EFSA calculator

So far relevant for the assessment, the default dislodgeable foliar residue of 3 µg/cm² of foliage/kg a.s. applied, allocation of sulfur as low volatile substance, and standard buffer strips of 5 m for grapes or 2-3 m for cereals were considered in the model. Assessments were made for an adult of 60 kg body weight and a child (resident/bystander) of 10 kg body weight.

'Sulfur 80% WG'

Dermal absorption

In the 1st EU review, a default dermal absorption rate of 10 % for the concentrate and the in-use dilution was agreed, which is confirmed as very conservative value by human data from the public domain, submitted and evaluated in this supplementary dossier. This rate was considered in all non-dietary exposures assessments for 'Sulfur 80% WG'.

Critical GAP uses

Exposure estimates were made for the following cGAPs:

Grapevine: 10-fold application of a maximum application rate of 10.0 kg a.s./ha with an interval of 7 days, a minimum spray volume of 200 L water/ha and vehicle-mounted foliar spraying to high crops.

Cereals: 4-fold application of a maximum application rate of 8.0 kg a.s./ha with an interval of 7 days, a minimum spray volume of 200 L water/ha and vehicle-mounted broadcast foliage directed boom spraying to low crops.

'Sulphur Dust'

Dermal absorption

A new *in vitro* dermal absorption study with 'Sulphur Dust' was performed using human skin.
Analysis of study results applied recommendations from EFSA Guidance on dermal absorption (EFSA, 2017)[17]. According to the latter guidance, variability within results should be considered by calculating the upper limit of the 95% confidence interval of the mean absorption value. This upper limit relies on Student's t distribution at n-1 degrees of freedom where n is the number of replicates. For 'Sulphur Dust' 8 replicates were used, and data from preparation II showed that the mean absorption value is 1.25, standard deviation is 0.64. The Student's t distribution value for 8-1 degrees of freedom is 2.36. The dermal absorption value is $1.25 + (2.36 * (0.64/\sqrt{8})) = 1.8\%$
This value of 1.8% was used for risk assessment

Critical GAP use

Exposure estimates were made for the following cGAPs:

Grapevine: 5 applications of a maximum application rate of 29.55 kg a.s./ha with an interval of 7 days between application and vehicle-mounted foliar spraying to high crops.

[16] EFSA Guidance (2014). Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products. EFSA Journal 2014;12(10):3874, 55 pp., doi:10.2903/j.efsa.2014.3874
[17] EFSA Journal 2017;15(6):4873 doi:10/2903/j.efsa.2017.4873

2.6.12 Operators

'Sulfur 80% WG'

The estimated potential exposure is far below the average background level of sulfur for both critical GAP uses (grapevine and cereals: 2.32% and 1.41% of average sulfur background level, respectively) in consideration of work wear covering arms, body and legs. Thus, it is concluded that the risk for the operator using 'Sulfur 80% WG' is acceptable.

'Sulphur Dust'

Raw data from Garofani operator study (KCP 7.2.1/01) were analysed and processed. As such, operator systemic exposure considered both dermal and inhalation routes data. Great variability was observed in calculated systemic exposure from 0.794 to 4.872 mg/kg/day i.e. by a 6-fold factor. Based on EFSA Guidance on uncertainty analysis in scientific assessments[18], RMS applied bootstrap resampling. From the obtained bootstrap distribution a conservative upper distribution limit of the 95% confidence interval of the mean was used. This upper confidence limit value is 3.61 mg/kg/day (without PPE). This estimate of 3.61 mg/kg/day for operator systemic exposure represents 15.04% of the background level of 24 mg/kg/day. It is concluded that Sulphur Dust operator exposure is acceptable

2.6.13 Bystander and resident exposure

'Sulfur 80% WG'

Resident exposure (child and adult) is clearly below the average background level for sulfur for all exposure groups and pathways assessed (all pathways: grapevine, child / adult: 5.15% / 2.79% of average sulfur background level; cereals, child / adult: 1.86% / 0.90% of average sulfur background level). It is concluded that the risk for residents during and after application of 'Sulfur 80% WG' is acceptable. Since the exposure assessments for residents cover bystander exposure, an acceptable risk for bystanders is also concluded.

'Sulphur Dust'

Resident exposure (adult and child) was estimated based on data available from Garofani operator study (KCP 7.2.1/01), in which resident/bystander study is nested considering dust residues on t-shirts. RMS additionally considered inhalation data from the operator study. Although the study didn't include the use of mannequins arranged at different distances from the application site, data were considered sufficiently robust to be used (number of replicates, details available in the study report etc…). Variability was observed in calculated systemic exposure for both children and adults. Based on EFSA Guidance on uncertainty analysis in scientific assessments[19],RMS applied bootstrap resampling procedure. From the obtained bootstrap distribution a conservative upper distribution limit of the 95% confidence interval of the mean was derived. These upper confidence limit values are 2.33 and 9.14 mg/kg/day respectively for adults and children, i.e. 9.7% and 38.1% of the background level of 24 mg/kg.day. It is concluded that exposure for residents during and after application of 'Sulphur Dust' is acceptable. Since the exposure assessments for residents cover bystander exposure, an acceptable risk for bystanders is also concluded.

2.6.14 Workers

'Sulfur 80% WG'

For the assessment of worker exposure in grapevine, 8 hours/day of hand harvesting and in cereals, 2 hours/day for inspection and irrigation were considered as proposed by the model. Transfer coefficient of 10100 cm^2/person/h and 1400 cm^2/person/h were used, also provided as default by the model for grapes and cereals, respectively.

[18] EFSA Journal 2017, 2018;16(1):5123 doi: 10.2903/j.efsa.2018.5123
[19] EFSA Journal 2017, 2018;16(1):5123 doi: 10.2903/j.efsa.2018.5123

The estimated exposure is below the average background level for sulfur in consideration of work wear covering arms, body and legs assessed (grapevine: 90.36%; cereals: 1.49% of average sulfur background level, respectively). It is concluded that the risk for workers re-entering vineyards for hand harvesting or cereals for inspection and irrigation after application of 'Sulfur 80% WG' is acceptable.

'Sulphur Dust'
For worker exposure, the working duration was considered to be 8 hours / day (hand harvesting for inspection and irrigation) and a transfer coefficient of 10100 cm2/hour was for covered worker (EFSA, 2014[20]). DFR and DT50 values were calculated based on data from Garofani study (KCP 7.3.1/01 and 7.3.1/02). This study investigated sulphur grapevine foliar residues in 3 differents fields in Northern Italy, over time with 3 measures performed at each timepoint. Variability was observed in foliar residues as well as in DT50. Based on EFSA Guidance on uncertainty analysis in scientific assessments[21], RMS applied bootstrap resampling procedure to estimate DFR and DT50. From the obtained bootstrap distribution a conservative upper distribution limit of the 95% confidence interval of the mean was derived for DFR. The upper confidence limit value is 15.23 µg/cm2 i.e. 0.54 µg/cm2/kg AS/ha, which is a conservative value. For DT50 the median of 12.6 days, conservative too since the resulting fitting curve covers the huge majority of measurements. For grapevine outdoor uses, worker exposure relates only to dermal route (EFSA, 2014) and the resulting worker exposure is 1.034 mg/kg/day i.e.4.31% of the background level of 24 mg/kg/day.

It is concluded that the risk for workers re-entering vineyards for hand harvesting, for inspection and irrigation after application of 'Sulphur Dust' is acceptable.

2.7 RESIDUE

2.7.1 Summary of storage stability of residues

Taking into consideration the stability of the molecular structure of the sulphur molecule (S8), its inactivity towards oxidising or reducing substances and the very low temperature of storage of the treated and untreated samples, ca. -20°C, it is considered that it is not necessary to carry out storage stability studies with crops containing residues of sulphur.

2.7.2 Summary of metabolism, distribution and expression of residues in plants, poultry, lactating ruminants, pigs and fish

Elemental sulphur (S8) exists naturally in the environment. The top 15 cm of agricultural soils often contain a concentration of total sulphur ranging from 50 to 1000 mg of sulphur per kg of soil.
Sulphur is an essential element for plant nutrition. Plants absorb sulphur from the leaf or from roots as sulphate ion, formed from the oxidation, chemical or microbial, of elemental or other forms of sulphur in the soil. Sulphur and its derivatives take part in the well-known natural process described as 'the sulphur cycle'.
Elemental sulphur applied to the target plants and any sulphur that consequently falls on the soil would therefore amount only as a small supplement to the reservoir of sulphur that already exists in the plants and in the soil.

A metabolism study with radiolabelled elemental sulphur (35S) in wheat showed that less than 2 % of sulphur was taken up by the leaves of higher plants. This sulphur is metabolised to sulphate ions and incorporated as natural organic compounds such as cystein, methionine and glutathion. It is not possible to distinguish between natural sulphur compounds and the sulphur linked to the treatment of the plants.

[20] EFSA Journal 2014 ;12(10):3874
[21] EFSA Journal 2017, 2018;16(1):5123 doi: 10.2903/j.efsa.2018.5123

For livestock, no metabolism studies are submitted. Elemental sulphur is commonly known to be used as feed supplement for ruminant for the rumen microbial synthesis of amino acids and vitamins. Moreover, EMEA stated that residues in animal tissues from sulfur administration could not be regarded as being of any concern, in terms of human health.

2.7.3 Definition of the residue

The residue definition for risk assessment was set as the parent compound elemental sulphur (S^8). No residue definition was set for livestocks.

2.7.4 Summary of residue trials in plants and identification of critical GAP

Table 63: Critical representative GAP uses of 'Sulfur 80% WG'and Sulphur Dust' considered for AIR

Use-No.	**Crop & regulatory zone**	**Pests or Group of pests controlled**	**Application**					**Application rate**		**PHI (days)**
			Formulation	Method / Kind	Timing / Growth stage of crop	Max. number a) per use b) per crop & season	Min. interval between applications (days)	kg as/ha a) max. rate per appl. b) max. total rate per crop/season	Water (L/ha) min / max	
3 (CP1)	Cereals (wheat, barley, oat, rye, triticale) (NNNGG) N-, C-, S-EU	Powdery mildew ERYSGR	WG	broadcast foliage directed boom spray, vehicle-mounted	Post-emergence, crop BBCH 15-69	a) 4 b) 4	7	a) 8.0 b) 32.0	200-400	35
1&2 (CP1)	Grapevine (wine and table grapes) (VITVI *Vitis vinifera*) N-, C-, S-EU	Powdery mildew UNCINE and Erineum leaf mite ERPHVI	WG	Foliar spray, vehicle-mounted	Post-emergence, crop BBCH 05-81	a) 10 b) 10	7	a) 10.0 b) 100	200-1000	28
1 (CP2)	Grapevine (wine and table grapes) (VITVI) C-EU, S-EU	Powdery mildew UNCINE	DP	Foliar dust	Post-emergence, crop BBCH 15 to 89	a) 5 b) 5	7	a) 29.55 b) 147.75	0	5

Residue trials in northern and southern Europe (Germany and France) were conducted with the 80% WG formulation on three different crops: wheat (2 NEU trials), barley (2 NEU trials) and grapes (6 NEU and 2 SEU trials). A second formulation, dry powder (DP) was also used on grape in both zones (14 SEU trials and 2 NEU trials).
For WG product, regarding cereals uses, trials were conducted at the following GAP: 2 applications at 7.8 kg/ha, BCH 59-71 with a PHI of 32-35 days and residues of sulphur active substance on/in cereal

grain were found to be at non-detectable levels (LOQ = 1 mg/kg) at PHI of 35 days for all trials. The level of elemental sulphur found in cereal straw was up to 65 mg/kg.
For grapes, no trials were carried out in accordance with critical representative GAP (10 applications at 10 kg S^0/ha performed until BBCH 81 with a PHI of 28 days). Considering the data provided (most critical GAP of trials is 7 or 8 applications at 10 kg S^0/ha), the residues measured on/in grapes were at 2.8 -10.7 mg a.s./kg at PHI of 28 days.
For DP products applied on grapes at a dose rate of 25-32 kg/ha, residues were in a range of 7.43 to 154 mg/kg 5-7 days after the last treatment.

Regarding guideline requirements, as cereals and grapes are major crops in both zones of Europe, data provided should be considered as insufficient. Indeed, for cereals, only 4 NEU trials are available. Furthermore, trials are conducted with a GAP less critical than the intended cGAP for cereals (2 applications performed instead of four). For grapes, trials are also not sufficient for WG formulation: only 6 NEU and 2 SEU trials have been provided with a number of applications less critical than intended one As no Toxicological Reference Values are required for Sulphur, no consumer risk is expected. Therefore residue trials are deemed unnecessary. Pending on inclusion of Sulphur at Annex IV of Regulation 396/2005, complementary data should not be required.

2.7.5 Summary of feeding studies in poultry, ruminants, pigs and fish

The highest residue level found in wheat straw was 65 mg/kg. Highest intake calculated for sheep was 1.61 mg/kg bw/d. Calculated dietary burden is above the threshold level of 0.04 mg/kg bw/d in the diet for all species that would justify livestock feeding studies in ruminants. However, it was demonstrated that elemental sulphur is rapidly metabolised in sulphate, amino acid and proteins that are incorporated into the natural pool of sulphur compounds in the animal. It should not be possible to quantify these producst or elemental sulphur in these natural conditions. Livestock's feeding studies are therefore not required

2.7.6 Summary of effects of processing

One study demonstrated that elemental sulphur found in grapes is not transferred to wine. The levels of elemental sulphur in wine were below the LOQ, however sulphur treatment of the grapes clearly increased the total level of sulphur in wine; suggesting that elemental sulphur is transformed during the wine making process, certainly into sulphate and sulphite.

2.7.7 Summary of residues in rotational crops

The route of degradation of sulfur in soil was considered satisfactorily addressed by an open literature review. There is a natural cycle of oxidation and reduction reactions, which transform elemental sulfur into both organic and inorganic products.

Plants absorb sulfur via the roots as sulfate ions ($SO4^{2-}$), formed by chemical or microbial oxidation of elemental sulfur or other forms of sulfur in the soil. In the plant, sulfate is reduced to sulphide, and subsequently incorporated in various sulfur-containing organic molecules, including plant proteins. This is a naturally driven process, and therefore the use of elemental sulfur as a plant protection product is not deemed to lead to any relevant residues in rotational crops.

2.7.8 Summary of other studies

None.

2.7.9 Estimation of the potential and actual exposure through diet and other sources

2.7.9.1 General considerations about toxicity of sulfur

During the first peer review of sulfur, no toxicological reference values were set due to the low toxicity of sulfur (EFSA, 2008).

Among derived forms of elemental sulfur, only sulfur-dioxide and sulfites are known to have a toxicity leading to establish an ADI of 0.7 mg/kg bw/d (initially proposed by JECFA and also considered in the frame of Re-evaluation of sulfur dioxide-sulfites, EFSA, 2016). This ADI is allocated for sulfur dioxide (E 220), sodium sulfite (E 221), sodium bisulfite (E 226), calcium bisulfite (E 227) and potassium bisulfite (E 228) commonly called "sulfites".
These sulfites are authorised as food additive in the European Union in accordance with Annex II and Annex III to Regulation (EC) n° 1333/2008).
For crops, it was concluded that the occurrence of sulfites is limited and is the result of sulfate reduction. Crops have their own detoxification system using sulfate oxidase enzyme.
Regarding sulfur, no international recommendation exists for human daily intakes. Therefore, based on available publications submitted by the applicant (see points 6.9.1, 6.9.2 and 6.9.3) or found by the Rapporteur Member State, different values of estimated intake of sulphur through food consumption are summarized in table 70. It should be highlighted that total sulphur is rarely measured in foods and it is difficult to have a realistic background level of sulphur since this element is analysed through other nutrients as amino acids (cysteine and methionine) and vitamins (B1: thiamin and B8: biotin) (table 71).

Table 64: Summary of dietary intake data provided by applicant

Source	Annex point	"Form of sulphur"	Intake expressed as "total sulphur" (mg/kg bw /d)
U.S, National Academy of Medecine	KCA 6.9.1	Sulfate	24
Expert Group on Vitamins and Minerals, 2003	KCA 6.9.2	Sulfur	167
Ingenbleek, Y. 2003	KCA 6.9.3	Sulfur	16.6 (based on the mean of sulphur content from a list of commodities)

Table 65: Summary of dietary reference of other nutrients containing sulfur (data not provided by applicant and given for information)

Source	"Form of sulphur"	Dietary reference value
Anses Opinion, PNNS, 2016	Thiamin (B1)	1.5 mg/d
EFSA, 2014	Biotin (B8)	40 µg/d
Kurpad and al, 2004[22]	Methionine	12.6 mg/kg bw/d
Kurpad and al, 2003[23]	Cysteine	Max 12 mg/kg bw/d

[22] Kurpad AV, Regan MM, Varalakshmi S, Gnanou J, Lingappa A, Young VR. Effect of cystine on the methionine requirement of healthy Indian men determined by using the 24-h indicator amino acid balance approach. Am J Clin Nutr. 2004; 80:1526–35

[23] Kurpad AV, Regan MM, Varalakshmi S, Vasudevan J, Gnanou J, et al. Daily methionine requirements of healthy Indian men, measured by a 24-h indicator amino acid oxidation and balance technique. Am J Clin Nutr. 2003; 77:1198–205.

2.7.9.2 Estimation of exposure to sulphur via food and drinking water

As for the first EU review of sulphur, databases of UK and Australian composition of foods (updated respectively in 2014 and in 2019) were used with PRIMo rev.3.1 model in order to estimate the natural exposition to sulphur through food. Data coming from paper of Ingenbleek, Y.2003 were also considered, in particular for cereal grains.

When available, the most critical value between both databases and data from paper of Ingenbleek was chosen for each raw commodity listed in Appendix 1 of Regulation (EC) n°396/2005.
All selected values were expressed in total sulfur in mg/kg. Regarding data from Canadian database, informations were provided into a list of nutrients including proteins, sugar, mineral elements, vitamins and amino acids reported per 100g of food portion. Inputs used are reported in table 72.

Table 73 below gives results of estimated intake of total sulphur in food.

According to PRIMo calculations, estimated intakes of sulphur ranges from **3.12 mg/kg bw/d for PL general to maximum of 48.1 mg/kg bw/d for NL toddler with the highest contribution of milk**.
estimated intake of total sulphur in food.

Table 66: Input values for the intake estimation of total sulfur in food

RAW COMMODITIES			
Code number		**commodities**	**inputs to be paste in PRIMo (mg/kg)**
0110010	.	Grapefruits	180,319
0110020	.	Oranges	210,7
0110030	.	Lemons	0,4
0110040	.	Limes	0,3
0110050	.	Mandarins	130,3
0120010	.	Almonds	5401,9
0120020	.	Brazil nuts	1506,1
0120030	.	Cashew nuts	8726,6
0120040	.	Chestnuts	29
0120050	.	Coconuts	300,13
0120060	.	Hazelnuts/cobnuts	1304,7
0120080	.	Pecans	874,45
0120090	.	Pine nut kernels	1105,7
0120100	.	Pistachios	1606,1
0120110	.	Walnuts	6073,49
0130010	.	Apples	60,31
0130020	.	Pears	40,206
0130030	.	Quinces	5
0130040	.	Medlars	17

0130050	. Loquats/Japanese medlars	0,1
0140010	. Apricots	130
0140020	. Cherries (sweet)	7
0140030	. Peaches	100,05
0140040	. Plums	5
0151010	. Table grapes	8
0152000	. (b) strawberries	210,22
0153010	. Blackberries	160,214
0153030	. Raspberries (red and yellow)	120,402
0154010	. Blueberries	0,3
0154020	. Cranberries	11
0154030	. Currants (black, red and white)	33
0154040	. Gooseberries (green, red and yellow)	16
0154060	. Mulberries (black and white)	9
0161010	. Dates	23
0161020	. Figs	13
0161030	. Table olives	390
0161040	. Kumquats	0,37
0161060	. Kaki/Japanese persimmons	0,1
0162010	. Kiwi fruits (green, red, yellow)	160,2
0162030	. Passionfruits/maracujas	0,3
0163010	. Avocados	510,456
0163020	. Bananas	460,4
0163030	. Mangoes	150,6
0163040	. Papayas	13
0163050	. Granate apples/pomegranates	12
0163070	. Guavas	14
0163080	. Pineapples	3
0211000	. (a) potatoes	600,85
0212010	. Cassava roots/manioc	6
0212020	. Sweet potatoes	530,3
0212030	. Yams	14
0212040	. Arrowroots	2
0213010	. Beetroots	16
0213020	. Carrots	170,4

0213030	. Celeriacs/turnip rooted celeries	15
0213050	. Jerusalem artichokes	15
0213060	. Parsnips	420,842
0213070	. Parsley roots/Hamburg roots parsley	1,7
0213080	. Radishes	38
0213090	. Salsifies	22
0213100	. Swedes/rutabagas	170,5
0213110	. Turnips	200,4
0220010	. Garlic	0,9
0220020	. Onions	360,4
0220030	. Shallots	51
0220040	. Spring onions/green onions and Welsh onions	50
0231010	. Tomatoes	33
0231020	. Sweet peppers/bell peppers	34
0231030	. Aubergines/eggplants	170,522
0231040	. Okra/lady's fingers	30
0232010	. Cucumbers	11
0232020	. Gherkins	150
0232030	. Courgettes	500,4
0233010	. Melons	12
0233020	. Pumpkins	670,5
0233030	. Watermelons	0,21
0234000	. (d) sweet corn	1740,5
0241010	. Broccoli	1190,9
0241020	. Cauliflowers	500,4
0242010	. Brussels sprouts	630,9
0242020	. Head cabbages	280,5
0243010	. Chinese cabbages/pe-tsai	0,9
0243020	. Kales	1,1
0244000	. (d) kohlrabies	480,8
0251020	. Lettuces	210,322
0251030	. Escaroles/broad-leaved endives	26
0251040	. Cresses and other sprouts and shoots	170
0251060	. Roman rocket/rucola	0,7
0251070	. Red mustards	0,6
0252000	. (b) spinaches and similar leaves	187
0252010	. Spinaches	760,625

0254000	. (d) watercresses	100
0256020	. Chives	0,6
0256030	. Celery leaves	15
0256040	. Parsley	1,7
0256050	. Sage	7,54
0256060	. Rosemary	0,36
0256070	. Thyme	5,13
0256080	. Basil and edible flowers	0,4
0260010	. Beans (with pods)	1192
0260020	. Beans (without pods)	470,6
0260030	. Peas (with pods)	1203,1
0260050	. Lentils	1000
0270010	. Asparagus	47
0270030	. Celeries	15
0270040	. Florence fennels	0,3
0270050	. Globe artichokes	15
0270060	. Leeks	570,525
0270070	. Rhubarbs	8
0280010	. Cultivated fungi	260,685
0300010	. Beans	999
0300020	. Lentils	5665
0300030	. Peas	1808,63
0401010	. Linseeds	16,44
0401030	. Poppy seeds	8,54
0401050	. Sunflower seeds	13237,29
0401070	. Soyabeans	400
0500030	. Maize/corn	514
0500060	. Rice	538
0500090	. Wheat	621
0610000	. Teas	0,07
0620000	. Coffee beans	2301
1011000	. (a) swine	
1011010	. Muscle	2366
1012000	. (b) bovine	
1012010	. Muscle	2136
1012020	. Fat	0,46
1012030	. Liver	2397
1013000	. (c) sheep	
1013010	. Muscle	1901,32
1014000	. d) goat	
1014010	. Muscle	5910,9
1016000	. (f) poultry	
1016010	. Muscle	9990,608
1016020	. Fat	9990,608

1016030	. Liver	3,05
1017000	. (g) other farmed terrestrial animals	0
1017010	. Muscle	
1020000	. Milk	
1020010	. Cattle	2590
1030000	. Birds eggs	
1030010	. Chicken	7770
1050000	. Amphibians and Reptiles	0,7
1070000	. Wild terrestrial vertebrate animals	2,2
	Fish	2265

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Table 67: Estimated intake of total sulphur in food

SULFUR

Toxicological reference values

Input values

Details - chronic risk | Supplementary results - chronic

Details - acute risk | Details - acute risk assessment/adults

Comments:

Normal mode

Chronic risk assessment: JMPR methodology (IEDI/TMDI)

TMDI/NEDI/IEDI calculation (based on average food consumption)

MS Diet	Exposure (µg/kg bw per day)	Exposure (mg/kg bw per day)	Commodity/ group of commodities	Commodity/ group of commodities	Commodity/ group of commodities
NL toddler	48103,20	48,10	Milk: Cattle	Poultry Muscle/meat	Sunflower seeds
FR child 3 15 yr	40751,13	40,75	Eggs: Chicken	Poultry Muscle/meat	Milk: Cattle
ES child	37245,32	37,25	Poultry Muscle/meat	Eggs: Chicken	Milk: Cattle
RO general	35667,40	35,67	Sunflower seeds	Poultry Muscle/meat	Eggs: Chicken
NL child	33908,33	33,91	Milk: Cattle	Poultry Muscle/meat	Sunflower seeds
UK infant	33540,90	33,54	Eggs: Chicken	Milk: Cattle	Poultry Muscle/meat
GEMS/Food G07	33517,84	33,52	Poultry Muscle/meat	Sunflower seeds	Swine: Muscle/meat
DE child	33233,42	33,23	Eggs: Chicken	Poultry Muscle/meat	Milk: Cattle
GEMS/Food G10	32535,01	32,54	Poultry Muscle/meat	Sunflower seeds	Wheat
FR toddler 2 3 yr	31927,45	31,93	Milk: Cattle	Eggs: Chicken	Poultry Muscle/meat
GEMS/Food G15	31816,76	31,82	Poultry Muscle/meat	Sunflower seeds	Swine: Muscle/meat
GEMS/Food G08	31276,30	31,28	Poultry Muscle/meat	Sunflower seeds	Swine: Muscle/meat
DK child	29564,64	29,56	Eggs: Chicken	Poultry Muscle/meat	Swine: Muscle/meat
SE general	26965,65	26,97	Bovine: Muscle/meat	Eggs: Chicken	Milk: Cattle
UK toddler	26513,46	26,51	Eggs: Chicken	Milk: Cattle	Poultry Muscle/meat
GEMS/Food G11	26410,53	26,41	Poultry Muscle/meat	Swine: Muscle/meat	Potatoes
IE adult	22333,51	22,33	Poultry Muscle/meat	Sunflower seeds	Eggs: Chicken
GEMS/Food G06	21449,74	21,45	Poultry Muscle/meat	Wheat	Sunflower seeds
ES adult	20598,58	20,60	Poultry Muscle/meat	Eggs: Chicken	Swine: Muscle/meat
NL general	20397,66	20,40	Poultry Muscle/meat	Sunflower seeds	Eggs: Chicken
DE women 14-50 yr	16845,23	16,85	Milk: Cattle	Poultry Muscle/meat	Eggs: Chicken
DE general	16790,27	16,79	Milk: Cattle	Swine: Muscle/meat	Poultry Muscle/meat
FR adult	16463,14	16,46	Eggs: Chicken	Poultry Muscle/meat	Swine: Muscle/meat
FI adult	14713,58	14,71	Coffee beans	Potatoes	Wheat
FR infant	13597,43	13,60	Milk: Cattle	Poultry Muscle/meat	Eggs: Chicken
LT adult	13232,64	13,23	Poultry Muscle/meat	Eggs: Chicken	Swine: Muscle/meat
DK adult	12075,36	12,08	Eggs: Chicken	Poultry Muscle/meat	Swine: Muscle/meat
UK adult	11922,06	11,92	Poultry Muscle/meat	Eggs: Chicken	Bovine: Muscle/meat
PT general	11169,76	11,17	Sunflower seeds	Potatoes	Wheat
UK vegetarian	7766,39	7,77	Eggs: Chicken	Wheat	Milk: Cattle
IT toddler	6386,09	6,39	Wheat	Potatoes	Bananas
IE child	6153,30	6,15	Poultry Muscle/meat	Eggs: Chicken	Milk: Cattle
FI 3 yr	5846,87	5,85	Potatoes	Wheat	Bananas
FI 6 yr	4599,89	4,60	Potatoes	Wheat	Bananas
IT adult	4320,25	4,32	Wheat	Potatoes	Beans (with pods)
PL general	3124,33	3,12	Potatoes	Walnuts	Apples

Data about fish commodities sulphur content are also available. The most critical input is 2265 mg/kg for salmon (Ingenbleek, Y.2003). Even if data consumption for fish are reported in PRIMo rev3.1 model, excel sheet doesn't allow calculation for this commodity. Therefore, calculation was made using maximum consumption for fish (data found in PRIMo tab "chronic_consumption") x intake data for fish (i.e 2265 mg/kg), depending on the availability of data consumption on fish reported in PRIMo rev.3.1 model (for instance, no data were provided by the Netherlands).
For FR child, intake calculation is 1.57 mg/kg bw/d leading to a total intake of 42.32 mg/kg bw/d.

Regarding drinking water consumption, data about sulphur content are given in the paper of Ingenbleek, Y.2003.
Based on requirements of guidance document on the assessment of the relevance of metabolites in groundwater (doc SANCO/221/2000- rev.10), a tentative was made to estimate daily intake of sulphur via drinking water.
Calculations that were performed following dietary criteria are reported in the table below:

Table 68: Daily water consumptions and mean body weights

	Adults	**Children**	**Infants**
Daily water consumption (L)	2	1	0.75
Mean body weight (kg)	60	10	5

Results of intakes are presented in the table 75 below:

Table 69: Estimated sulphur intakes through water consumption

Brand name	country	intake of sulfate (mg/L)	equivalent total sulfur (mg/L)	daily intake (mg/kg bw/d)		
				adult	children	infant
Bru	Belgium	5	1,67	0,05566667	0,167	0,2505
Chaudfontaine		40	13,36	0,44533333	1,336	2,004
Spa Reine		4	1,336	0,04453333	0,1336	0,2004
Badoit	France	40	13,36	0,44533333	1,336	2,004
Bagatelle		1,8	0,6012	0,02004	0,06012	0,09018
Evian		32	10,688	0,35626667	1,0688	1,6032
Hepar		1,479	0,493986	0,0164662	0,0493986	0,0740979
Valvert		18	6,012	0,2004	0,6012	0,9018
Vichy		135	45,09	1,503	4,509	6,7635
Vittel		306	102,204	3,4068	10,2204	15,3306
Volvic		57	19,038	0,6346	1,9038	2,8557
Wattwiler		678	226,452	7,5484	22,6452	33,9678
Appolinaris	Germany	80	26,72	0,89066667	2,672	4,008
Falkenberg		698	233,132	7,77106667	23,3132	34,9698
Geroldsteiner		20	6,68	0,22266667	0,668	1,002
Tönisteiner		41,7	13,9278	0,46426	1,39278	2,08917
Voslauer		229	76,486	2,54953333	7,6486	11,4729
Cristallo	Italy	597	199,398	6,6466	19,9398	29,9097
Dolomiti		7,3	2,4382	0,08127333	0,24382	0,36573
San Pellegrino		444	148,296	4,9432	14,8296	22,2444
Aqua D'Or	Scandinavia	8	2,672	0,08906667	0,2672	0,4008
Voss		5	1,67	0,05566667	0,167	0,2505
Aproz		910	303,94	10,1313333	30,394	45,591
Arkina	Switzerland	8,8	2,9392	0,09797333	0,29392	0,44088
Aquella		842	281,228	9,37426667	28,1228	42,1842
Henniez		13	4,342	0,14473333	0,4342	0,6513
Decantae	UK	17,5	5,845	0,19483333	0,5845	0,87675
Glenlivet		4	1,336	0,04453333	0,1336	0,2004
Heartsease		15	5,01	0,167	0,501	0,7515
Highland Spring		6	2,004	0,0668	0,2004	0,3006
Hildon		4	1,336	0,04453333	0,1336	0,2004
Llandllyr		17	5,678	0,18926667	0,5678	0,8517
Ty Nant		3,2	1,0688	0,03562667	0,10688	0,16032

STMR intake (mg/kg bw/d)			Mean intake (mg/kg bw/d)		
adult	**children**	**infant**	**adult**	**children**	**infant**
0,2004	0,6012	0,9018	1,78429514	5,35288541	8,02932812
75 perc. Intake (mg/kg bw/d)			95 perc. Intake (mg/kg bw/d)		
adult	**children**	**infant**	**adult**	**children**	**infant**
1,503	4,509	6,7635	8,41234667	25,23704	37,85556

The mean intake calculated for drinking water is 1.78 mg/kg bw/d for adult, 5.35 mg/kg bw/d for children and 8.03 mg/kg bw/d for infant.

Therefore, taking into account all data and calculations presented above, **the maximum intake calculated for sulphur is 56.13 mg/kg bw/ d for NL toddler.**

RMS is aware that calculations made are probably overestimated. Nevertheless, RMS is of the opinion that information reported give a large scope of possible exposure of sulphur via food and drinking water and are a good way to compare exposure via agronomic uses of sulphur in a second time.

2.7.9.3 Dietary Exposure Calculations related to the intended uses of sulfur in agriculture

In order to compare natural exposure of sulphur via food and drinking water with agronomic uses intended in the frame of the renewal, PRIMo rev.3.1 model was also used.

Inputs data used to carry out exposure calculations are reported in the table below:

Table 70: Input values for the consumer exposure linked to the uses of elemental sulfur

Commodity	**Chronic exposure assessment**	
	Input value (mg/kg)	**Comment**
Wine grapes	19.635	STMR residue trials (see point B.7.3)
Table grapes	154	HR residue trials (see point B.7.3)
Cereals (wheat, barley, oat, rye and triticale)	1	STMR residue trials (see point B.7.3)

According to PRIMo calculations, estimated intakes of sulphur ranges from 0 mg/kg bw/d for FR infant to maximum of 0.24 mg/kg bw/d for NL toddler with the highest contribution of table grapes.

Therefore, exposure contribution through food and drinking water **is 234 times higher** than exposure linked to intended crops treated with elemental sulphur.

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European Food Safety Authority

SULFUR

Toxicological reference values

Input values

Details - chronic risk | Supplementary results - chronic | Details - acute risk | Details - acute risk assessment/adults

Comments:

Normal mode

Chronic risk assessment: JMPR methodology (IEDI/TMDI)

TMDI/NEDI/IEDI calculation (based on average food consumption)

MS Diet	Expsoure (mg/kg bw per day)	Commodity / group of commodities	Commodity / group of commodities	Commodity / group of commodities
NL toddler	0,24	Table grapes	Wheat	Rye
DE child	0,22	Table grapes	Wheat	Rye
GEMS/Food G06	0,17	Table grapes	Wheat	Wine grapes
NL child	0,16	Table grapes	Wheat	Rye
PT general	0,10	Wine grapes	Table grapes	Wheat
GEMS/Food G11	0,09	Table grapes	Wine grapes	Wheat
GEMS/Food G07	0,09	Table grapes	Wine grapes	Wheat
GEMS/Food G08	0,08	Table grapes	Wine grapes	Wheat
GEMS/Food G15	0,08	Table grapes	Wine grapes	Wheat
IE adult	0,07	Table grapes	Wine grapes	Wheat
RO general	0,07	Wine grapes	Table grapes	Wheat
FR child 3 15 yr	0,07	Table grapes	Wine grapes	Wheat
DE women 14-50 yr	0,07	Table grapes	Wine grapes	Wheat
FR adult	0,07	Wine grapes	Table grapes	Wheat
GEMS/Food G10	0,06	Table grapes	Wine grapes	Wheat
DE general	0,06	Table grapes	Wine grapes	Wheat
NL general	0,05	Table grapes	Wine grapes	Wheat
PL general	0,05	Table grapes	FRUIT AND TREE NUTS	
DK adult	0,05	Table grapes	Wine grapes	Wheat
UK toddler	0,04	Table grapes	Wheat	Wine grapes
DK child	0,04	Table grapes	Rye	Wheat
FI 3 yr	0,04	Table grapes	Wheat	Rye
UK adult	0,03	Wine grapes	Table grapes	Wheat
UK vegetarian	0,03	Wine grapes	Table grapes	Wheat
FI 6 yr	0,03	Table grapes	Wheat	Rye
IT adult	0,02	Table grapes	Wheat	Other cereals
IT toddler	0,02	Table grapes	Wheat	Other cereals
FI adult	0,02	Table grapes	Wine grapes	Rye
ES adult	0,02	Wine grapes	Table grapes	Wheat
ES child	0,01	Table grapes	Wheat	Wine grapes
IE child	0,01	Table grapes	Wheat	Oat
FR toddler 2 3 yr	0,01	Wine grapes	Wheat	Table grapes
UK infant	0,01	Table grapes	Wheat	Wine grapes
LT adult	0,00	Table grapes	Rye	Wheat
SE general	0,00	Wheat	Rye	
FR infant	0,00	Wheat	Wine grapes	Table grapes

2.7.10 Proposed MRLs and compliance with existing MRLs

Sulfur is currently included to the Annex IV of regulation 396/2005/EC which comprised active substances for which no MRL are required for the following reasons.

Sulfur occurs abundantly in nature in different forms. Sulfur is essential for growth and physiological functioning of plants, but may also negatively affect plant metabolism (e.g. air polluting sulfur gases). Against this background, extensive literature on function, uptake and metabolism of sulfur compounds in plants exist. It was also demonstrated that consumer exposure to the sulfur linked to use as PPP is considered as negligible compared to other uses in the food chain.
Furthermore, due to its low toxicity no ADI nor ARfD is set or proposed for this active substance.

According to guidance document on criteria for the inclusion of active substances into Annex IV of

regulation (EC) N° 396/2005 (SANCO/11188/2013, Rev. 2, September 2015[24]), if a compound is naturally occurring in food and if it has no identified hazardous properties, it is a candidate for inclusion in Annex IV of Regulation (EC) No 396/2005.
Consequently, in the framework of the renewal, it is proposed to maintain sulfur in the Annex IV of regulation 396/2005/EC.

2.7.11 Proposed import tolerances and compliance with existing import tolerances

Not relevant.

2.8 FATE AND BEHAVIOUR IN THE ENVIRONMENT

2.8.1 Summary of fate and behaviour in soil

Route of degradation (Vol. 3 B.8 (AS); Points B.8.2.1, and B.8.2.2)

As already concluded in the previous approval of the active substance Sulphur (EFSA, 2010), as long as sulfur cycle is well known, the route of sulfur 'degradation' in soil described by the literature review is sufficient and no further study is deemed necessary. Due to the absence of raw data, the studies are considered supportive to describe the overall behaviour of sulfur in the environment, as well as conditions (pH, temperature, …), that influenced sulfur fate.

Elemental sulfur occurs abundantly in nature, and is found in all the three environmental compartments (soil, water, air). It is stable under sterile conditions, but readily undergoes transformation through oxidative or reductive processes under aerobic or anaerobic conditions by specific microbial organisms to sulfate ions (SO_4^{2-}) or sulfites (-S-), respectively, both of which in turn are abundant in nature. The following figure presents the general sulfur cycle in the environment.

[24] European Commission, 2015. Guidance document on criteria for the inclusion of active substances into Annex IV of Regulation (EC) No 396/2005. SANCO/11188/2013-Rev.2, 14 September 2015.

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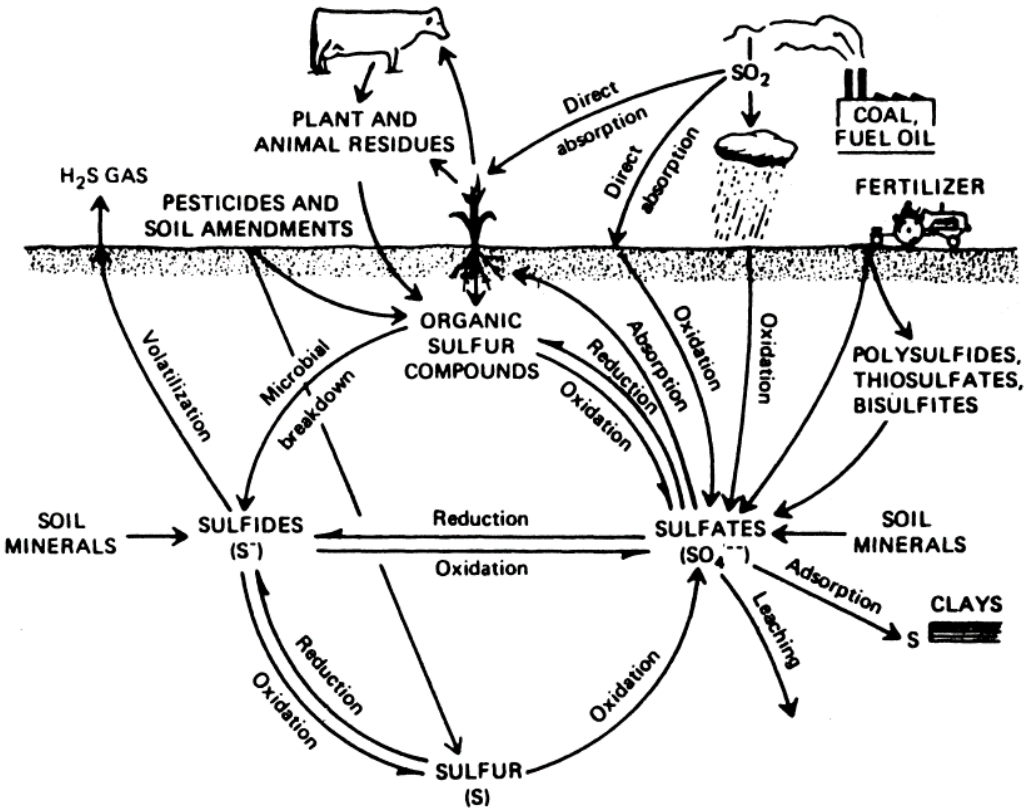

Figure B.8- 1: General sulfur cycle in the environment (from Stevenson and Cole, 1999; Vol. 3 B.8 (AS))

Overall, the processes (chemical and biological transformation, oxidation-reduction) that govern the behaviour of naturally occurring sulfur in the environment, will also govern the fate of sulfur added as a fungicide to the same environment.

Rate of degradation (Vol. 3 B.8 (AS); Point B.8.2.3)

The rate of oxidation of elemental sulfur is the process that determines the rate, at which sulfate is available to plants. In soils, oxidation of elemental sulfur is preceded by a short incubation period allowing the formulated granules to absorb moisture from the soil, and then disintegrate to release sulfur. Oxidation then proceeds quickly and smoothly, the kinetics being a function of temperature, soil pH, organic content of soil, and particle size of elemental sulfur. The oxidation rate of sulfur increases with the particle size of the elemental sulfur used, and with temperature.

It was concluded in the EFSA Scientific Report (2008) 221 (sulfur) that the available information only enables a qualitative assessment on the oxidation rates of elemental sulfur. The view of the Member State experts was that because of the complexity of the processes governing the oxidation rate of elemental sulfur and some deficiencies in the laboratory studies, including the lack of information on the method of calculation of the oxidation rates, the results of these studies should not be used quantitatively (i.e. derived "DT_{50}", *i.e.* transformation rate = time required for the oxidation of 50% of the applied elemental sulphur) in the exposure assessment. Consequently, no EU DT_{50} endpoint was agreed on aerobic soil transformation. As part of the renewal approval of the active substance sulphur, this conclusion is still valid.

Sulfur is not expected to be persistent in elemental form (due to its dissipation in soils), and therefore no accumulation of elemental sulfur in soil is expected to happen.

Mobility (Vol. 3 B.8 (AS); Points B.8.2.5 and B.8.2.6)

A study for the determination of sulfur adsorption to soil was submitted by the applicants. As long as this study was not valid due to technical problems, the notifier submitted an estimation of sorption constants using the empirical equation of Briggs (1981). As already specified for the European assessment for the previous approval of the active substance sulphur, no clear justification was given by the notifier for the choice of the selected equation for deriving Koc value. Therefore, the RMS used a number of available similar equations in order to determine the most conservative K_{om} and K_{oc} values, estimated from water solubility (16 µg/L; Please refer to Vol. 1, Point 2.2.1 and Vol. 3 B.2.5 for more detail). This led to a K_{oc} of 3615.3 L/kg, to be used for the risk assessment in the PEC calculations.

A lysimeter study was available, where a sandy loam soil was treated with bentonite/elemental sulfur mixture, micronized elemental sulfur, and ammonium sulfate applied in the solid form to the soil surface at 50 kg/ha. Additionally, atmospheric deposition of sulfur varied between 6.7-7.8 kg a.s./ha/year. The average annual rainfall for the three years was 615 mm. Results indicated that sulfate was highly mobile and prone to leaching under the experimental conditions, whereas the slow release characteristics of elemental sulfur led to smaller leaching losses. The second lysimeter study submitted by the notifier was not accepted by the RMS, but both reached to the same conclusion: very slow sulfur leaching from soil. Therefore, even if the laboratory study, due to the lack of experimental information, is considered as not acceptable, these results can be considered as confirmatory, and no further study is required. In conclusion, the RMS considers that there are no concerns for sulfur leaching to groundwater. However, RMS is concerned by the mobility of sulfates, degradation products of sulfur by oxidation, which are soluble in water, and highly mobile in soil. They therefore represent an issue for groundwater.

The experts agreed during PRAPeR Expert Meeting 57 (08 – 10 October 2008) and EFSA (EFSA Scientific Report (2008) 221, 1-70) that sulfur is not of concern for the contamination of groundwater, but that the potential for groundwater contamination for sulfates needed to be addressed, as they are highly mobile in soil. As part of the renewal approval of the active substance sulphur, this conclusion is still valid.

2.8.2 Summary of fate and behaviour in water and sediment [equivalent to section 11.1 of the CLH report template]

Sulfur is insoluble in water (maximum determined water solubility: 16 µg/L; Vol. 1, Point 2.2.1 and Vol. 3 B.2 Point B.2.5). It has been demonstrated to be rapidly degraded by direct photolysis on a glass plate in a laboratory study, after dilution in organic solvents. The DT_{50} derived from this study is 4.25 hours. However, this study describes only direct photolysis, and does not presume of sulfur degradation rate by photolysis in water.

Sulfur is considered as not readily biodegradable.

No hydrolysis study has been conducted by the Applicants. Due to its low solubility in water, the hydrolysis test does not need to be conducted.

No aerobic mineralisation in surface water study has been conducted by the Applicants. Sulfur cannot be mineralised so consequently data are not required.

No water-sediment system study has been submitted by the Applicants. Taking into consideration that sulfur, when entering an aquatic system, is expected to preferentially adsorb to sediment and then be oxidised, the rapporteur Member State questioned in the DAR (EFSA Scientific Report (2008) 221, 1-70), if a water/sediment study would be necessary for a better understanding of the behaviour and oxidation rate of sulfur in the sediment system. The view of the Member State experts was that the cycle of sulfur in the environment is well understood, and consequently it was agreed that it was not necessary to require additional data to address the route and rate of degradation of sulfur in natural aquatic systems (EFSA journal, 2008).

In the context of the renewal approval of the active substance sulphur, the information on the behaviour of sulphur in aquatic systems has been amended by the Applicants. The applicants provide a review article (summarized in Vol.3 B.8 under Point B.8.3.2.3) that allows updating current knowledge on sulphate reduction and the processes that are related to the reductive and oxidative pathways of sulphur

cycling in lake sediments. The review focuses on the factors that control sulphur cycling in different types of lakes. Lakes are categorized here into three main groups (oligotrophic, mesotrophic and eutrophic), whereas acidic lakes will be considered separately, as their sulphur cycling is quite different from that found in alkaline lakes. In addition, the article reviews sulfur cycling and sulfate reduction in lake sediments. It can be concluded that elemental or organically bound sulfur is not persistent in sediment but instead subject to a general cycle mainly driven by sulfate reduction and sulfide oxidation, and transfer of organically bond sulfur and pyrite formation.

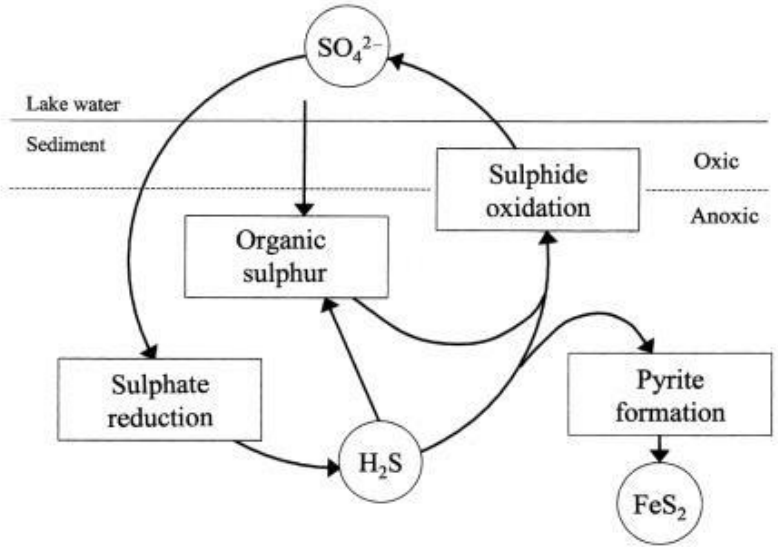

Figure B.8- 2: Schematic presentation of the sulfur cycle in freshwater sediments as proposed by Holmer and Storkholm (2001).

Sulfur is not expected to be persistent in elemental form (due to its dissipation in aquatic systems), and therefore no accumulation of elemental sulfur in sediment is expected to happen.

Please also refer to Points 2.8.2.2.5 and 2.8.2.2.6.

2.8.2.1 Rapid degradability of organic substances

Not relevant for inorganic compounds.

2.8.2.1.1 Ready biodegradability

Ready biodegradation studies are not relevant for inorganic compounds, such as sulfur. Sulfur is therefore considered as non ready biodegradable.

2.8.2.1.2 BOD5/COD

No data available.

2.8.2.2 Other convincing scientific evidence

2.8.2.2.1 Aquatic simulation tests

Please refer to 2.8.2.

2.8.2.2.2 Field investigations and monitoring data (if relevant for C&L)

The available monitoring data are presented under 2.8.4.

2.8.2.2.3 Inherent and enhanced ready biodegradability tests

Please refer to 2.8.2.1.1.

2.8.2.2.4 Soil and sediment degradation data

Please refer to 2.8.1 for soil degradation and to 2.8.2 for sediment degradation (water/sediment systems).

2.8.2.2.5 Hydrolysis

No study is submitted by the Applicants. The solubility of the active substance sulfur in water is very low (16 µg/L; Please refer to Vol. 1, Point 2.2.1 and Vol. 3 B.2.5 for more details). Thus, the hydrolysis test was not needed to be conducted.

2.8.2.2.6 Photochemical degradation

A laboratory study (Redeker (1991, KCA 7.2.1.2/01 summarised in Vol. 3 B.8 (AS), Point B.8.3.1.2) was conducted with sulfur dissolved in organic solvents, which were evaporated before exposure to light for 24 hours. As long as sulfur is insoluble in water, the study is considered acceptable to assess direct photolysis and does not presume sulfur degradation rate by photolysis in water. Pure elemental sulfur was determined to have a half-life (DT_{50}) of 4.25 hours under the simulated sunlight condition at 25°C. After 1.15 hours, 80% of the sulfur remains unchanged.

2.8.2.2.7 Other / Weight of evidence

No data available.

2.8.3 Summary of fate and behaviour in air

The vapour pressure of sulfur at 20°C is 9.8×10^{-5} Pa. This is slightly higher than the trigger defined in the FOCUS Air guidance document for volatilisation from plants, but lower than the trigger for volatilisation from soil. Thus, significant volatilisation of sulphur is not expected. No experimental study showing that volatilisation of sulphur from soil and plant was conducted. It was concluded in the EFSA Scientific Report (2008) 221 (sulfur) that "sulphur is therefore non-volatile, even if its Henry's Law Constant was determined at 0.05 Pa m^3/mol, which is due to its very low water solubility. Sulfur is therefore not expected to transfer to the air compartment".

The reaction of sulfur in the atmosphere with hydroxyl radicals cannot be estimated using the method of Atkinson as developed in the Atmospheric Oxidation Program v1.92 since sulfur S_8 is an inorganic compound. However, it has been demonstrated to be rapidly degraded by direct photolysis on a glass plate in a laboratory study, after dilution in organic solvents. The DT_{50} of sulfur derived from this study is 4.25 hours.

Compounds of sulfur exist in the atmosphere in the gaseous, aqueous and particulate states. In the atmosphere, the major forms are sulfur dioxide (SO_2), sulfur trioxide (SO_3), and hydrogen Sulfide (H_2S).

The potential for sulfur to adversely affect the atmosphere has been investigated by the Applicants. The following topics: global warming, ozone depletion, photochemical smog formation and acidification and eutrophication has been considered. The acidification potential is about 2-times that of SO_2 reference gas. Local and global effects of sulphur is unlikely to happen.

Sulfur is therefore not expected to be persistent in air and is unlikely to be subject to significant concerns relating to long range atmospheric transport and atmospheric accumulation.

2.8.3.1 Hazardous to the ozone layer

Based on the available data presented under 2.8.3, there is no evidence that sulphur may present a danger to the structure and/or the functioning of the stratospheric ozone layer.

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

A broad database for S-concentrations in soil, surface water and sediment is given by FOREGS (Forum of European Geological Surveys and GEMAS project (Geochemical Mapping of Agricultural and Grazing land Soil). Monitoring data are summarized in Vol. 3 B.8 (AS) Part B.8.5.

A summary of the monitoring data is shown in the following table.

Table 71: Monitoring data available from FOREGS and GEMAS monitoring programs. Extraction methods for solids: *Aqua regia* (ICP-AES)

Media	**Number of samples**	**Minimum**	**10th Percentile**	**Median 50th percentile**	**Mean**	**Standard deviation**	**90th Percentile**	**Maximum**
		[mg kg^{-1}]						
S – Sulfur								
Subsoil[1)]	784	<50	-	105	**262**	1478	331	32800
Topsoil (0-25 cm)[1)]	837	<50	-	227	**437**	3890	551	112000
Stream sediment[1)]	845	<50	-	510	**923**	1740	1752	33500
Floodplain sediment[1)]	747	<50	-	287	**423**	493	816	5440
Ploughed fields (0-20 cm)[2)]	2108	< 5	89	**207**	**-**	-	487	68226
Grazing land soil (0-10 cm)[2)]	2024	< 5	106	**295**	**-**	-	795	98190
SO_4^{2-}/ - Sulfate								
Water[1)]	808	<0.3	-	16.1	**52.1**	153	103	2420

[1] FOREGS: Salminen *et al.* (2004);
[2] GEMAS: Reimann *et al.* 2014

RMS underlines that the FOREGS soil data should not be considered as good quality baseline data to be retained as a representative value of agricultural background concentration for the topsoil compartment. In the context of the FOREGS soil data, the organic layer of soils before sampling was removed; that could significantly affect the results.

For both databases, the available data are overall concentration of sulfur in soil since the *aqua regia* digestion was used for quantification of residues in soil. Please refer to Vol. 3 (AS) B.8 for more details. RMS is of the opinion that specific data/information on the soil concentration of elemental sulfur should be provided by the notifiers in order to assess the impact of the applied amounts of elemental sulfur following the use of sulphur on the soil concentration (data gap).
In addition, the agricultural background concentration of sulfates in soil is difficult to establish as the level of sulfates in soil varies temporally and spatially (due to crop uptake factor, application of fertiliser, soil mobility…). Please refer to Vol. 3 (AS) B.8 for more details.

Monitoring data for groundwater are also available from a bibliography search. Monitoring data are summarized in Vol. 3 B.8 (AS) Part B.8.5. The mean annual concentrations of sulfates in the groundwater were stable over the years: 42.1 mg/L for the last ten years and 35.2 mg/L on the period 1955-2019. More than 98.5% of the measured concentration of sulfates in French groundwater were lower than the regulatory trigger of 250 mg/L for drinking and raw water in the period 1955-2019. Sulfur, measured in a very few samples, was found in groundwater at concentrations of 18.7 mg/L (geomean, n = 32) with 44 mg/L at maximum. In view of the low water solubility of sulfur (16 µg/L) the amount probably refers to sulfur dispersed in water.

No monitoring data for air are provided by the applicants. RMS is of the opinion that monitoring data on the sulphur compounds in air should be provided by the Applicants (data gap).

2.8.5 Definition of the residues in the environment requiring further assessment

The residue definitions provided in the EFSA Scientific Report (2008) 221 for sulfur has been updated for exposure and risk assessments in soil, groundwater, surface water, sediment and air:

Soil:

For risk assessment: Sulfur

Groundwater:

For exposure assessment: Sulfur and sulfates

Surface water:

For risk assessment: Sulfur and sulfates

Sediment:

For risk assessment: Sulphur and sulphates

Air:

For risk assessment: Sulfur (free S, particulate S)

2.8.6 Summary of exposure calculations and product assessment

- *Soil:*

- SULFUR 80% WG product and SULPHUR DUST product:

For both representative products, the approach and the corresponding PEC_{soil} calculations are detailed in Vol. 3 B.8 (CP), B.8.2.
An estimation of the predicted environmental concentration (PEC_{soil}) of sulfur in soil was performed according to FOCUS guidance and is based on the worst-case considerations. The 'risk envelope' GAP uses were considered for PECsoil calculations. According to the discussions occurred during the

PRAPeR Expert Meeting of October (2008), as no valid DT_{50} could be determined for sulfur in soil, the exposure calculations were based on the maximum annual total dose of the product.

No accumulation of sulfur in soil is expected, thus no PEC plateau calculation is needed. For both representative products, RMS is of the opinion that specific data on the soil concentration of elemental sulfur should be provided by the notifiers in order to assess the impact of the applied amounts of elemental sulfur following the use of sulphur on the soil concentration. From the information reported in the literature, it cannot be excluded that the use of sulfur will have an impact on the natural levels of sulfates in the soil. A data gap was identified for information on the natural buffering capacity of agricultural soils in Europe to neutralize acid inputs from sulfate ions potentially formed following the use of sulfur and on the possible adverse effects on non-target terrestrial organisms.

For soil, the PEC values are presented together with the corresponding TER in section 2.9.9.

- *Groundwater:*

For both representative products, the Applicants proposed two approaches. First set of modelling was performed according to the 'Flux method' (Approach 1) as previously proposed for the previous EU assessment. A second set of modelling was conducted using the FOCUS models (Approach 2). The approaches and results are detailed under Vol. 3 B. 8 (CP).

Due to some deviations identified in the Applicants modelling, the notifiers' calculations were not considered as reliable. The following modellings (Approaches 1 and 2) are performed by RMS considering the following assumptions:

For approach 1 ('Flux method'): The PECgw of sulfate have been assessed on basis of the percolated water volumes of the FOCUS PELMO 5.5.3 and FOCUS PEARL 4.4.4 standard scenarios. A 100 % transformation of applied sulfur to sulfate was assumed and the complete fraction assumed to be dissolved in the percolate (derived from FOCUS scenarios). The total amount of SO_4^{2-} formed from applied sulfur was calculated within 26 years. Neither crop uptake *via* roots nor sorption onto soil was considered. These calculations are not considered as realistic worst-case situations.

- SULFUR 80% WG product

The results are presented in the following table.

Table 72: PECgw of sulfate (mg/L)

Uses	**Vines 10 x 10 kg a.s./ha**		**Spring cereals 4 x 8 kg a.s./ha**		**Winter cereals 4 x 8 kg a.s./ha**	
Weather/Soil scenario	**PELMO**	**PEARL**	**PELMO**	**PEARL**	**PELMO**	**PEARL**
Châteaudun, irrigated	56.98	48.74	53.41	56.06	69.02	64.58
Hamburg	40.37	35.59	31.40	37.96	31.96	31.53
Jokioinen	-	-	35.15	38.81	39.38	40.52
Kremsmünster	37.60	32.56	32.05	31.55	31.41	28.15
Okehampton	-	-	19.04	21.12	19.39	19.68
Piacenza, irrigated	27.61	38.24	-	-	29.34	26.01
Porto, irrigated	21.09	20.50	16.01	17.87	17.42	18.24
Sevilla, irrigated	90.61	43.62	-	-	75.99	170.96
Thiva, irrigated	128.71	81.92	-	-	109.33	196.18

The maximum PECgw results for all intended uses is 196.2 mg SO_4^{2-}/L. Under these conservative assumptions, no exceedance of the trigger value of 250 mg/L is expected for sulfates for all weather/Soil scenarios.

- SULPHUR DUST product:

The results are presented in the following table.

Table 73: PECgw of sulfate (mg/L)

Uses	**Vines 5 x 29.55kg a.s./ha**	
Weather/Soil scenario	**PELMO**	**PEARL**
Châteaudun, irrigated	191.32	163.66
Hamburg	135.57	119.51
Jokioinen	-	-
Kremsmünster	126.26	109.33
Okehampton	-	-
Piacenza, irrigated	92.71	128.41
Porto, irrigated	70.81	68.84
Sevilla, irrigated	**304.25**	146.47
Thiva, irrigated	**432.22**	**275.09**

The maximum PECgw results for all intended uses is 432.2 mg SO_4^{2-}/L. Under these conservative assumptions, an exceedance of the trigger value of 250 mg/L cannot be excluded for sulfates for some weather/Soil scenarios.

For approach 2 (FOCUS models):

As specified in the EFSA Scientific Report (2008) sulfur is not of concern for the contamination of groundwater, but that the potential for groundwater contamination for sulfates needed to be addressed, as they are highly mobile in soil.

The PECgw of sulfur and sulfates have been assessed with two FOCUS models (PELMO 5.5.3 and PEARL 4.4.4 models). The following endpoints are considered appropriated for modelling purpose.

Table 74: Summary of input parameters for sulfur and sulfates for PECgw calculations

Parameter	**Sulfur S_8**	**Sulfates**
DT_{50} soil (d) at 20 °C and pF 2 *	0.01 PELMO 0.1 PEARL (lowest value accepted by model)	100000
maximum formation fraction in soil (-)	-	Sulfur → sulfate 8.0
$K_{f,oc}$ (mL g^{-1})	3615.3	0
Freundlich exponent 1/n (-)	1.0	1.0

* "DT_{50}" estimations (*i.e.* transformation rate = time required for the oxidation of 50% of the applied elemental sulphur

- SULFUR 80% WG product

The results are presented in the following table.

Table 75: PECgw of sulfate (mg/L) for multiple applications every year

Uses	**Vines 10 x 10 kg a.s./ha**		**Spring cereals 4 x 8 kg a.s./ha**		**Winter cereals 4 x 8 kg a.s./ha**	
Weather/Soil scenario	**PELMO**	**PEARL**	**PELMO**	**PEARL**	**PELMO**	**PEARL**
Châteaudun	41.23	65.08	33.49	71.59	46.60	94.39
Hamburg	34.36	44.57	22.04	63.55	25.62	48.18
Jokioinen	-	-	42.08	68.02	40.79	78.85
Kremsmünster	27.46	31.24	22.32	34.21	17.75	27.32
Okehampton	-	-	-	-	16.11	25.55
Piacenza	26.41	81.15	15.66	27.96	20.48	50.73
Porto	14.61	25.61	11.99	29.09	10.58	24.50
Sevilla	67.51	58.91	-	-	23.33	208.54
Thiva	71.33	137.80	-	-	31.11	181.35

The maximum PECgw results for all intended uses is 208.5 mg SO_4^{2-}/L. No exceedance of the trigger value of 250 mg/L for sulfates is expected according to the intended uses.

- SULPHUR DUST product:

The results are presented in the following table.

Table 76: PECgw of sulfate (mg/L) for multiple applications every year

Uses	**Vines 5 x 29.55kg a.s./ha**	
Weather/Soil scenario	**PELMO**	**PEARL**
Châteaudun, irrigated	138.77	215.34
Hamburg	125.48	149.65
Jokioinen	-	-
Kremsmünster	91.22	107.39
Okehampton	-	-
Piacenza, irrigated	90.45	**271.29**
Porto, irrigated	50.55	85.55
Sevilla, irrigated	238.54	198.20
Thiva, irrigated	248.70	**459.63**

The maximum PECgw results for all intended uses is 459.6 mg SO_4^{2-}/L. An exceedance of the trigger value of 250 mg/L for sulfates cannot be excluded for two FOCUS scenarios according to the intended uses.

For both representative products, RMS is of the opinion that specific data on the soil concentration of elemental sulfur should be provided by the notifiers in order to assess the impact of of the applied amounts of elemental sulfur following the use of sulphur on the soil concentration.

- *Surface water:*

For both representative products, the use of FOCUS modelling is not appropriate in the specific case of sulphur since the use of FOCUS for PECsw calculations lead to concentrations above the water solubility limit. As previously agreed in the EFSA Scientific Report (2008), sulfur is only slightly soluble with a water solubility of 16 µg/L (Vol. 3 B.2 (AS)). For the previous approval of the active substance, the Member State experts agreed with the rapporteur Member State that the use of FOCUS modelling is not appropriate for inorganic compounds, and supported the RMS's approach to address the risk assessment to aquatic organisms taking into account an absence of effects to organisms at the highest water solubility limit of sulfur. Therefore, the PECsw calculation with FOCUS model is not required and the proposed water solubility was considered to be the maximum PECsw of 16 µg/L.

For both representative formulations, it cannot be excluded that the use of sulfur will have an impact on the natural levels of sulfates in the aquatic environment. No PECsw for sulfates was provided by the notifier. A data gap was identified for information on the natural buffering capacity of surface water bodies in Europe to neutralize acid inputs from sulfate ions potentially formed following the use of sulfur and on the possible adverse effects on non-target aquatic organisms.

- *Sediment:*

- SULFUR 80% WG product

The PECsed calculations have been performed for a risk envelope GAP uses based on Step 1 and 2 surface water tool (version 3.2) assumptions. The approach and results are detailed under Vol. 3 B. 8 (CP).

For sediment, the PEC values are presented together with the corresponding TER in section 2.9.9.

- SULPHUR DUST product:

A concern on the use of the spray drift % value BBA (FOCUS value) that are designed for spray applications to dustable powder formulation is raised. A study was provided by the notifier to support the use of such data, but this study was not designed for assessing the sedimentation drift following the application of dustable powder formulation. The results of this study cannot hence be used for modelling purpose (Please refer to Vol.3 B.8 (CP) Sulphur Dust for more details). RMS is of the opinion that there is a need of more information/data on the extrapolation of the drift % value (BBA, 2000) to foliar dust applications before their use in further calculations. Specific data on the drift value for the application of dustable powder formulation could help for conducting a robust environmental risk assessment (data gap).
In addition, no crop interception should be considered for such formulations in the absence of robust justification. Please refer to Vol. 3 B.8 CP Sulphur Dust for more details. In the absence of reliable drift % value for dustable powder product, exposure calculations were calculated by RMS considering a conservative spray drift % value.

For sediment, the PEC values are presented together with the corresponding TER in section 2.9.9.

- SULFUR 80% WG product and SULPHUR DUST product:

For both representative formulations, no reliable PECsed are available for sulfate. In addition, it cannot be excluded that the use of sulfur will have an impact on the natural levels of sulfates in the aquatic environment. A data gap was identified for information on the natural buffering capacity of surface water bodies in Europe to neutralize acid inputs from sulfate ions potentially formed following the use of sulfur and on the possible adverse effects on aquatic organisms.

- *Air:*

The short- and long-range transport potential of sulfur in air was assessed according to FOCUS Air (2008) with regard to dry deposition following volatilisation. Significant short- and long-range transport of sulfur is not expected due to its low vapour pressure, and its short DT_{50}.

- *Other routes of exposure:*

For both representative products, no exposure *via* other routes (e.g., by deposition of dust; indirect exposure of surface water from Sewage Treatment Plant; from amenity use) were considered by the Applicants.

2.9 EFFECTS ON NON-TARGET SPECIES

2.9.1 Summary of product exposure and risk assessment

2.9.1.1 Summary of product exposure and risk assessment for birds

- **Acute risk assessment for Sulfur 80% WG**

Screening assessment

For the initial screening assessment, "indicator species" and exposure scenarios were selected as recommended in EFSA Journal 2009; 7(12): 1438. A summary of the critical GAP uses and relevant indicator species is given in the table below.

Table 77: DDD and TER values for birds (screening level)

Intended use	Bare soil (1× 10.0 kg a.s./ha, BBCH < 10)				
Active substance	Sulfur				
Application rate (kg a.s./ha)	1× 10.0				
Acute toxicity (mg a.s./kg bw)	> 3451				
TER criterion	10				
Crop scenario Growth stage	**Indicator species**	**SV_{90}**	**MAF_{90}**	**DDD_{90} (mg/kg bw/d)**	**TER_A**
Bare soil, BBCH 09	Small granivorous bird	25.3	1.0	253	> 13.6
Intended use	Grapevine (10× 10.0 kg a.s./ha, i = 7d, BBCH 10-81)				
Active substance	Sulfur				
Application rate (kg a.s./ha)	10× 10.0				
Acute toxicity (mg a.s./kg bw)	> 3451				
TER criterion	10				
Crop scenario Growth stage	**Indicator species**	**SV_{90}**	**MAF_{90}**	**DDD_{90} (mg/kg bw/d)**	**TER_A**
Vineyard, BBCH ≥ 10	Small omnivorous bird	95.3	2	1906	**> 1.8**
Intended use	Cereals (4× 8.0 kg a.s./ha, i = 7 d, BBCH 15-69)				
Active substance	Sulfur				

Application rate (kg a.s./ha)	4× 8.0				
Acute toxicity (mg a.s./kg bw)	> 3451				
TER criterion	10				
Crop scenario **Growth stage**	**Indicator species**	**SV_{90}**	**MAF_{90}**	**DDD_{90}** **(mg/kg bw/d)**	**TER_A**
Cereals	Small omnivorous bird	158.8	1.77	2286.2	**> 1.5**

SV: shortcut value; MAF: multiple application factor; DDD: daily dietary dose; TER: toxicity to exposure ratio.

The TER_A value calculated for the pre-emergence application in grapevine is above the corresponding trigger values of 10, established for acute exposure, indicating an acceptable acute risk for granivorous birds. For all other exposure scenarios, further refinement steps are considered to be required at Tier-1.

Tier-1 risk assessment

The risk for birds at Tier-1 was assessed by calculating Toxicity Exposure Ratios (TER) considering the toxicity endpoints already used for the screening step above and exposure expressed as Daily Dietary Dose (DDD). The results are presented in the tables below.

Table 78: DDD and TER values for birds (Tier-1 level): Grapevine

Intended use	Grapevine (10× 10.0 kg a.s./ha, i = 7d, BBCH 10-81)				
Active substance	Sulfur				
Application rate (kg a.s./ha)	10 × 10.0				
Acute toxicity (mg a.s./kg bw)	> 3451				
TER criterion	10				
Crop scenario Growth stage	Generic focal species	SV_{90}	MAF_{90}	DDD_{90} (mg/kg bw/d)	TER_A
Vineyard, BBCH 10-19	Small insectivorous bird “Redstart”	27.4	1.97	539.8	**> 6.3**
Vineyard, BBCH ≥ 20	Small insectivorous bird “Redstart”	25.7	1.97	506.3	**> 6.7**
Vineyard, BBCH 10-19	Small granivorous bird “finch”	14.8	1.97	291.6	> 11.7
Vineyard, BBCH 20-39	Small granivorous bird “finch”	12.4	1.97	244.3	> 13.9
Vineyard, BBCH ≥ 40	Small granivorous bird “finch”	7.4	1.97	145.8	> 23.3
Vineyard, ripening	Frugivorous bird “Trush/starling”	28.9	1.97	569.3	**> 6.0**
Vineyard, BBCH 10-19	Small omnivorous bird “lark”	14.4	1.97	283.7	> 12.0
Vineyard, BBCH 20-39	Small omnivorous bird “lark”	12.0	1.97	236.4	> 14.4
Vineyard, BBCH ≥ 40	Small omnivorous bird “lark”	7.2	1.97	141.8	> 24.0

SV: shortcut value; MAF: multiple application factor; DDD: daily dietary dose; TER: toxicity to exposure ratio.

As outlined in the table above, an acceptable risk for birds at Tier-1 can be concluded for vineyards for almost all generic focal species, except for a small insectivorous bird and a frugivorous bird. Thus, further refinements at Tier-2 have to be taken into account for the species of concern in vineyards.

Table 79: DDD and TER values for birds (Tier-1 level): Cereals

Intended use	Cereals (4× 8.0 kg a.s./ha, i = 7 d, BBCH 15-69)				
Active substance	Sulfur				
Application rate (kg a.s./ha)	4× 8.0				
Acute toxicity (mg a.s./kg bw)	> 3451				
TER criterion	10				
Crop scenario Growth stage	Generic focal species	SV_{90}	MAF_{90}	DDD_{90} (mg/kg bw/d)	TER_A
Cereals, early (shoots) autumn-winter, BBCH 10-29	Large herbivorous bird "goose"	30.5	1.77	437.5	**> 7.9**
Cereals, BBCH 10-29	Small omnivorous bird "lark"	24.0	1.77	393.7	> **9.9**
Cereals, BBCH 30-39	Small omnivorous bird "lark"	12.0	1.77	172.4	> 20.0
Cereals, BBCH ≥ 40	Small omnivorous bird "lark"	7.2	1.77	103.6	> 33.3

SV: shortcut value; MAF: multiple application factor; DDD: daily dietary dose; TER: toxicity to exposure ratio.

As outlined in the table above, an acceptable risk for birds can be concluded for cereals for some generic focal species, except for a large herbivorous bird and for a small omnivorous bird (BBCH 10-29). Thus, further refinements at Tier-2 have to be taken into account for the species of concern in cereals.

Tier-2 risk assessment – Extrapolated LD_{50} value from limit dose tests for birds

The risk for birds at Tier-2 was assessed by calculating Toxicity Exposure Ratios (TER) considering the extrapolated LD_{50} of 5570 mg a.s./kg bw and exposure expressed as Daily Dietary Dose (DDD). The results are presented in the tables below.

Representative GAP use in grapevine

Table 80: DDD and TER values for birds (Tier-2 level): Grapevine

Intended use	Grapevine (10× 10.0 kg a.s./ha, i = 7d, BBCH 10-81)				
Active substance	Sulfur				
Application rate (kg a.s./ha)	10 × 10.0				
Acute toxicity (mg a.s./kg bw)	5570 (extrapolated)				
TER criterion	10				
Crop scenario Growth stage	Indicator species	SV_{90}	MAF_{90}	DDD_{90} (mg/kg bw/d)	TER_A
Vineyard, BBCH 10-19	Small insectivorous bird "Redstart"	27.4	1.97	539.8	10.2

Vineyard, BBCH ≥ 20	Small insectivorous bird "Redstart"	25.7	1.97	506.3	10.8
Vineyard, ripening	Frugivorous bird "Trush/starling"	28.9	1.97	569.3	**9.6**

SV: shortcut value; MAF: multiple application factor; DDD: daily dietary dose; TER: toxicity to exposure ratio.

According to the applicant it can be assumed that an acceptable acute risk for all indicator species of concern can be concluded at Tier-2 at the latest. Indeed, although the TER_A value for a frugivorous bird is very slightly below the trigger of 10 (*i.e.* TER_A = 9.6), it should be emphasized that the Tier-2 assessment presented above is still based on conservative exposure assumptions:

RMS agrees to consider the acute risk assessment as acceptable for all crop scenario using the extrapolated LD_{50} value of 5570 mg sulfur/kg bw. Indeed:
All other bird acute toxicity values available are NOED value since no mortality or other toxicity (mainly related to effects on body weight) were reported showing that sulfur is not acutely toxic toward birds.
The worst-case assessment for frugivorous birds presented above still considers a default MAF value as recommended in the EFSA Journal 2009; 7(12): 1438 (Appendix H). It should be noted that it is not very likely that fruits (when they are matured and may be consumed by birds) are exposed to the maximum number of applications within the timeframe of the respective exposure scenario proposed by EFSA. Therefore, it is RMS opinion that use of 10 applications for the scenario 'Vineyard, ripening' appears overly conservative. In addition, sulfur is known to be washed-off of the plants (including fruits) after rain events. Therefore, even if, no data have been provided by the applicant to support his assumption that 'two applications might occur in this time, using a rate of 10 kg a.s./ha', RMS highlighted that a TER_A value of 10.1 is obtained by using 8 applications for the scenario 'ripening'. It is RMS opinion that the exposure from 8 applications remained conservative as it is unlikely that the amount of residue from 8 applications can be found on mature grapes considering that the intended application window (BBCH 10-81).

Representative GAP use in cereals

Table 81: DDD and TER values for birds (Tier-1 level): Cereals

Intended use	Cereals (4× 8.0 kg a.s./ha, i = 7 d, BBCH 15-69)				
Active substance	Sulfur				
Application rate (kg a.s./ha)	4× 8.0				
Acute toxicity (mg a.s./kg bw)	5570 (extrapolated)				
TER criterion	10				
Crop scenario Growth stage	Indicator species	SV_{90}	MAF_{90}	DDD_{90} (mg/kg bw/d)	TER_A
Cereals, early (shoots) autumn-winter BBCH 10-29	Large herbivorous bird "goose"	30.5	1.77	431.9	12.7
Cereals, BBCH 10-29	Small omnivorous bird "lark"	24.0	1.77	393.7	16.1

SV: shortcut value; MAF: multiple application factor; DDD: daily dietary dose; TER: toxicity to exposure ratio.

As outlined in the table above, an acceptable acute risk for all indicator species of concern can be excluded at Tier-2 at the latest. Thus, no further refinements are considered to be required for the representative GAP use in cereals.

- **Long-term risk assessment**

Regarding the long-term assessment, no study was conducted because sulphur is non-toxic, it is naturally present in soil and not persistent; therefore, long term exposure for birds related to pesticide use is not expected to present any unacceptable risk.

- **Assessment of the risk arising from drinking water**

Birds may drink contaminated water from puddles formed on the soil surface of a field after heavy rainfall events.
For sulfur a K_{oc} value is available, *i.e.* 3615.3 mL/g; The effective application rate is calculated by multiplying the proposed application rates by MAF values based on the DT_{50} in soil (EFSA, 2009) for the active substance; for sulfur a soil DT_{50} is not available (see Volume 3 CA B8 for more details), therefore as a worst-case approach the maximum yearly application rate for SULFUR 80% WG (100 kg/ha/yr for vineyards) is assumed to be the maximum effective application rate.
The ratios of the effective application rate to the relevant endpoints are presented in the following table.

Table 82: Drinking water assessment for the proposed use of SULFUR 80% WG

Time scale	Proposed application rate	MAF	Effective application rate	Endpoint (mg a.s./kg bw)	Ratio	Trigger value
Acute	10000 g a.s./ha	Not applicable	100000 g a.s./ha	LD_{50} > 3451	< 29.0	3000

The acute ratio is below the relevant trigger value demonstrating no concerns to birds *via* contaminated drinking water from the proposed uses of SULFUR 80% WG.

- **Assessment of the risk arising from bioaccumulation in food chains**

Generally, the potential of sulfur bioaccumulation is considered to be negligible as sulfur is a naturally occurring mineral and an essential element in the metabolism of all living organisms (as stated in the DAR for sulfur (March 2008) and its Corrigendum). Furthermore, it is of low toxicity to birds and mammals. Biomagnification of sulfur in terrestrial food chains is thus not considered to be of concern.

- **Risk assessment conclusions for the product Sulfur 80% WG**

Based on the risk assessment presented above, no unacceptable risk for birds is expected for exposure to contaminated food indicated by TER_A values above the corresponding trigger value of 10. Furthermore, no unacceptable risks are expected arising from other routes of exposure (residue uptake from drinking water or bioaccumulation in food chains). In conclusion, an acceptable overall risk for birds is indicated for the representative GAP uses of ‘Sulfur 80% WG’.

- **Acute oral toxicity to bird for ‘Sulphur Dust’**

Screening assessment (indicator focal species)

The results of the acute screening risk assessments are summarised in the following table. Long-term risk assessment is not required since sulfur is non-toxic, naturally present in soil and not persistent (please refer to Volume 3 CA B.9.1.1.3 for further details).

Table 83: Screening assessment of the acute risk for birds due to the use of Sulphur Dust on grapevine

Intended use	grapevine				
Active substance/product	sulfur / Sulphur Dust				
Application rate (kg a.s./ha)	5 × 29.55 (7 days)				
Acute toxicity (mg a.s./kg bw)	> 3451				
TER criterion	10				
Crop scenario Growth stage	**Indicator focal species**	**SV_{90}**	**MAF_{90}**	**DDD_{90} (mg/kg bw/d)**	**TER_a**
Grape BBCH 15-89	Small omnivorous bird	95.3	1.9	5351	**> 0.64**

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

The TER_A value of sulfur obtained for the indicator species small omnivorous bird is lower than the trigger value of 10 proposed in the Guidance Document on Risk Assessment for Birds and Mammals (EFSA Journal 2009; 7(12): 1438); therefore Tier-1 risk assessment is required.

- **Tier I assessment (generic focal species)**

The results of the Tier I acute risk assessments is summarised in the following table. The MAF=1.9 for 5 applications has been used for all scenarios.

Table 84: Tier I assessment of the acute risk for birds due to the use of Sulphur Dust on grapevine

Crop	**Scenario**	**MAF**	**Short-cut value**	**DDD multiple applications**	**LD_{50} mg/kg bw/day**	**TER_A**
Vineyard	BBCH 10-19 – Insectivorous “redstart”	1.9	27.4	1538.37	>3451	> **2.24**
Vineyard	BBCH >20 – Insectivorous “redstart”	1.9	25.7	1442.93	>3451	> **2.39**
Vineyard	BBCH 10-19 – Granivorous “finch”	1.9	14.8	830.95	>3451	> **4.16**
Vineyard	BBCH 20-39 – Granivorous “finch”	1.9	12.4	696.20	>3451	> **4.96**
Vineyard	BBCH >40 – Granivorous “finch”	1.9	7.4	415.47	>3451	> **8.32**
Vineyard	Ripening – Frugivorous “thrush/starling”	1.9	28.9	1622.59	>3451	> **2.13**
Vineyard	BBCH 10-19 – Omnivorous “lark”	1.9	14.4	808.49	>3451	> **4.28**
Vineyard	BBCH 20-39 – Omnivorous “lark”	1.9	12.0	673.74	>3451	> **5.13**
Vineyard	BBCH >40 – Omnivorous “lark”	1.9	7.2	404.24	>3451	> **8.56**

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

In all scenarios the TER_A values of sulfur obtained for the generic focal species of birds are lower than the trigger value of 10 proposed in the Guidance Document on Risk Assessment for Birds and Mammals (EFSA Journal 2009; 7(12): 1438) indicating an unacceptable risk to birds after the use of Sulphur Dust on grapevine. Thus, a refined risk assessment is required.

- **Tier II risk assessment – Extrapolated LD_{50} value from limit dose tests for birds**

The Tier II was assessed by calculating Toxicity Exposure Ratios (TER) considering the extrapolated LD_{50} of 5570 mg a.s./kg bw and exposure expressed as Daily Dietary Dose (DDD). The results are presented in the tables below.

Table 85: Tier II assessment of the acute risk for birds due to the use of Sulphur Dust on grapevine

Crop	**Scenario**	**MAF**	**Short-cut value**	**DDD multiple applications**	**Extrapolated LD_{50} mg/kg bw/day**	**TER_A**
Vineyard	BBCH 10-19 – Insectivorous “redstart”	1.9	27.4	1538.37	5570	**3.62**
Vineyard	BBCH >20 – Insectivorous “redstart”	1.9	25.7	1442.93	5570	**3.86**
Vineyard	BBCH 10-19 – Granivorous “finch”	1.9	14.8	830.95	5570	**6.70**
Vineyard	BBCH 20-39 – Granivorous “finch”	1.9	12.4	696.20	5570	**8.00**
Vineyard	BBCH >40 – Granivorous “finch”	1.9	7.4	415.47	5570	13.41
Vineyard	Ripening – Frugivorous “thrush/starling”	1.9	28.9	1622.59	5570	**3.43**
Vineyard	BBCH 10-19 – Omnivorous “lark”	1.9	14.4	808.49	5570	**6.89**
Vineyard	BBCH 20-39 – Omnivorous “lark”	1.9	12.0	673.74	5570	**8.27**
Vineyard	BBCH >40 – Omnivorous “lark”	1.9	7.2	404.24	5570	13.78

The applicant proposed to refine the MAF value for some scenario considering that, according to the GAP, during BBCH 15-19, the product is applied no more than 1 time. Therefore, the appropriate MAF=1 for 1 application should be used for this scenario.

Table 86: Tier II assessment of the acute risk for birds due to the use of Sulphur Dust on grapevine considering one application between BBCH 15-19 and maximum four applications between BBCH 20-39 (considering a different number of applications).

Crop	**Scenario**	**MAF**	**Short-cut value**	**DDD multiple applications**	**Extrapolated LD_{50} mg/kg bw/day**	**TER_A**
Vineyard	BBCH 10-19 – Insectivorous “redstart”	n.a	27.4	809.67	5570	**6.87**
Vineyard	BBCH >20 – Insectivorous “redstart”	1.9	25.7	1442.93	5570	**3.86**
Vineyard	BBCH 10-19 – Granivorous “finch”	n.a	14.8	437.34	5570	12.73

Vineyard	BBCH 20-39 – Granivorous "finch"	1.8	12.4	659.56	5570	**8.44**
Vineyard	Ripening – Frugivorous "thrush/starling"	1.9	28.9	1622.59	5570	**3.43**
Vineyard	BBCH 10-19 – Omnivorous "lark"	n.a	14.4	425.52	5570	13.09
Vineyard	BBCH 20-39 – Omnivorous "lark"	1.8	12.0	638.28	5570	**8.72**

However, without new informations and data it is RMS opinion that the risk for granivorous and omnivorous birds is not acceptable and needs to be addressed. Indeed, RMS considered that some TER values are not close enough to the trigger to conclude to an acceptable risk based on the weight of evidence approach as done forSulfur 80% WG. Further data are therefore needed.

- **Tier II risk assessment - Refinement of the RUD**

RMS does not agree with the refinement provided by the applicant as the studies performed by Ertus (2018 and 2019) were not considred as reliable and therefore should not be used for risk assessment purpose.

Therefore, no reliable data are available to refine the risk assessment for insectivorous birds.

RMS performed a calculation to estimate a 90th percentile RUD value for frugivorous birds eating grapes from the 2 studies performed by Garofani (2006 and 2008 ; KCA 6.3.4/01 and KCA 6.3.4/03, respectively) as they are considered sufficiently robust to be used in the risk assessment. Results are provided below:

Table 87: RUD for sulfur in field grapes fruit, at 0 DALA

Trial number	**Number and rate of applications [kg ai/ha]**	**Date of application**	**Residues at zero DALA [mg sulfur/kg]**
KCA 6.3.4/01 CH-302/2005/ A5052 IT2, 15050 Casasco, Italy S-EU	32.51 32.51 27.09 21.67 21.67	23/08/05 29/08/05 05/09/05 13/09/05 19/09/05	10.2
KCA 6.3.4/01 CH-302/2005/ A5052 IT3, 15059 Costa Vescovato, Italy S-EU	32.51 32.51 27.09 21.67 21.67	26/08/05 01/09/05 07/09/05 13/09/05 20/09/05	14.3
KCA 6.3.4/01 CH-302/2005/ A5052 GR2, 59200 Marina, Greece S-EU	32.51 32.51 27.09 21.67 21.67	26/08/05 01/09/05 07/09/05 13/09/05 20/09/05	34.6
KCA 6.3.4/01 CH-302/2005/ A5052 TL1, 31620 Fronton, France S-EU	31.27 30.78 26.10 20.19 20.93	17/08/05 25/08/05 01/09/05 07/09/05 13/09/05	309
KCA 6.3.4/03 CH-179/2007 SRF07-010-76FR 69460 St. Etienne des Ouilières, France S-EU	28.50 34.20 26.60 20.90 19.00	25/07/07 01/08/07 06/08/07 12/08/07 17/08/07	10.67

KCA 6.3.4/03 CH-179/2007 SRS07-064(DP)-76FR 46841 Castello de Rugat, Spain S-EU	29.55 29.55 24.63 19.70 19.70	03/08/07 09/08/07 14/08/07 21/08/07 27/08/07	17.04
Mean RUD at 0 DALA			77.12
90th RUD at 0 DALA			171.8

The 90th percentile RUD value retrieved from the data provided by the applicant is 171.8 mg sulphur/kg which is more than 10 times higher than the 90th percentile RUD default value for Tier I risk assessment (i.e. 16.7 mg/kg for berries) available in the table 1 of the appendix F of the guidance document on risk assessment for birds and mammals.
Therefore, although residue data on grapes are available for sulfur, these data do not allow to refine the exposure of frugivorous birds following the application of Sulphur Dust on grapevine according to the GAP.

Based on a comment made by co-RMS, RMS reconsiders the dataset and it appears now that the data retrieved from the study CH-302/2005/A5052 TL1 (KCA 6.3.4/01) is an outlier (i.e. 309 mg a.s./kg). This data has been removed from the original data package used to calculate mean and 90th percentile RUD at 0 DALA.
Therefore, considering the new data package here are the results of the new calculations made by RMS:
- Mean RUD value at 0 DALA = 19.15 mg a.s./kg.
- 90th percentile RUD value at 0 DALA = 27.6 mg a.s./kg.

New values show that the 90th percentile is in the same range (or slightly higher) than the default values for Tier I risk assessment (i.e. 16.7 mg/kg for berries) available in the table 1 of the appendix F of the guidance document on risk assessment for birds and mammals. Therefore, the conclusion drawn earlier by RMS is still considered accurate. The data provided by the applicant do not allow to refine the exposure of frugivorous birds following the application of Sulphur Dust on grapevine according to the GAP.

Thus, further refinement of the risk assessment is still needed for the small insectivorous birds and the frugivorous birds (ripening).

- **Long-term risk assessment**

Regarding the long-term assessment, no study was conducted because sulphur is non-toxic, it is naturally present in soil and not persistent; therefore, long term exposure for birds related to pesticide use is not expected to present any unacceptable risk.

- **Drinking water exposure**

Birds may drink contaminated water from puddles formed on the soil surface of a field after heavy rainfall events.
For sulfur a K_{oc} value is available, *i.e.* 3615.3 mL/g; The effective application rate is calculated by multiplying the proposed application rates by MAF values based on the DT_{50} in soil (EFSA, 2009) for the active substance; for sulfur a soil DT_{50} is not available (see Volume 3 CA B.8 for more details), therefore as a worst-case approach the maximum yearly application rate for Sulphur Dust (147.75 kg/ha/yr for vineyards) is assumed to be the maximum effective application rate.
The ratios of the effective application rate to the relevant endpoints are presented in the following table.

Table 88: Drinking water assessment for the proposed use of Sulphur Dust

Time scale	Proposed application rate	MAF	Effective application rate	Endpoint (mg a.s./kg bw)	Ratio	Trigger value
Acute	29550 g a.s./ha	Not applicable	147750 g a.s./ha	LD_{50} = 3451	42.81	3000

The acute ratio is below the relevant trigger value demonstrating an acceptable acute risk to birds *via* contaminated drinking water from the proposed uses of Sulphur Dust.

Effects of secondary poisoning

Assessment of secondary poisoning is not required for sulfur since, according to the Guidance Document on Risk Assessment for Birds and Mammals (EFSA Journal 2009; 7(12): 1438), the potential for bioaccumulation is indicated by a log $K_{ow} \geq 3$. In the case of sulfur, it is not practical or relevant to determine a partition coefficient due to the low water solubility (16 µg/L) but it is expected to be very low.

Biomagnification in terrestrial food chains

As a naturally occurring mineral and an essential element in the metabolism of all living organisms (as stated in the DAR for sulfur (March 2008)), sulfur bioaccumulation potential is considered to be negligible. No biomagnification of sulphur in terrestrial food chains is then expected.

- **Risk assessment conclusions for 'Sulphur Dust'**

Based on the risk assessment presented above, further refinements of the risk assessment are still needed for the small insectivorous birds (BBCH 10-19 and >20), the frugivorous birds (ripening) and for granivorous and omnivorous birds at BBCH stages 20-39.
Furthermore, no unacceptable risks are expected arising from other routes of direct exposure or secondary poisoning (residue uptake from drinking water or bioaccumulation in food chains).
In conclusion, an unacceptable acute risk has been identified for frugivorous, small insectivorous, omnivorous and granivorous birds at Tier-II. Further refinements are therefore deemed required for the requested uses of Sulphur Dust.

2.9.1.2 Summary of product exposure and risk assessment for other terrestrial vertebrates

- **Acute risk assessment for Sulfur 80% WG**

Screening assessment

The acute risk for mammals was assessed by calculating Toxicity Exposure Ratios (TER_A) considering the most relevant toxicity endpoint and exposure expressed as Daily Dietary Dose (DDD_A). The results are presented in the table below.

Table 89: DDD and TER values for mammals (screening level)

Intended use	Bare soil (1× 10.0 kg a.s../ha, BBCH 05-09)
Active substance	Sulfur

Application rate (kg a.s./ha)	1× 10.0				
Acute toxicity (mg a.s./kg bw)	> 34475				
TER criterion	10				
Crop scenario Growth stage	**Indicator species**	**SV_{90}**	**MAF_{90}**	**DDD_{90} (mg/kg bw/d)**	**TER_A**
Bare soil, BBCH 09	Small granivorous mammal	14.4	1.0	144.0	> 239.4
Intended use	Grapevine (10× 10.0 kg a.s./ha, i = 7d, BBCH 10-81)				
Active substance	Sulfur				
Application rate (kg a.s./ha)	10× 10.0				
Acute toxicity (mg a.s./kg bw)	> 34475				
TER criterion	10				
Crop scenario Growth stage	**Indicator species**	**SV_{90}**	**MAF_{90}**	**DDD_{90} (mg/kg bw/d)**	**TER_A**
Vineyard, BBCH ≥ 10	Small herbivorous mammal	136.4	1.97	2728	> 12.6
Intended use	Cereals (4× 8.0 kg a.s../ha, i = 7 d, BBCH 15-69)				
Active substance	Sulfur				
Application rate (kg a.s./ha)	4× 8.0				
Acute toxicity (mg a.s./kg bw)	> 34475				
TER criterion	10				
Crop scenario Growth stage	**Indicator species**	**SV_{90}**	**MAF_{90}**	**DDD_{90} (mg/kg bw/d)**	**TER_A**
Cereals, BBCH ≥ 10	Small herbivorous mammal	118.4	1.77	1705	> 20.2

SV: shortcut value; MAF: multiple application factor; DDD: daily dietary dose; TER: toxicity to exposure ratio.

All TER_A values calculated for the pre-emergence application in grapevine and the post-emergence applications in grapevine and cereals are above the corresponding trigger values of 10, established for acute exposure, indicating an acceptable risk for mammals at the screening level. Thus, no further refinement steps are considered to be required.

- **Long-term risk assessment**

No long-term multiple dosing studies have been performed with technical sulfur as it has been used for agricultural purposes for decades and is generally regarded as safe for human exposure. The toxicology studies reported and the open literature database provide sufficient evidence of the safety in use of sulfur and sulfur-containing products. This view is supported by the US-EPA Office of Pesticide Programs (USEPA OPP) and therefore long-term exposure for mammals related to pesticide use is not expected to present any unacceptable risk.

- **Assessment of the risk arising from drinking water**

Mammals may drink contaminated water from puddles formed on the soil surface of a field after heavy rainfall events.

For sulfur a K_{oc} value is available, *i.e.* 3615.3 mL/g; The effective application rate is calculated by multiplying the proposed application rates by MAF values based on the DT_{50} in soil (EFSA, 2009) for the active substance; for sulfur a soil DT_{50} is not available (see Volume 3 CA B8 for more details), therefore as a worst-case approach the maximum yearly application rate for SULFUR 80% WG (100 kg/ha/yr for vineyards) is assumed to be the maximum effective application rate.
The ratios of the effective application rate to the relevant endpoints are presented in the following table.

Table 90: Drinking water assessment for the proposed use of SULFUR 80% WG

Time scale	Proposed application rate	MAF	Effective application rate	Endpoint (mg a.s./kg bw)	Ratio	Trigger value
Acute	10000 g a.s./ha	Not applicable	100000 g a.s./ha	LD_{50} > 34475	< 2.90	3000

The acute ratio is below the relevant trigger value demonstrating no concerns to mammals *via* contaminated drinking water from the proposed uses of SULFUR 80% WG.

- **Assessment of the risk arising from bioaccumulation in food chains**

Generally, the potential of sulfur bioaccumulation is considered to be negligible as sulfur is a naturally occurring mineral and an essential element in the metabolism of all living organisms (as stated in the DAR (2008) for sulfur and its Final Addendum to the DAR (2008)). Furthermore, it is of low toxicity to birds and mammals. Biomagnification of sulfur in terrestrial food chains is thus not considered to be of concern.

- **Risk assessment conclusions for Sulfur 80% WG**

Based on the risk assessment presented above, no unacceptable risk for mammals is expected for exposure to contaminated food indicated by TER_A values above the corresponding trigger value of 10. Furthermore, no unacceptable risks are expected arising from other routes of exposure (residue uptake from drinking water or bioaccumulation in food chains). In conclusion, an acceptable overall risk for mammals is indicated for the representative GAP uses of 'Sulfur 80% WG'.

- **Acute risk assessment for 'Sulphur Dust'**

Screening assessment (indicator focal species)

For the initial screening assessment, "indicator species" and exposure scenarios were selected as recommended in EFSA/2009/1438. If a low risk is estimated for the indicator species of concern, then an overall low risk can be concluded for all other (real) mammalian species exposed to Sulphur Dust.

Table 91: Screening assessment of the acute risk for mammals due to the use of Sulphur Dust on grapevine

Intended use	grapevine
Active substance/product	sulfur / Sulphur Dust
Application rate (kg a.s./ha)	5 × 29.55 (7 days)
Acute toxicity (mg a.s./kg bw)	> 34475
TER criterion	10

Crop scenario Growth stage	**Indicator focal species**	**SV_{90}**	**MAF_{90}**	**DDD_{90} (mg/kg bw/d)**	**TER_a**
Grape BBCH 15-89	Small herbivorous mammals	136.4	1.9	7658	**> 4.50**

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

The TER_A value of sulfur obtained for the indicator species small herbivorous mammals is lower than the trigger value of 10 proposed in the Guidance Document on Risk Assessment for Birds and Mammals (EFSA Journal 2009; 7(12): 1438); therefore a First-Tier Risk Assessment is needed.

Tier I (generic focal species)

As a first step, a Multiple Application Factor (MAF) of 1.9 was used for vineyards, as the product is applied maximum five times at an average interval of 7 days.

The results of the Tier I acute risk assessments is summarised in the following table.

Table 92: Tier I assessment of the acute risk for mammals due to the use of Sulphur Dust on grapevine

Crop	**Scenario**	**MAF**	**Short-cut value**	**DDD multiple applications**	**LD_{50}**	**TER_A**
Vineyard	BBCH 10-19 (vole)	1.9	81.9	2457	> 34475	**> 7.5**
Vineyard	BBCH 20-39 (vole)	1.9	68.2	3274	> 34475	**> 9.0**
Vineyard	BBCH > 40 (vole)	1.9	40.9	2331	> 34475	> 15
Vineyard	BBCH 10-19 (mouse)	1.9	10.3	309	> 34475	> 59.6
Vineyard	BBCH 20-39 (mouse)	1.9	8.6	413	> 34475	> 71.4
Vineyard	BBCH > 40 (mouse)	1.9	5.2	296.4	> 34475	> 118

According to the description above, in all, except one vineyard scenarios presented, the TER_A values obtained for the generic focal species of mammals are above the trigger value of 10 proposed in the Guidance Document on Risk Assessment for Birds and Mammals (EFSA/1438/2009), indicating that Sulphur Dust poses an acceptable acute risk to mammals following application according to the proposed use patterns, except for the small herbivorous (BBCH 10-19, vole). For this scenario, further refinement is needed.

Please note that the TER_A is also below the trigger value for the vole at BBCH 20-39 indicating an unacceptable risk following the application of Sulphur Dust at the requested GAP. A refinement is therefore requested.

The initial reviewed GAP was 5 applications of the products, on grapes [application window: BBCH stages 15-89] at an application rate of 29.55 kg a.s./ha with an interval between each application of 7 days. After, the first review performed by RMS, the applicant chose to add some precisions about the timing of application of its product on grapes; However, it is RMS opinion, that these precisions remain imprecise and may not represent all the situations that may be encountered in the field.

RMS provides below a risk assessment based on 3 applications for scenario taking place between BBCH stages 20 and 39 (+ one additional application accounting for application occurring during BBCH 15-19). A MAF = 1.8 (4 applications) is thus applied to this specific scenario.

Table 93: Tier I assessment of the acute risk for mammals due to the use of Sulphur Dust on grapevine

Crop	Scenario	MAF (4 applications)	Short-cut value	DDD	LD_{50}	TER_A
Vineyard	BBCH 20-39 (vole)	1.8	81.9	3591	> 34475	**> 9.6**

When taking into account only four applications, the calculated TER for the small herbivorous (BBCH20-39, vole) is still below the trigger value of 10 is indicating that Sulphur Dust poses an unacceptable acute risk to mammals following application according to the proposed use patterns.

RMS comment: The following arguments may be considered in light of the data available to perform the risk assessment:

- For all other mammals acute toxicity values available, no mortality or other toxicity (mainly related to effects on body weight) were reported showing that sulfur is not acutely toxic toward mammals.
- The LD_{50} value used to perform the risk assessment is an unbounded value showing that the real LD_{50} is certainly higher that 34475 mg sulfur/kg b.w.

Therefore, considering the argument above, it is RMS opinion that the risk is acceptable for small herbivorous mammals at BBCH stages 30-39.

As a second step, according to the GAP, during BBCH 15-19, the applicant assumed that the product is applied no more than 1 time. Therefore, a MAF=1 for 1 application has been used for this scenario. The risk assessment considering the appropriate MAF is presented in the following table.

Table 94: Tier I assessment of the acute risk for mammals due to the use of Sulphur Dust on grapevine

Crop	Scenario	MAF	Short-cut value	DDD multiple applications	LD_{50}	TER_A
Vineyard	BBCH 10-19 (vole)	n.a.	81.9	2457 (single application)	> 34475	> 14

When taking into account only one application during BBCH 15-19, the calculated TER for the small herbivorous (BBCH10-19, vole) is above the trigger value of 10 is indicating that Sulphur Dust poses an acceptable acute risk to mammals following application according to the proposed use patterns.

The initial reviewed GAP was 5 applications of the products, on grapes [application window: BBCH stages 15-89] at an application rate of 29.55 kg a.s./ha with an interval between each application of 7 days. After, the first review performed by RMS, the applicant chose to add some precisions about the timing of application of its product on grapes and requested only one application between BBCH stages 15 and 19. Even if no information is provided to support this assumption it is RMS opinion that it can be reasonably assumed that no more than 1 application would occur between BBCH 15 and 19. Therefore, the acute risk for vole for BBCH 10-19 is considered acceptable.

- **Long-term risk assessment**

No long-term multiple dosing studies have been performed with technical sulfur as it has been used for agricultural purposes for decades and is generally regarded as safe for human exposure. The toxicology studies reported and the open literature database provide sufficient evidence of the safety in use of sulfur and sulfur-containing products. This view is supported by the US-EPA Office of Pesticide Programs

(USEPA OPP) and therefore long-term exposure for mammals related to pesticide use is not expected to present any unacceptable risk.

- **Drinking water exposure**

Mammals may drink contaminated water from puddles formed on the soil surface of a field after heavy rainfall events.

For sulfur a K_{oc} value is available, *i.e.* 3615.3 mL/g; The effective application rate is calculated by multiplying the proposed application rates by MAF values based on the DT_{50} in soil (EFSA, 2009) for the active substance; for sulfur a soil DT_{50} is not available (see Volume 3 CA B.8 for more details), therefore as a worst-case approach the maximum yearly application rate for Sulphur Dust (147.75 kg/ha/yr for vineyards) is assumed to be the maximum effective application rate.
The ratios of the effective application rate to the relevant endpoints are presented in the following table.

Table 95: Drinking water assessment for the proposed use of Sulphur Dust

Time scale	Proposed application rate	MAF	Effective application rate	Endpoint (mg a.s./kg bw)	Ratio	Trigger value
Acute	29550 g a.s./ha	Not applicable	147750 g a.s./ha	LD_{50} > 34475	4.296	3000

The acute ratio is below the relevant trigger value demonstrating an acceptable acute risk to mammals *via* contaminated drinking water from the proposed uses of Suphfur Dust.

- **Effects of secondary poisoning**

As long as no biomagnification of sulfur in terrestrial food chains is expected and because sulfur is not toxic, is a naturally occurring mineral and an essential element in the metabolism of all living organisms (as stated in the DAR (2008) for sulfur and its Final Addendum to the DAR (2008)), no secondary risk via food chain was assessed neither by the notifier nor by the RMS. Moreover, no long-term toxicity study on mammals is available.

- **Risk assessment conclusions for 'Sulphur Dust'**

Based on the risk assessment presented above, no unacceptable risk for mammals is expected for acute exposure to contaminated food indicated by TER_A values above the corresponding trigger value of 10 and long-term exposure for mammals related to pesticide use is not expected to present any unacceptable risk. Furthermore, no unacceptable risks are expected arising from other routes of direct exposure or secondary poisoning (residue uptake from drinking water or bioaccumulation in food chains). In conclusion, an acceptable overall risk for mammals is indicated for the representative GAP uses of Sulphur Dust.

2.9.1.3 Summary of product exposure and risk assessment for aquatic organisms

As evaluated in Volume 3 CA B.9.2 for all aquatic toxicity tests with sulfur and/or the representative products, the endpoints observed in the tests with aquatic organisms were above the solubility limit of sulfur, regardless if sulfur was applied as 'Sulphur Dust' or 'Sulfur 80% WG'.

In agreement with the conclusion of the first EU review and confirmed by the current evaluations, the water solubility limit of sulfur defines the endpoint for all groups of aquatic organisms exposed to sulfur in surface water. Hence, the water solubility limit of sulfur is the relevant endpoint for acute and chronic exposure of all groups of aquatic organisms in the water column.

As verified in Volume 3 CA B.2.5, sulfur is practically insoluble in water (water solubility = 16 µg/L according to a newly generated study (KCA 2.5/03; Rigamonti, E. (2018)).
Accordingly, the endpoint for effects on aquatic organisms in the water column is adjusted to 16 µg/L, the new endpoint to be used in the risk assessment.

Overall, the risk to aquatic organisms in the water column can be considered in general as low because the water solubility limit of the active substance sulfur is very low, and no effects were observed at concentrations which clearly exceeded the water solubility by several orders of magnitude. Further, there is no risk of bioconcentration of sulfur. Therefore, it is not necessary to assess the risk for aquatic organisms by calculating PECsw/RAC[25] ratios and sulfur can be considered of no concern for aquatic organisms in the water column.

Please note that according to the e-fate section, it cannot be excluded that the use of sulfur will have an impact on the natural levels of sulfates in the aquatic environment. Neither PECsw/sed nor endpoints (except for chironomus) for sulfate were provided by the applicant. A data gap was identified for information on the natural buffering capacity of surface water bodies in Europe to neutralize acid inputs from sulfate ions potentially formed following the use of sulfur and on the possible adverse effects on aquatic organisms, other than sediment-dwelling organisms. A risk assessment might be necessary. Without further data upon exposure and toxicity of sulfate toward aquatic organisms the risk assessment is considered as not finalized.

- **Relevant endpoints and risk assessment for sediment dwelling organisms for 'Sulfur 80% WG'**

An overall acceptable risk can be concluded for the organisms of the aquatic environment exposed to sulfur after application of 'Sulfur 80 % WG' according to the intended use patterns. Nevertheless, since sulfur might adsorb to sediment after entering the surface water, a risk assessment for sediment dwelling organisms was performed.

Tier-1 effect assessment on the basis of sediment-dwelling organisms

According to EFSA 2013, the Regulatory Acceptable Concentration (RAC) relevant for the risk assessment was determined. The RAC is defined as concentration at which no adverse effects are expected for aquatic organisms. The results of this assessment are presented in the following tables including the ratio between predicted environmental concentrations in sediment (PEC_{sed}) and regulatory acceptable concentrations (RAC) for aquatic organisms.

Table 96: Acceptability of risk (PEC/RAC < 1) for sediment-dwelling organisms and maximum FOCUS Step-1 and Step-2 PEC_{sed} values following a multiple application of 'Sulfur 80% WG' in vineyards (10× 10 kg a.s./ha, i = 7 d, BBCH 05-81)

Group		Sediment dweller chronic
Test species		*C. riparius*
Endpoint (mg/kg sed_{dw})		NOEC 592.9
AF		10
RAC (mg/kg sed_{dw})		59.3
FOCUS Scenario	$PEC_{sed\ max}$ (mg/kg sed_{dw})	
Step 1	270.07	**4.55**

[25] PECsw = Predicted Environmental Concentration in surface water; RAC = Regulatory Acceptable Concentration

Group		Sediment dweller chronic
Test species		*C. riparius*
Endpoint (mg/kg sed_{dw})		NOEC 592.9
AF		10
RAC (mg/kg sed_{dw})		59.3
FOCUS Scenario	$PEC_{sed\ max}$ (mg/kg sed_{dw})	
Step 2	59.43*	**1.002**

AF: Assessment factor; PEC: Predicted environmental concentration; RAC: Regulatory acceptable concentration
Bold: PEC/RAC ratios are above the trigger of 1, *i.e.* no acceptable risk can be concluded at this step
*Considering the highest PEC_{sed} value estimated in the Volume 3 CP B8

Considering FOCUS Step-2 PEC_{sed} values for the use of 'Sulfur 80% WG' in grapevine, the corresponding PEC/RAC values are above the trigger value of 1, indicating an unacceptable risk for sediment-dwelling organisms.

The risk assessment for sediment dwelling organisms for the representative use upon grapevine indicates an unacceptable risk. However, one may notice that:
- The PEC/RAC value is very close (actual value: 1.002) to the trigger value of 1;
- The endpoint used is a NOEC corresponding to the highest concentration tested;
- Available PECsed do not go further than step 2 which is based on calculations made for realistic worst-case application patterns, PECsed are therefore certainly overestimated.

Therefore, for all reasons cited above, RMS considered that the risk assessment for sediment-dwelling organisms is acceptable for use of Sulfur 80% WG on grapevine.
No further refinement steps are considered to be required.

Table 97: Acceptability of risk (PEC/RAC < 1) for sediment-dwelling organisms and maximum FOCUS Step-1 and Step-2 PEC_{sed} values following a multiple application of 'Sulfur 80% WG' in cereals (4× 8 kg a.s./ha, i = 7 d, BBCH 15-69)

Group		Sediment dweller chronic
Test species		*C. riparius*
Endpoint (mg/kg sed_{dw})		NOEC 592.9
AF		10
RAC (mg/kg sed_{dw})		59.3
FOCUS Scenario	$PEC_{sed\ max}$ (mg/kg sed_{dw})	
Step 1	82.21	**1.39**
Step 2	37.49*	0.63

AF: Assessment factor; PEC: Predicted environmental concentration; RAC: Regulatory acceptable concentration
Bold: PEC/RAC ratios are above the trigger of 1, *i.e.* no acceptable risk can be concluded at this step
*Considering the highest PEC_{sed} estimated in the Volume 3 CP B8.

Considering FOCUS Step-2 PEC_{sed} values for the envisaged GAP uses of 'Sulfur 80% WG' in cereals, the corresponding PEC/RAC values are below the trigger value of 1, indicating an acceptable risk for sediment-dwelling organisms. No further refinement steps are considered to be required.

- **Potential for bioconcentration**

In general, the potential of bioconcentration for sulfur is considered to be negligible as sulfur is a naturally occurring mineral and an essential element in the metabolism of all living organisms. Elemental sulfur is known to enter the sulfur cycle immediately after application, *i.e.* elemental sulfur is transformed by water bacteria into various stages of oxidation which are soluble and thus made available for further uptake by various organisms such as plants and animals. No reliable experimental log Kow value exists (related to its extremely low water solubility). The active substance is not expected to accumulate in fish. In conclusion, the risk arising from bioaccumulation of the active substance is considered to be acceptable.

- **Risk assessment conclusions for 'Sulfur 80% WG'**

Based on the results of the standard risk assessment at Tier-1, a safe use (with respect to an acceptable risk for aquatic and sediment-dwelling organisms) was demonstrated for the representative GAP uses of 'Sulfur 80% WG' in grapevine and cereals. No mitigation measures have to be applied.

However, please note that according to the e-fate section, it cannot be excluded that the use of sulfur will have an impact on the natural levels of sulfates in the aquatic environment. Neither PECsw/sed nor endpoints (except for chironomus) for sulfate were provided by the applicant. A data gap was identified for information on the natural buffering capacity of surface water bodies in Europe to neutralize acid inputs from sulfate ions potentially formed following the use of sulfur and on the possible adverse effects on aquatic organisms, other than sediment-dwelling organisms. A risk assessment might be necessary. Without further data upon exposure and toxicity of sulfate toward aquatic organisms the overall risk assessment is considered as not finalized.

- **Risk assessment for sediment dwelling organisms for 'Sulphur Dust'**

Tier-1 effect assessment on the basis of sediment-dwelling organisms

Table 98: Acceptability of risk (PEC/RAC < 1) for sediment-dwelling organisms and maximum FOCUS Step-1 and Step-2 PECsed values following a multiple application of 'Sulphur Dust' in vineyards (5× 29.55 kg a.s./ha, i = 7 d, BBCH 15-89)

Group		Sediment dweller chronic
Test species		*C. riparius*
Endpoint (mg/kg sed_{dw})		NOEC 592.9
AF		10
RAC (mg/kg sed_{dw})		59.3
FOCUS Scenario	$PEC_{sed\ max}$ * (mg/kg sed_{dw})	
Step 1 (1 application)	147.75	**2.49**
Step 1 (5 applications)	738.75	**12.46**
Step 2 (1 application)	103.43	**1.74**

Group		Sediment dweller chronic
Test species		*C. riparius*
Endpoint (mg/kg sed_{dw})		NOEC 592.9
AF		10
RAC (mg/kg sed_{dw})		59.3
FOCUS Scenario	$PEC_{sed\ max}$ * (mg/kg sed_{dw})	
Step 2 (5 applications)	517.13	**8.72**
Step 2 (5 applications) (Run-off + drainage 80% attenuation)	398.93	**6.73**
Step 2 (5 applications) (Run-off + drainage 90% attenuation)	384.15	**6.48**

AF: Assessment factor; PEC: Predicted environmental concentration; RAC: Regulatory acceptable concentration
Bold: PEC/RAC ratios are above the trigger of 1, i.e. no acceptable risk can be concluded at this step
*Considering the highest PEC_{sed} value for the scenarios estimated in the Volume 3 CP B8.

Considering FOCUS Step-2 PEC_{sed} values for the envisaged GAP uses of 'Sulphur Dust' in grapevine, the corresponding PEC/RAC values are all above the trigger value of 1, indicating an unacceptable risk for sediment-dwelling organisms. Further refinement steps are therefore considered to be required.

Please note that the PECsed used for the risk assessement are those considering a worst-case approach with a particulate drift of 100%. Indeed, given all uncertainties identified in the Volume 3 CP B8. for Sulphur Dust, part 8.5.2. the BBA drift rate values (Rautmann, 2000) are not considered as relevant for application of dust from dustable powder product (e.g. Sulphur dusting in vineyards).
RMS is of the opinion that there is a need of more information on the extrapolation of the drift % value (BBA, 2000) to foliar dust applications before their use in further calculations. Compared to the size of the droplets produced by nozzles during spray applications on vines (around 100 µm), the size distribution of sulfur particulate in the formulated product Sulphur Dust are really smaller (median value = 18 µm; 5.6-53.5 µm (10^{th} cxentile-90^{th} centile, please refer to Vol.3 B.2 for more details). As a worst-case approach, conservative drift values should be considered in calculations until an agreement on the drift % value to be used for dustable powder formulation is reached at the EU level.

- **Potential for bioconcentration**

In general, the potential of bioconcentration for sulfur is considered to be negligible as sulfur is a naturally occurring mineral and an essential element in the metabolism of all living organisms. Elemental sulfur is known to enter the sulfur cycle immediately after application, *i.e.* elemental sulfur is transformed by water bacteria into various stages of oxidation which are soluble and thus made available for further uptake by various organisms such as plants and animals. No reliable experimental log Kow value exists (related to its extremely low water solubility). The active substance is not expected to accumulate in fish. In conclusion, the risk arising from bioaccumulation of the active substance is considered to be acceptable.

- **Risk assessment conclusions for 'Sulphur Dust'**

Based on the results of the standard risk assessment at Tier-1, a safe use (with respect to an acceptable risk for aquatic organisms) was demonstrated for the representative GAP uses of Sulphur Dust in grapevine.

For sediment-dwelling organisms, the corresponding PEC/RAC values are all above the trigger value of 1, indicating an unacceptable risk for sediment-dwelling organisms. Further refinement steps are therefore considered to be required.

In addition, please note that according to the e-fate section, it cannot be excluded that the use of sulfur will have an impact on the natural levels of sulfates in the aquatic environment. Neither PECsw/sed nor endpoints (except for chironomus) for sulfate were provided by the applicant. A data gap was identified for information on the natural buffering capacity of surface water bodies in Europe to neutralize acid inputs from sulfate ions potentially formed following the use of sulfur and on the possible adverse effects on aquatic organisms, other than sediment-dwelling organisms. A risk assessment might be necessary. Without further data upon exposure and toxicity of sulfate toward aquatic organisms the overall risk assessment is considered as not finalized.

2.9.1.4 Summary of product exposure and risk assessment for bees

- **Risk assessment for 'Sulfur 80% WG'**

Acute oral and contact risk assessment

As recommended in the underlying guidance document SANCO/10329/2002 (2002), the risk for bees is evaluated on the basis of Hazard Quotients (HQ). Hazard Quotients [expressed as application rate (in g a.s./ha) / LD_{50} (in µg a.s./bee)] were calculated considering the lowest LD_{50} values and the maximum single application rates for the uses in grapevine and cereals, respectively. The specific protection goal is achieved, if the calculated HQ value is smaller or equal to the trigger value for honeybees.

Table 99: Hazard Quotients (HQ) for oral and contact exposure of *Apis mellifera*

Intended use	Grapevine (10× 10 kg prod./ha, BBCH 05-81)		
Active substance Application rate (g/ha)	Sulfur 10× 10000 g a.s./ha		
Test design	LD_{50} (lab.) (µg a.s./bee)	Single application rate (g a.s./ha)	$HQ_{contact/oral}$ criterion: HQ ≤ 50
Contact toxicity	> 700.1	10000	< 14.3
Oral toxicity	> 700.1	10000	< 14.3
Intended use	Cereals (4× 8 kg prod./ha, BBCH 15-69)		
Active substance Application rate (g/ha)	Sulfur 4× 8000 g a.s./ha		
Test design	LD_{50} (lab.) (µg a.s./bee)	Single application rate (g a.s./ha)	$HQ_{contact/oral}$ criterion: HQ ≤ 50
Contact toxicity	> 700.1	8000	< 11.4
Oral toxicity	> 700.1	8000	< 11.4

As outlined in the table above, HQ values for acute oral (Q_{HO}) and contact (Q_{HC}) in-field exposure of bees are below the trigger of 50 indicating an acceptable acute risk for bees for the intended GAP uses of 'Sulfur 80% WG'.

- **Chronic risk assessment for adult bees and bee larvae**

Chronic oral exposure

Chronic oral toxicity data on adult honeybees and honeybee larvae were generated to address the new data requirements set in the Annex to Reg. (EU) 283 and 284/2013.

Chronic risk assessment for adult bees and bee larvae according to EPPO (2010)

The applicant has only provided a risk assessment according to EPPO (2010), which is considered not sufficient by RMS as a risk assessment according to EFSA 2013 should have been provided. However, as a tunnel test has been provided it is possible to draw an overall conclusion for bees.

Chronic risk assessment for bees based on semi-field studies
In addition, the effects of 'Sulfur 80% WG' on honeybees were examined under semi-field conditions (KCP1 10.3.1.5/01). In this tunnel test, the test item was applied via foliar spray at a single application rate of 10 kg a.s./ha (12.5 kg product/ha) on full-flowering Phacelia during bee-flight. The exposure lasted for 7 days, thereafter, bee colonies were removed from the tunnels and placed to a remote site for further 20 days. Following the application and during the entire course of the study, no significant differences on adult and pupal bee mortality, foraging activity, bee behaviour, colony and brood development were observed between the test item treatment and the control. When assessing the brood area, for larvae, the initial mean areas were 2050, 2192 and 1547 cm^2 /colony for the control, test item and reference item treatment at the beginning of the test, respectively. The mean areas of the single stages (eggs, larvae and pupae) as well as the total mean brood area of the control and test item treatment developed within the natural variability in a comparable manner during the course of the study. At the last assessment on day 29 after application, the mean brood area/colony amounted to 2089 cm^2 (+ 2 %) and 2359 cm^2 (+ 8 %) for larvae in the control and test item treatment, respectively. As the bee brood development was not affected by the test item during the entire trial, it can be concluded that 'Sulfur 80% WG' has no adverse effects on honeybees and their brood and colony development when applied according to the critical intended GAP.

Chronic risk assessment conclusions
The exposure scenarios described above are covering the expected chronic exposure of adult honeybees as well as the exposure of honeybee brood. In conclusion, risks for honeybees following the application of Sulfur 80% WG are acceptable. Therefore, an overall acceptable risk for bees can be expected in consideration of the intended GAP uses of 'Sulfur 80% WG'.

- **Risk assessment conclusions for 'Sulfur 80% WG'**

Based on the risk assessment for honeybees performed for acute (HQ-approach) and in consideration of higher tier data (tunnel test), an acceptable risk for bees is concluded for the intended uses of 'Sulfur 80% WG'.

- **Risk assessment for 'Sulphur Dust'**

Risk assessment for bees according to SANCO/10329/2002 rev 2 (final), October 17, 2002

Acute oral and contact risk assessment.

The acute risk assessment for bees performed in accordance with the recommendations of the "Guidance Document on Terrestrial Ecotoxicology", as provided by the Commission Services (SANCO/10329/2002 rev 2 (final), October 17, 2002).

Table 100: Hazard Quotients (HQ) for oral and contact exposure of *Apis mellifera*

Intended use	Grapevine (BBCH 15-89)		
Active substance	Sulfur		
Active substance	sulfur		
Application rate (g/ha)	5× 29550 g a.s./ha		
Test design	**LD_{50} (lab.) (µg a.s./bee)**	**Single application rate (g a.s./ha)**	**$HQ_{contact/oral}$ criterion: HQ ≤ 50**
Contact toxicity	> 700.1	29550	< 42.2
Oral toxicity	> 700.1	29550	< 42.2

As outlined in the table above, HQ values for acute oral (Q_{HO}) and contact (Q_{HC}) in-field exposure of bees are below the trigger of 50 indicating an acceptable acute risk for bees for the intended GAP uses of Sulphur Dust.

Risk assessment for bees according to EFSA Guidance Document for bees (2013)

The evaluation of the risk for bees was performed in accordance with the "EFSA Guidance Document on the risk assessment of plant protection products on bees (*Apis mellifera, Bombus* spp.) and solitary bees, Journal 2013; 11(7):3295.
The results of the acute and chronic screening / Tier-1 risk assessments are summarised in the following tables.

Screening step

Table 101: Screening acute contact exposure assessment of the risk for bees due to the use of Sulphur Dust in grapevine

Intended use	Grapevine		
Active substance	sulfur		
Application rate (g/ha)	5 × 29550		
Test design	**LD_{50} (lab.) (µg a.s./bee)**	**Single application rate (g a.s./ha)**	**HQ criterion: HQ ($_{SW}$) ≤ 85**
Contact toxicity	> 700.1	29550	< 42.21

The HQ values for the acute contact exposure fall below the trigger value of 85 for sideward spray, indicating an acceptable acute contact risk to bees following application of Sulphur Dust at the proposed label rate.

Table 102: Screening assessment of the acute/chronic oral risk for bees and larvae due to the use of Sulphur Dust in grapevine

Intended use	Grapevine
Active substance	sulfur
Application rate (g/ha)	5 × 29550

Test design	**End-point (µg a.s./adult bee - larvae)**	**Single application rate (kg/ha)**	**SV Side-ward**	**ETR**	**Trigger value**
Acute oral exposure adult bees					
Screening ETRbees= AR*SV/LD_{50}	LD_{50} > 700.1	29.55	10.6	**< 0.45**	< 0.2
Chronic oral exposure adult bees					
Screening ETRbees= AR*SV/10dLDD_{50}	LDD_{50} > 149.3	29.55	10.6	**< 2.18**	< 0.03
Chronic oral exposure adult larvae					
Screening ETRlarvae= AR*SV/NOELlarvae	no relevant endpoint	29.55	6.1	not calculable*	< 0.2

* No relevant endpoint can be estimated from the larvae study
ETR: Exposure toxicity ratio.
Bold: HQ values that exceed the trigger value (need a refinement)

All the calculated ETR values of acute and chronic oral toxicity for adult bees exceed the trigger value of 0.2 and 0.03 indicating that a refinement is needed. Tier-1 risk assessments, according to EFSA Guidance Document on the risk assessment of plant protection products on bees (EFSA Journal 2013; 11(7):3295), are presented in the following tables.

Tier-I risk assessement

Table 103: Tier-I assessment of the acute oral risk for adults due to the use of Sulphur Dust in grapevine

Intended use	Grapevine				
Active substance	sulfur				
Application rate (g/ha)	5 × 29550				
LD_{50} adult	> 700.1 µg a.s./bee				
twa	-				
Test design	**Single application rate (kg/ha)**	**Ef**	**SV Side-ward**	**ETR**	**Trigger value**
Risk from foraging on the treated crop					
Tier I (BBCH 10 - 69) ETRacute adult oral=AR*Ef*SV/LD_{50}	29.55	1	10.6[1]	**0.45**	< 0.2
Tier I (BBCH ≥ 70) ETRacute adult oral=AR*Ef*SV/LD_{50}			0	0.00	
Risk from foraging on an adjacent crop					
Tier I (BBCH 10 -19) ETRacute adult oral=AR*Ef*SV/LD_{50}	29.55	0.0047	7.6	0.0015	< 0.2
Tier I (BBCH ≥ 20) ETRacute adult oral=AR*Ef*SV/LD_{50}		0.0143		0.0046	
Risk from foraging on weeds in the treated field					

Tier I (BBCH 10 -19) ETRacute adult oral=AR*Ef*SV/LD_{50}	29.55	0.6	3.7^{2}	0.09	< 0.2
Tier I (BBCH 20 -39) ETRacute adult oral=AR*Ef*SV/LD_{50}		0.5		0.08	
Tier I (BBCH ≥ 40) ETRacute adult oral=AR*Ef*SV/LD_{50}		0.3		0.05	
Risk from foraging in the field margin					
Tier I (BBCH 10 -19) ETRacute adult oral=AR*Ef*SV/LD_{50}	29.55	0.009	3.7^{2}	0.0014	< 0.2
Tier I (BBCH ≥ 20) ETRacute adult oral=AR*Ef*SV/LD_{50}		0.027		0.0042	
Risk from foraging the following year on a permanent crop or on a succeeding crop for annual crops					
Tier I (BBCH 15 -89) ETRacute adult oral=AR*Ef*SV/LD_{50}	29.55	1	0.7	0.03	< 0.2

ETR: Exposure toxicity ratio.
[1)] Treated crop – application after emergence (sideward spraying)
[2)] Weeds in the field – application after emergence of weeds and plants in field margins
Bold: HQ values that exceed the trigger value

Table 104: Tier-I assessment of the chronic oral risk for adults due to the use of Sulphur Dust in grapevine

Intended use	Grapevine				
Active substance	sulfur				
Application rate (g/ha)	5 × 29550				
$10dLDD_{50}$ adult	>143.9 µg a.s./bee				
twa	0.72				
Test design	**Single application rate (kg/ha)**	**Ef**	**SV Side-ward**	**ETR**	**Trigger value**
Risk from foraging on the treated crop					
Tier I (BBCH 10 -19) ETRchronic adult oral= AR*Ef*SV*twa/$10dLDD_{50}$	29.55	1	8.2^{1}	**1.21**	< 0.03
Tier I (BBCH ≥ 20) ETRchronic adult oral = AR*Ef*SV*twa/$10dLDD_{50}$			0	0	
Risk from foraging on an adjacent crop					
Tier I (BBCH 10 - 19) ETRchronic adult oral = AR*Ef*SV*twa/$10dLDD_{50}$	29.55	0.047	5.8	0.004	< 0.03
Tier I (BBCH ≥ 20) ETRchronic adult oral = AR*Ef*SV*twa/$10dLDD_{50}$		0.0143		0.012	

Risk from foraging on weeds in the treated field						
Tier I (BBCH 10 -19) ETRchronic adult oral = AR*Ef*SV*twa/10dLDD$_{50}$	=	29.55	0.6	2.9[2]	**0.257**	< 0.03
Tier I (BBCH 20 -39) ETRchronic adult oral = AR*Ef*SV*twa/10dLDD$_{50}$	=		0.5		**0.214**	
Tier I (BBCH ≥ 40) ETRchronic adult oral = AR*Ef*SV*twa/10dLDD$_{50}$	=		0.3		**0.129**	
Risk from foraging in the field margin						
Tier I (BBCH 10 - 19) ETRchronic adult oral = AR*Ef*SV*twa/10dLDD$_{50}$	=	29.55	0.009	2.9[2]	0.004	< 0.03
Tier I (BBCH ≥ 20) ETRchronic adult oral = AR*Ef*SV*twa/10dLDD$_{50}$	=		0.027		0.012	
Risk from foraging the following year on a permanent crop or on a succeeding crop for annual crops						
Tier I (BBCH 15 -89) ETRchronic adult oral = AR*Ef*SV*twa/10dLDD$_{50}$	=	29.55	1	0.54	**0.080**	< 0.03

ETR: Exposure toxicity ratio.
[1)] Treated crop – application after emergence (sideward spraying)
[2)] Weeds in the field – application after emergence of weeds and plants in field margins
Bold: HQ values that exceed the trigger value

The ETR values at Tier-1 for oral acute exposure from sulfur applications for adult bees on treated crops (except for the use of product on grape crop during its ripening stage, BBCH ≥ 70) are higher than the trigger value of 0.2 proposed in the EFSA Guidance Document on the risk assessment of plant protection products on bees (EFSA Journal 2013; 11(7):3295), at the proposed label rate. Therefore, a Higher-Tier risk assessment is necessary.

The ETR values at Tier-1 for oral chronic exposure from sulfur applications for adult bees on treated crops (except for the use of product on grape at BBCH ≥ 20), on weed and on following year are higher than the trigger value of 0.03 proposed in the EFSA Guidance Document on the risk assessment of plant protection products on bees (EFSA Journal 2013; 11(7):3295), at the proposed label rate. Therefore, a Higher-Tier risk assessment is necessary.

The ETR values at Tier-I step for oral chronic exposure from applications for larvae cannot be calculated since the toxicity study for larvae is not considered relevant for the risk assessement.

According to the EFSA Guidance Document (EFSA Journal 2013; 11(7):3295), Higher-Tier risk assessment is necessary.

For all these reasons a semi-field test like a tunnel test is required in order to conduct a Higher-Tier risk assessment.

In this tunnel test, the test item was applied foliar at a single application rate of 29.55 kg a.s./ha (30 kg product/ha) on full-flowering Phacelia during bee-flight. The exposure lasted for 7 days, thereafter, bee colonies were removed from the tunnels and placed to a remote site for further 20 days. Following the application and during the entire course of the study, no significant differences on adult and pupal bee

mortality, foraging activity, bee behaviour, colony and brood development were observed between the test item treatment and the control. As in particular, the bee brood development was not affected by the test item during the entire trial, it can be concluded that Sulphur Dust has no adverse effects on honeybees and their brood and colony development when applied according to the critical intended GAP.
Thus, the exposure scenarios described above are covering the expected chronic exposure of adult honeybees as well as the exposure of honeybee brood. In conclusion, no unacceptable risks for honeybees need to be expected. Therefore, an overall acceptable risk for bees can be expected in consideration of the intended GAP uses of Sulphur Dust.

Exposure to contaminated water

Since sulfur is an inorganic compound, the PECsw was not calculated with FOCUS modelling but is the water solubility to be considered as the maximum PECsw = 0.016 mg/L. This value should be used in the assessment of risk from exposure to contaminated water (guttation and surface water)

Assessment of risk from exposure to guttation water

The ETR values for adult bees are calculated as follows:

Acute oral adult LD_{50} (OECD 213, 1998):
$ETR_{acute} = W*PEC/LD_{50}$
$ETR_{acute} = (11.4*0.000016/>100) = 1.824\text{-}E6$
Where W = 11.4 µL/bee per day and is the uptake of adult bees. Where the PEC is the concentration in the guttation water in µg/µL and is assumed to be 100% of the water solubility for the acute risk assessment in the first tier. The risk is therefore considered acceptable.

Chronic adult (10-day LDD_{50})
$ETR_{chronic} = W * PEC/LDD_{50}$
$ETR_{chronic} = (11.4 * 0.54*0.000016/149.3) = 6.60\text{-}E7$
where W = 11.4 µL/bee and is the uptake of adult bees and PEC is the concentration in the guttation water in µg/µL and is assumed to be 54% of the water solubility for the chronic risk assessment in first tier. The LC_{50} is the LC_{50} (in µg/bee per day) based on an exposure period of 10 days.
The risk is therefore considered acceptable.

The ETR for larvae is calculated as follows:

Chronic larvae (NOED)
The chronic ETR value cannot be calculated since the toxicity study for larvae is not considered relevant for the risk assessement. However, the results from the semi-field study are considered sufficient to conclude that this route of exposure is not an area of concern for honey bee development.

Assessment of risk from exposure to surface water

Please refer to the evaluation of exposure to guttation water.

Assessment of risk from exposure to water in puddles

EFSA Guidance Document on the risk assessment of plant protection products on bees (EFSA Journal 2013; 11(7):3295) recommends that the concentrations in the puddle water should be estimated from the concentrations in the runoff water from the FOCUS runoff scenarios (R1, R2, R3, R4; see FOCUS, 2001) relevant for the use. Since sulfur is an inorganic compound, the use of FOCUS model for PECsw calculations is not recommended since it gave values that exceed the water solubility of the compound (16 µg/L) and consequently no PECsw value for runoff scenarios are available.
For the calculation the max PECsw, corresponding to the sulfur water solubility, is used so please refer to the risk assessment presented from exposure to guttation water.

2.9.1.5 Summary of product exposure and risk assessment for non-target arthropods other than bees

- **Exposure and Risk assessment non-target arthropods other than bees for 'Sulfur 80% WG'**

The exposure of non-target arthropods to 'Sulfur 80% WG' expressed as Predicted Environmental Rates (PER) was assessed separately for the in-field area and the off-field area. The PERs were calculated according to the following formula derived from ESCORT 2 guidance document.

- **Risk assessment for in-field exposure**

The results of the Tier-1 and Tier-2 are presented in the table below.

Table 105: Tier-1 and Tier-2 assessment of the in-field risk for non-target arthropods due to the use of 'Sulfur 80% WG' in grapevine and cereals

Intended use	Grapevine (10× 10.0 kg a.s./ha, BBCH 05-81)		
Active Substance Application rate (kg a.s./ha) MAF	Sulfur 10× 10 kg a.s./ha 3.5		
Test species Tier-1	LR_{50} (kg a.s./ha)	$PER_{in\text{-}field}$ (kg a.s./ha)	$HQ_{in\text{-}field} \leq 2$
Aphidius rhopalosiphi	< 10	35.0	**No (HQ > 3.5)**
Test species **Tier II-standard test with non-standard species**	LR_{50} (extended lab) **(kg a.s./ha)**	$PER_{in\text{-}field}$ **(kg a.s./ha)**	$HQ_{in\text{-}field}$ **:** HQ ≤ 1
Poecilus cupreus	> 10	35.0	**No (HQ = 3.5)**
Chrysoperla carnea	> 10	35.0	**No (HQ = 3.5)**
Aleochara bilineata	> 10	35.0	**No (HQ = 3.5)**
Test species Tier-2, extended laboratory studies	Rate with ≤ 50 % effect (kg a.s./ha)	$PER_{in\text{-}field}$ (kg a.s./ha)	$PER_{in\text{-}field}$ below rate with ≤ 50 % effect?
Aphidius rhopalosiphi	> 20.16	35.0[1)]	**No**
Typhlodromus pyri	> 1.25	35.0	**No**
Trichogramma cacoeciae	0.0648	17.5[1)]	**No**
Intended use	Cereals (4× 8.0 kg prod./ha, BBCH 15-69)		
Active Substance Application rate (kg a.s./ha) MAF	Sulfur 4× 8 kg a.s./ha 2.7		
Test species Tier-1	LR_{50} (kg a.s./ha)	$PER_{in\text{-}field}$ (kg a.s./ha)	$HQ_{in\text{-}field} \leq 2$
Aphidius rhopalosiphi	< 10	21.6	**No (HQ > 2.2)**

Test species **Tier II-standard test with non-standard species**	LR_{50} (extended lab) **(kg a.s./ha)**	$PER_{in\text{-}field}$ **(kg a.s./ha)**	**$HQ_{in\text{-}field}$: HQ ≤ 1**
Poecilus cupreus	> 10	21.6	**No (HQ = 2.2)**
Chrysoperla carnea	> 10	21.6	**No (HQ = 2.2)**
Aleochara bilineata	> 10	21.6	**No (HQ = 2.2)**
Test species Tier-2, extended laboratory studies	Rate with ≤ 50 % effect (kg a.s./ha)	$PER_{in\text{-}field}$ (kg a.s./ha)	$PER_{in\text{-}field}$ below rate with ≤ 50 % effect?
Aphidius rhopalosiphi	> 20.16	21.6	**No**
Typhlodromus pyri	> 1.25	21.6	**No**
Trichogramma cacoeciae	0.0648	21.6	**No**

MAF: Multiple application factor; PER: Predicted environmental rate

[1)] According to ESCORT 2 the application rate for 3-dimensional crops, e.g. orchards and vineyards can be multiplied by a correction factor of 0.5. This correction factor can only be used when the test is done on flat surface.

As outlined in the table above, further considerations are necessary.

Refined risk assessment for in-field exposure

Refinement for Trichogramma cacoeciae and Aphidius rhopalosiphi

According to ESCORT 2, the main criterion for the acceptability of effects in in-field habitats is defined by the potential for recovery of any affected non-target arthropod population, *i.e.* demonstrating that residual toxicity declines sufficiently rapid to allow a recovery within one year. Such tests should be conducted with the most sensitive species, which is *Trichogramma cacoeciae* in the case of sulfur.

For this reason, extended laboratory studies with aged residues on plant surfaces has been performed to determine the effects and the duration of the residual activity of the test item ‘Sulfur 80% WG’ on the egg parasitoid *Trichogramma cacoeciae.*

The aged residue study (Röhlig 2016) was conducted on vine leaves maintained outdoor for aging of residues after spray application of ‘Sulfur 80% WG’. Extrapolation of the results from vine as surrogate crop to other crops is in agreement with guidance document ESCORT 2. The use of a standardised crop allows optimisation of the test system for maintenance of the test species and for greater flexibility for test timing.

The newly generated aged residue test (KCP1 10.3.2.2/02, Röhlig 2016) involved multiple applications, which cover the critical use pattern of ‘Sulfur 80% WG’ under most realistic conditions. Adults of the parasitoid were exposed in bioassays to freshly dried or aged residues of ‘Sulfur 80% WG’ on excised grapevine leaves at several time points after application. Effects on reproduction were assessed by the number of parasitized host eggs per female. The potted test plants were sprayed outdoor under semi-field conditions. From Day After Last Treatment (DALT) -14 until DALT 0 the spray residues aged under semi-field conditions with rain protection. After residues of the last application were dried, spray residues are allowed to age outdoor under field conditions without rain-protection.
Bioassays were initiated on DALT 0, 14, 28, 42, 56, 70, 84, and 98.

Tested under extended laboratory conditions and using aged spray residues on detached grapevine leaves, the effects on parasitisation capacity of the egg parasitoid *T. cacoeciae* were below the ESCORT 2 trigger value of 50 % in two consecutive bioassays initiated at the following dates:

- 56 and 70 days after the last application of 4×7.5 kg prod./ha applied at interval of 4-5 days (PER = 16.2 kg a.s./ha, *see below*)
- 84 and 98 days after the last application of 4× 12.5 kg prod./ha applied at an interval of 4-5 days (PER = 27.0 kg a.s./ha, *see below*)

The results indicate a dissipation of residual effects of sulfur within an acceptable delay (less than 100 days).
Based on the results of the new aged residue study, evidence was provided that recovery of the in-field area by the most sensitive arthropod species, i.e. *T. cacoeciae*, is possible within a significantly shorter period than one year after application of up to 4× 6.0 and 4× 10.0 kg a.s./ha. As displayed in the Table below, these rates correspond to in-field PERs of 27.0 kg a.s./ha and 16.2 kg a.s./ha, respectively, in consideration of a 5-day spray interval.

Table 106: Predicted exposure rates from the aged residue test with *Trichogramma cacoeciae* after application of 4× 6.0 kg a.s/ha and 4× 10.0 kg a.s./ha and comparison with the PER for the intended GAP uses of 'Sulfur 80% WG'

Use pattern of 'Sulfur 80% WG' in	**Single appl. rate [kg a.s./ha]**	**Number of applications**	**Interval between applications [days]**	**MAF according to ESCORT 2**	**PER in-field after last application [kg a.s./ha]**
Aged residue test [1)]	6.0	4	5	2.7	16.2
	10.0		5	2.7	27.0
GAP in grapes	10.0	10	7	3.5	35
GAP in cereals	8.0	4	7	2.7	21.6

1) Aged residue test with *Trichogramma cacoeciae* [KCP1 10.3.2.2/05; Röhlig, U., 2016]

In view of in-field PER values of 35 kg a.s./ha and 21.6 kg a.s./ha for the GAPs of 'Sulfur 80% WG' in grapes and cereals, respectively, the PER of 27.0 kg/ha of the aged residue study is forwarded in the risk assessment as displayed in Table 113.

Table 107: Higher tier assessment of the in-field risk for non-target arthropods due to the use of 'Sulfur 80% WG' in grapevine and cereals based on data from the new aged residue study (KCP1 10.3.2.2/02)

Intended use	Grapevine (10× 10.0 kg a.s./ha, BBCH 05-81)		
Active Substance Application rate (kg a.s./ha) MAF	Sulfur 10× 10 kg a.s./ha 3.5		
Most sensitive test species			
Test species Higher tier (aged residue study)	Rate with ≤ 50 % effect at DALT 84 (kg a.s./ha)	$PER_{in\text{-}field}$ (kg a.s./ha)	$PER_{in\text{-}field}$ below or at rate with ≤ 50 % effect?
Trichogramma cacoeciae	27.0	35	**No**
Intended use	Cereals (4× 8.0 kg prod./ha, BBCH 15-69)		
Active Substance Application rate (kg a.s./ha) MAF	Sulfur 4× 8 kg a.s./ha 2.7		

Most sensitive test species			
Test species Higher tier (aged residue study)	Rate with ≤ 50 % effect at DALR 84 (kg a.s./ha)	$PER_{in-field}$ (kg a.s./ha)	$PER_{in-field}$ below rate with ≤ 50 % effect?
Trichogramma cacoeciae	27.0	21.6	Yes

MAF: Multiple application factor; PER: Predicted environmental rate; DALT: Days after last treatment

The calculated in-field exposure rates of the representative use on grapevines of 'Sulfur 80% WG' (35 kg a.s./ha) is above the threshold PER value of 27.0 kg a.s./ha derived from the new aged residue study and representing the exposure level at which residues had decreased to an acceptable level with regard to adverse effect on *T. cacoeciae*, the most sensitive arthropod indicator species.

The calculated in-field exposure rates of the representative use on cereals of 'Sulfur 80% WG' is below the threshold PER value of 27.0 kg a.s./ha derived from the new aged residue study and representing the exposure level at which residues had decreased to an acceptable level with regard to adverse effect on *T. cacoeciae*, the most sensitive arthropod indicator species.

Overall, for *T. cacociae*, it can be concluded that no adverse long-term effects need to be expected for the intended GAP use of 'Sulfur 80% WG' in cereals as they do not exceed the in-field exposure rate of 27 kg a.s./ha and therefore fully meet the ESCORT 2 requirement of 'potential for recovery in in-field habitats within a period of 1 year'. For the reprensentative use in grapevine, the intended GAP use of 'Sulfur 80% WG' exceed the in-field exposure rate of 27 kg a.s./ha. Therefore, further refinement are needed for *T. cacociae* for this use.

Refinements are also needed for other arthropods species. No refinements were provided by the applicant. The ones proposed by the RMS are presented below. Indeed, based on the available data, the risk assessment for *T. cacociae* is not considered sufficient to cover all the non-target arthropods species.

Refinement for predatory mites

From the literature search performed by the applicant about effects of sulfur exposure toward non-target arthropods, studies considered as supportives were identified by RMS.

A study was performed with *Typhlodromus pyri* (Gadino et al. (2011) (B.9 KCA 8.3.2.3/14). From this study that may be considered as similar to an extended study, a $NOEC_{repoducution}$ was determined as being below 4.5 kg product/ha. This clearly demonstrates the sensitivity of *T. pyri* toward sulfur exposure.

Studies were performed using other related specie:
In Göven and Güven (2008) (B.9. KCA 8.3.2.3/09), a laboratory study (glass plate exposure) using a sulfur 80% WP product, a LR_{50} and an ER_{50} > 4.0 product kg sulfur/ha (eq. 3.2 kg sulfur/ha), has been derived for the predatory mite *Typhlodromus perbibus.*
On the contrary, in Güven and Madanlar (2010), (B.9. KCA 8.3.2.3/10), from a laboratory study (glass plate exposure) using a sulfur 80% WP product, a LR_{50} < 4.0 product kg sulfur/ha (eq. 3.2 kg sulfur/ha), has been derived for another predatory mite *Typhlodromus athiasae.*
In 2007, Laurin and Bostanian (KCA 8.3.2.3/15), showed that a sulfur product (92% WP product) did not induce significant mortality of the predatory mite *Anystis baccarum*. Nevertheless, it was not possible to retrieved the exact application rate that has been used to perform this study (described as 32-fold of the recommended concentration (132.48 g sulfur/L)).
Another study performed in 2010 (Bernard *et al.*; KCA 8.3.2.3/17), using juveniles of the Australian predatory mite species *Euseius victoriensis* (Womersley) in a "worst-case scenario" direct overspray assays, showed that a wettable sulfur product (80% WP), may induce strong effects both on mortality (ranging from 48.7 to 90.4% 7 days after spraying) and reproduction (from 69.7 to 94.7% fecundity reduction 12 days after spraying). It is RMS opinion, that this study clearly shows that sulfur product may have a strong impact upon mortality and reproduction on predatory mites. From the conclusion of this

study, it is concluded that application of sulfur may disrupt biological control of pest organisms via predator suppression.

The literature search provides usefull information about the sensitivity of predatory mites toward sulfur exposure, reinforcing the fact that further refinement is needed to conclude to an acceptable in-field risk for the 2 representative uses requested in the present RAR.

No data were provided by the applicant to further refine the in-field risk of predatory mites. However, a field study is available in the B.9. CP for Sulphur Dust (KCP2 10.3.2.4/01, Rosenkranz, B., Pavić, B., 2007). The study design is: 5 applications of Sulphur Dust on grapevine at the following rate: 30, 30, 25, 20 and 20 kg product/ha (e.q. 28.86, 28.86, 24.05, 19.24 and 19.24 kg a.s./ha, respectively) with a 5-10 days interval. The results of the study demonstrate no unacceptable effect (less than 50% effect on abundance) on predatory mite populations (Acari: Phytoseiidae) 31 days after the last application of Sulphur Dust.
All determined mites were identifed as the phytoseiid predator *Phytoseius plumifer* in plot from the first and last simpling point.

Therefore, to compare the representativeness of the exposure in this field study to the 2 requested uses on grapevine and cereals for the product sulfur 80% WP, RMS determined a theoretical PER in-field calculated using the following worst-case scenario:
5 applications at 20 kg a.s./ha, interval: 5 days. This scenario intentionally underestimates the amount of sulfur applied to grapevine in order to reduce uncertainty resulting from the different application rate and interval between applications used in this field study.

Use pattern of sulfur product expressed as a.s. in	**Single appl. rate [kg a.s./ha]**	**Number of applications**	**Interval between applications [days]**	**MAF according to ESCORT 2**	**PER in-field after last application [kg a.s./ha]**
Field study[1)]	20.0	5	5	3.0	60
GAP in grapes	10.0	10	7	3.5	35
GAP in cereals	8.0	4	7	2.7	21.6

[1)]KCP2 10.3.2.4/01, Rosenkranz, B., Pavić, B., 2007

From the table above, the theoretical PERin-field retrieved from the field study is calculated as being 60 kg a.s./ha. This is above the PERin-field calculated for the representative uses on grapevine and cereals that are 35 and 21.6 kg sulfur/ha, respectively.
Therefore, it is RMS opinion, that using this field study, the in-field risk for predatory mites can be considered acceptable for the repesentative uses of 'Sulfur 80% WG' on grapevine and cereals.

Refinement for the foliage-dwelling predator, Chrysoperla carnea and Aleochara bilineata

RMS considers that a refinement for the in-field risk assessment for *Chrysoperla carnea* is needed considering the results of the risk assessment for this species and also based on the available data from the literature search.

No data were provided to further refine the in-field risk of lacewing *Chrysoperla carnea*. However, it is known that at dose rate of 10 000 g a.s./ha no significant effects on both mortality and reproduction were recorded in a study performed on glass plate with the product Sulfur 80% WG (Baxter, 2000; KCA 8.3.2.3/03). Similar results were observed for another foliage-dwelling predator *Aleochara bilineata* for which both LR_{50} and ER_{50} above 10 kg sulfur/ha were derived from a laboratory study (Vinall, 2000; KCA 8.3.2.3/06).

RMS considers that conclusion drawn for *Chrysoperla carnea* also applies to *Aleochara bilineata*.

In addition, from the literature search performed by the applicant about effects of sulfur exposure toward non-target arthropods, studies considered as supportives were identified by RMS.
Only one study was available for *Chrysoperla carnea* and 2 other for a closely related species distributed in North and South America, *i.e. Chrysoperla externa*.

In the laboratory study performed by Amarasekare et al. (2016) (B.9. KCA 8.3.2.3/16) sulphur application (application rate not clearly specified, study performed with a sulfur 80% WG product, 19.2 g a.i./L) did not significantly affect survival and daily fecundity of larvae of *C. carnea*. However, larvae had a longer larva to adult developmental time and the daily fecundity of adults was significantly reduced compared to the control.

Concerning the 2 studies performed with *C. externa*, contradictory results were observed about effect of sulfur exposure of eggs. In these 2 laboratory studies, Sulfur 80% WP products were directly sprayed upon eggs which is considered by RMS as a worst-case exposure.
In Vilela et al. (2010) (B.9. KCA 8.3.2.3/28) sulphur did not impair the duration of the embryonic period and the viability of eggs of *C. externa.* Slight effects on survival were recorded for fist instar larvae at the highest dose tested (8.0 g a.i./L), however, in the second and third-instar larvae and in the *C. externa* pre-pupa and pupa phases, sulphur did not affect survival rates and no effect on survival were observed for pupae.
On the contrary, Silva et al. (2012) (B.9. KCA 8.3.2.3/23) show that Sulphur reduced the treated egg viability and the survival of first-instar larvae of *C. externa*.

Therefore, it is RMS opinion, that using all data available in the literature search and from the whole data package provide by the applicant for non-target arthropods, it is not possible to conclude to an acceptable in-field risk for the foliage-dwelling arthropods predator *Chrysoperla carnea* for exposure above 10 000 g a.s./ha. Further refinements are still needed for both uses on cereals and grapevine.

Refinement for the ground-dwelling arthropod, Poecilus cupreus.

RMS considers that a refinement for the in-field risk assessment for *Poecilus cupreus* is needed considering the results of the risk assessment for this species presented in Table B.9.6.2.2-1.

No data were provided to further refine the in-field risk of *Poecilus cupreus*. However, from the whole data package available for the active substance suphur (CA B.9.3.2.3.3), it is known that at rate of 88.65 kg a.s./ha no significant effects both on mortality and reproduction were recorded in a study performed on quartz sand using a Sulphur Dust product (Schmitzer, 2005; KCA 8.3.2.3/02). This is above the PER in-field calculated for both uses (cereals and grapevine), with a PER in-field = 21.6 and 35 kg a.s./ha, respectively. Therefore, it is RMS opinion, the in-field risk is addressed for *Poecilus cupreus*.

Risk assessment for off-field exposure

As outlined in the ESCORT 2 guidance document, *by testing additional species, uncertainty can be reduced, and a safety factor less than 5 can be applied.* The effects of 'Sulfur 80% WG' on non-target arthropods have been evaluated on 6 different arthropod species comprising the two standard test species *Typhlodromus pyri* and *Aphidius rhopalosiphi* as well as the species *Trichogramma cacoeciae, Poecilius cupreus, Chrysoperla carnea and Aleochara bilineata*.

In addition, the available toxicity data show that *Trichogramma cacoeciae* (ER_{50} = 64.8 g a.s./ha) is > 19 times more sensitive to sulfur than the second most sensitive species, *i.e. A. rhopalosiphi* (ER_{50} > 1250 g a.s./ha) and > 154 times more sensitive to all other tested arthropod species (e.g. *Chrysoperla carnea, Aleochara bilineata, Typhlodromus pyri;* with an ER_{50} of at least 10,000 g a.s./ha). Thus, the applicant proposed that it is justified to compare the predicted off-field exposure directly with the most

sensitive endpoint of 64.8 g a.s./ha recorded in an extended lab test with *T. cacoeciae* without applying a correction factor for interspecies variation in sensitivity. Since the test item was sprayed on detached bean leaves, which is a 2-dimensional test system, a vegetation distribution factor of 10 was implemented in the exposure assessment.

RMS acknowledges the fact that it is mentioned in the guidance document ESCORT 2 that the correction factor of 5 may be reduced if testing on addition species are performed. RMS also acknowledges the fact that *T. cacoeciae* is significantly more sensitive than the other tested species. RMS agrees that this reduces uncertainty about potential toxicity of sulfur toward non-target arthropods. However, ESCORT 2 does not give any information to what extend and how this correction factor may be reduced. Therefore, due to the lack of recommendations to explain how to implement this reduction, RMS performed an off-field risk assessment using the correction factor of 5.

Table 108: Tier-1 and Tier-2 risk assessment of the off-field risk for non-target arthropods due to the uses of 'Sulfur 80% WG' in grapevine and cereals

Intended use	Grapevine (10× 10.0 kg a.s./ha, BBCH 05-81)			
Active Substance Application rate (kg a.s./ha) Vdf/correction factor MAF	Sulfur 10× 10 10 (2-D) or 1 (3-D)/ 10 for Tier -I; 5 for Tier-II 3.5			
Test species Tier-1	$LR_{50,\ corr}$ (lab.) (kg a.s./ha)	Drift rate **(Vineyard, 3 m)**	$PER_{off\text{-}field}$ (kg a.s./ha)	$HQ_{off\text{-}field}$< 2
Aphidius rhopalosiphi	**< 1**	**0.0216[j] (67th) Early application**	**0.076**	No **(HQ > 0.11)**
Aphidius rhopalosiphi	**< 1**	**0.0626 (67th) Late application**	**0.219**	No **(HQ > 0.2)**
Test species **Tier 2-standard test with non-standard species**	$LR_{50,\ corr}$ (extended) **(kg a.s./ha)**	Drift rate	$PER_{off\text{-}field}$ **(kg/ha)**	$HQ_{in\text{-}field}$, HQ ≤ 1
Poecilus cupreus	**> 2**	**0.0216 (67th) Early application**	**0.076**	**Yes (HQ = < 0.04)**
Chrysoperla carnea	**> 2**		**0.076**	**Yes (HQ = < 0.04)**
Aleochara bilineata	**> 2**		**0.076**	**Yes (HQ = < 0.04)**
Poecilus cupreus	**> 2**	**0.0626 (67th) Late application**	**0.219**	**Yes (HQ = < 0.1)**
Chrysoperla carnea	**> 2**		**0.219**	**Yes (HQ = < 0.1)**
Aleochara bilineata	**> 2**		**0.219**	**Yes (HQ = < 0.1)**
Test species Tier-2, extended laboratory studies	$ER_{50,\ corr}$ (lab.) (kg a.s./ha)	Drift rate **(Vineyard, 3 m)**	$PER_{off\text{-}field}$ (kg a.s./ha)	$PER_{off\text{-}field}$ below rate with ≤ 50 % effect?

T. cacoeciae	**0.01296**	**0.0216 (67th) Early application** [3]	**0.076**	No
		0.0626 (67th) Late application [4]	0.219	**No**
*Aphidius rhopalosiphi**	4.032	**0.0216 (67th)** Early application [3]	0.76	Yes
		0.0626 (67th) Late application [4]	2.191	Yes
Typhlodromus pyri	0.250	**0.0216 (67th)** Early application [3]	0.076	Yes
		0.0626 (67th) Late application [4]	0.219	Yes
Intended use	Cereals (4× 8.0 kg a.s./ha, BBCH 15-69)			
Active Substance Application rate (kg a.s./ha) Vdf/correction factor MAF	Sulfur 4× 8 10 (2-D) or 1 (3-D)/ 10 for Tier -I; 5 for Tier-II 2.7			
Test species Tier-1	$LR_{50,\ corr}$ (lab.) (kg a.s./ha)	Drift rate **(Cereals , 1 m)**	$PER_{off\text{-}field}$ (kg a.s./ha)	$HQ_{off\text{-}field} < 2$
Aphidius rhopalosiphi	**< 1**	**0.0185 (74th)**	**0.040**	No **(HQ > 0.1)**
Test species **Tier 2-standard test with non-standard species**	$LR_{50,\ corr}$ (extended) **(kg a.s./ha)**	Drift rate	$PER_{off\text{-}field}$ **(kg/ha)**	$HQ_{in\text{-}field}$, $HQ \leq 1$
Poecilus cupreus	**> 2**	**0.0185 (74th)**	**0.040**	**Yes (HQ < 0.02)**
Chrysoperla carnea	**> 2**		**0.040**	**Yes (HQ < 0.02)**
Aleochara bilineata	**> 2**		**0.040**	**Yes (HQ < 0.02)**
Test species Tier-2 extended laboratory studies	$ER_{50,\ corr}$ (lab.) (kg a.s./ha)	Drift rate **(Cereals, 1 m)**	$PER_{off\text{-}field}$ (kg a.s./ha)	$PER_{off\text{-}field}$ below rate with ≤ 50 % effect?
T. cacoeciae	**0.01296**	**0.0185 (74th)**		**No**

Aphidius rhopalosiphi*	**4.032**		**0.040 (0.4 if 3D)**	**Yes**
Typhlodromus pyri	**0.250**			**Yes**

MAF: Multiple application factor; vdf: Vegetation distribution factor; PER: Predicted environmental rate, Criteria values shown in bold breach the relevant trigger.
* VDF=1 for 3D studies

As outlined in the table above, at Tier-1 and Tier-2 an acceptable risk is concluded for each of the tested species, except *Trichogramma cacoeciae*.
For the use on cereals and the early and late application of 'Sulfur 80% WG' in grapevine, drift-reducing measures (*i.e.* unsprayed in-field buffer strips and/or the use of drift reducing nozzles) are required to derive an acceptable risk. The results of the risk assessment using typical mitigation measures (no-spray buffer zone of 5 m, 10m, 15m and 20m; drift-reducing nozzles with reduction by 50 % and 75 %) are summarised in the following tables.

Table 109: Higher-tier assessment of the off-field risk for non-target arthropods due to the use of 'Sulfur 80% WG' in cereals considering risk mitigation measures

Intended use		Cereals (4 × 8.0 kg a.s./ha, BBCH 15-69) (considering the drift values in ESCORT 2)		
Active substance		Sulfur		
Application rate (kg a.s./ha)		4× 8		
vdf		10 (2-D)		
MAF		2.7		
ER_{50} (kg a.s./ha), corrected		0.01296 (*T. cacoeciae*, extended lab test)		
Buffer strip (m)	Drift rate (%)	corr. $PER_{off-field}$ (kg/ha) (below rate with ≤ 50 % effect?)	corr. $PER_{off-field}$ (kg/ha) + 50 % drift red. (below rate with ≤ 50 % effect?)	corr. $PER_{off-field}$ (kg/ha) + 75 % drift red. (below rate with ≤ 50 % effect?)
3	0.0185	**0.040 (No)**	**0.020 (No)**	0.010 (Yes)
5	0.0038	0.008 (Yes)	0.004 (Yes)	-

MAF: Multiple application factor; PER: Predicted environmental rates; HQ: Hazard quotient; Criteria values shown in bold breach the relevant trigger.

As outlined in the table above, an acceptable off-field risk can also be concluded for use of 'Sulfur 80% WG' in cereales with consideration of an unsprayed buffer zone of 5 meters, or the use of drift-reducing nozzles with reduction by 75 %.

Table 110: Higher-tier assessment of the off-field risk for non-target arthropods due to the use of 'Sulfur 80% WG' in grapevine considering risk mitigation measures

Intended use	Grapevine (10× 10.0 kg a.s./ha, BBCH 05-81) – **early application** (considering the drift values in ESCORT 2)
Active substance	Sulfur
Application rate (kg a.s./ha)	10× 10
vdf	10 (2-D)

MAF		3.5		
ER_{50} (kg a.s./ha), corrected		0.01296 (*T. cacoeciae*, extended lab test)		
Buffer strip (m)	Drift rate (%)	corr. $PER_{off-field}$ (kg/ha) (below rate with ≤ 50 % effect?)	corr. $PER_{off-field}$ (kg/ha) + 50 % drift red. (below rate with ≤ 50 % effect?)	corr. $PER_{off-field}$ (kg/ha) + 75 % drift red. (below rate with ≤ 50 % effect?)
3	0.0216	**0.076 (No)**	**0.038 (No)**	**0.019 (No)**
5	0.0091	**0.032 (No)**	**0.016 (No)**	0.008 (Yes)
10	0.0028	0.010 (Yes)	0.005 (Yes)	-
Intended use		Grapevine (10× 10.0 kg a.s./ha, BBCH 05-81) – **late application** (considering the drift values in ESCORT 2)		
Active substance		Sulfur		
Application rate (kg a.s./ha)		10× 10		
vdf		10 (2-D)		
MAF		3.5		
ER_{50} (kg a.s./ha), corrected		0.01296 (*T. cacoeciae*, extended lab test)		
Buffer strip (m)	Drift rate (%)	corr. $PER_{off-field}$ (kg/ha) (below rate with ≤ 50 % effect?)	corr. $PER_{off-field}$ (kg/ha) + 50 % drift red. (below rate with ≤ 50 % effect?)	corr. $PER_{off-field}$ (kg/ha) + 75 % drift red. (below rate with ≤ 50 % effect?)
3	0.0626	**0.219 (No)**	**0.110 (No)**	**0.055 (No)**
5	0.0278	**0.097 (No)**	**0.049 (No)**	**0.024 (No)**
10	0.0093	**0.033 (No)**	**0.016 (No)**	0.008(Yes)
15	0.0049	**0.017 (No)**	0.009 (Yes)	-
20	0.0031	0.011 (Yes)	-	-

MAF: Multiple application factor; PER: Predicted environmental rates; HQ: Hazard quotient; Criteria values shown in bold breach the relevant trigger.

As outlined in the table above, an acceptable off-field risk can also be concluded for use of 'Sulfur 80% WG' for early applications of 'Sulfur 80% WG' in grapevine with consideration of an unsprayed buffer zone of 10 meters or an unsprayed buffer zone of 5 meters with the use use of drift-reducing nozzles with reduction by 75 %.

For the late application of 'Sulfur 80% WG' in grapevine an acceptable off-field risk can also be concluded with consideration of an unsprayed buffer zone of 20 meters, or an unsprayed buffer zone of 15 meters with the use use of drift-reducing nozzles with reduction by 50 %, or an unsprayed buffer zone of 10 meters with the use use of drift-reducing nozzles with reduction by 75 %.

- **Risk assessment conclusions for 'Sulfur 80% WG'**

Based on the results derived from an aged residue study conducted with the most sensitive test species, *i.e. Trichogramma cacoeciae*, the ESCORT 2 requirement of the 'potential for recovery in 'in-field' habitats within a period of 1 year' is fully met for the use of 'Sulfur 80% WG' on cereals and thus no

unacceptable in-field risk has to be expected for non-target arthropods for the representative use on cereals.
Concerning the requested use on grapevine, the exposure due to the intended GAP use of 'Sulfur 80% WG' exceed the threshold PER value of 27.0 kg a.s./ha derived from the aged residue study. Therefore, it is no possible to conclude to an acceptable in-field risk and further refinement are still needed.

In addition, further refinement are requested to address the in-field risk for foliage-dwelling arthropods other than *Trichogramma cacoeciae* for the representative uses of 'Sulfur 80% WG' in grapevine and cereals.

For the risk off-field:
An acceptable off-field risk can be concluded for the use in cereals with consideration of an unsprayed buffer zone of 5 meters.

For the early application of 'Sulfur 80% WG' in grapevine an acceptable risk is reached with consideration of an unsprayed buffer zone of 10 meter.

For the late application of 'Sulfur 80% WG' in grapevine an acceptable risk is reach with consideration of an unsprayed buffer zone of 20 meters.

In conclusion, the in-field risk for non-target arthropods is unacceptable and further refinements are still needed for the representative use of 'Sulfur 80% WG' **on grapevine and cereals**.

The off-field risk for terrestrial non-target arthropods is acceptable for the representative use of 'Sulfur 80% WG' **on cereals and grapevine** with implementation of mitigations measures.

- **Exposure and Risk assessment non-target arthropods other than bees for 'Sulphur Dust'**

Risk assessment for in-field exposure

Table 111: First and second tier assessments of the in-field risk for non-target arthropods due to the use of Sulphur Dust in grapevine

Intended use	Grapevine		
Active substance/product	Sulfur/ Sulphur Dust		
Application rate (g/ha)	5 x 29550		
MAF	3.0		
Test species Tier I	LR_{50} (lab.) (g a.s./ha)	$PER_{in\text{-}field}$ (g a.s./ha)	$HQ_{in\text{-}field}$ criterion: HQ ≤ 2
A. rhopalosiphi	486.6	88650	**182**
T. pyri	10340	88650	**8.6**
Test species **Tier II-standard test with non-standard species**	LR_{50} (extended lab) **(g a.s./ha)**	$PER_{in\text{-}field}$ **(g a.s./ha)**	$HQ_{in\text{-}field}$ **criterion: HQ ≤ 1**
P. cupreus	> 88650	44325[1)]	< 0.5
Test species **Tier II-extended laboratory studies**	LR_{50} (extended lab) **(g a.s./ha)**	$PER_{in\text{-}field}$ **(g a.s./ha)**	$HQ_{in\text{-}field}$ **criterion: HQ ≤ 1**
T. cacoeciae	**64.8**	44325[1)]	**684**

A. rhopalosiphi	**19306**	88650	**4.6**
T. pyri	**8406.98**	44325[1)]	**5.5**
C. carnea	**1970**	44325[1)]	**27.5**

MAF: Multiple application factor; vdf: Vegetation distribution factor; (corr.) PER: (corrected) Predicted environmental rate; CF: Correction factor; HQ: Hazard quotient

[1)] According to ESCORT 2 the application rate for 3-dimensional crops, e.g. orchards and vineyards can be multiplied by a correction factor of 0.5. This correction factor can only be used when the test is done on flat surface (e.g. glass plate).

As the above table shows, the Tier I in-field HQ values for exposure to maximum residues on leaves for all tested species are greater than the ESCORT 2 trigger value of 2.

In Tier II risk assessment, the HQ values for all the species, with the exeption of *P. cupreus*, were still above the relevant trigger value. Therefore, further considerations are necessary.

Refined risk assessment for in-field exposure

Refinement for Trichogramma cacoeciae and Aphidius rhopalosiphi

According to ESCORT 2, the main criterion for the acceptability of effects in in-field habitats is defined by the potential for recovery of any affected non-target arthropod population, i.e. demonstrating that residual toxicity declines sufficiently rapid to allow a recovery within one year.

An extended laboratory studies with aged residues on plant surfaces has been performed to determine the effects and the duration of the residual activity of the test item Sulphur Dust on the egg parasitoid *Trichogramma cacoeciae*.

The study on *T. cacoeciae* is an aged residues study that shows the absence of mortality and absence of effects on parasitisation at all the concentrations tested (Sublethal effects < 50% up to and including 105 kg prod./ha (103.42 kg a.s./ha)) in the bioassay intiated on DAT 28. These data demonstrate the potential for recolonisation of an affected non-target arthropod population.

RMS agrees with applicant that the aged-residue study performed with *T. cacoeciae* demonstrate the potential for recovery of this arthropod species in treated areas in less than one year following the last application of the product. The in-field risk for the egg prasitoid *T. cacoeciae* is therefore considered as addressed for the requested GAP (5 applications at 29.55 kg product/ha) on grapevine.

Refinement for predatory mites

Refinement for predatory mites is required as the in-field HQ is above the trigger value for *Typhlodromus pyri* when using a Tier II-extended laboratory study.

Two field tests on predatory mites have been conducted, one for Northern and one for Southern European scenarios (Rosenkranz, B. and Pavić, B., 2007).

The field study on predatory mites performed in Italy is considered reliable and acceptable for use for non-target arthropods risk assessment.
Please note that the second study on predatory mites, performed in Germany, is not considered reliable by RMS. Therefore, results of this study are not used in the risk assessment.

In a study conducted in Italy, when the vines were treated with field rates of Sulphur Dust, the safety of the product for non-target arthropods under field conditions is clearly demonstrated by the results, where no significant effect was ever reported on the population of predatory mites in vines (the mite abundance before treatment was statistically not different in all treatment groups and no statistically significant differences were observed between control and the test item groups at the respective sampling dates). No

unacceptable effects on predatory mite populations (Acari: Phytoseiidae) were observed 31 days after the last application of Sulphur Dust which is applied 5 times at an application rate between 20 and 30 kg/ha in grapevine.

The application rate (5 applications of Sulphur Dust at the following rate: 30, 30, 25, 20 and 20 kg product/ha) differs from the GAP (5 applications at 29.55 kg product/ha), even if the first two application are comparable the following three are performed at a lower rate compared to the GAP. The studies gives some indication that the risk is acceptable for the application rates of 5 x 29.5 kg a.s./ha, although not all five applications in the field study were conducted at the highest recommended rate. Even if some uncertainties are present due to the application rate, these data coupled with the results of the aged residues test on *T. cacoeciae* are considered sufficient to demonstrate the potential for recolonization and therefore an acceptable risk for non-target arthropods in-field.

RMS still considers that the application rate used in the field study on predatory mites does not fully cover the requested use in the present RAR (5 applications at 29.55 kg a.s./ha). In addition, this study has been performed in southern Europe (Italy) and therefore, all European zones are not considered covered by this study alone. Therefore, the in-field risk assessment is not considered as fully addressed for predatory mites.

RMS considers that a refinement for the in-field risk assessment is needed for *Chrysoperla carnea* considering the results of the risk assessment for this species and also based on the available data from the literature search.

Refinement for the foliage-dwelling predator, Chrysoperla carnea

No data were provided to further refine the in-field risk of lacewing *Chrysoperla carnea*. However, from the whole data package available for the active substance suphur, it is known that at dose rate of 10 000 g a.s./ha no significant effects both on mortality and reproduction were recorded in a study performed on glass plate with the product Sulfur 80% WG (Baxter, 2000; KCA 8.3.2.3/03).

In addition, from the literature search performed by the applicant about effects of sulfur exposure toward non-target arthropods, studies considered as supportives were identified by RMS.
Only one study was available for *Chrysoperla carnea* and 2 other for a closely related species distributed in North and South America, *i.e. Chrysoperla externa*.

In the laboratory study performed by Amarasekare et al. (2016) (B.9. KCA 8.3.2.3/16) sulphur application (application rate not clearly specified, study performed with a sulfur 80% WG product, 19.2 g a.i./L) did not significantly affect survival and daily fecundity of larvae of *C. carnea*. However, larvae had a longer larva to adult developmental time and the daily fecundity of adults was significantly reduced compared to the control.

Concerning the 2 studies performed with *C. externa*, contradictory results were observed about effect of sulfur exposure of eggs. In these 2 laboratory studies, Sulfur 80% WP products were directly sprayed upon eggs which is considered by RMS as a worst-case exposure.
In Vilela et al. (2010) (B.9. KCA 8.3.2.3/28) sulphur did not impair the duration of the embryonic period and the viability of eggs of *C. externa.* Slight effects on survival were recorded for fist instar larvae at the highest dose tested (8.0 g a.i./L), however, in the second and third-instar larvae and in the *C. externa* pre-pupa and pupa phases, sulphur did not affect survival rates and no effect on survival were observed for pupae.
On the contrary, Silva et al. (2012) (B.9. KCA 8.3.2.3/23) show that Sulphur reduced the treated egg viability and the survival of first-instar larvae of *C. externa*.

Therefore, it is RMS opinion, that using all data available in the literature search and from the whole data package provide by the applicant for non-target arthropods, it is not possible to conclude to an acceptable in-field risk for the foliage-dwelling arthropods predator *Chrysoperla carnea* for exposure above 10 000 g a.s./ha. Further refinements are still needed.

Risk assessment for off-field exposure

RMS comment: During the review process RMS questioned the use of the drift values used for spray drift applications (Rautmann et al., 2009) for dustable powder formulation (DP) such as the one for Sulphur Dust.

The applicant proposed to use a different set of drift values to perform the off-field risk assessment for non-target risk assessment.

However, these drift values are not considered fully reliable and were not used for the present off-field risk assessment for non-target arthropods.

In addition, a concern on the use of the spray drift % value (Rautmann et al., 2009) that are designed for spray applications to dustable powder formulation is identified. Given the high uncertainties identified above and in the Volume 3 CP for Sulphur Dust a worst-case approach might be to consider a conservative drift values until an agreement on the drift % value to be used for dustable powder formulation is reached at the EU level.
Without new robust data RMS will consider a worst-case approach with a drift value of 100%:

Therefore, using a 100% drift rate and without new data to estimate the exposure of non-target arthropods off-field, it is RMS opinion that it is not possible perform a reliable and relevant off-field risk assessment. The off-field risk assessment is therefore considered as not finalized.

Overall conclusion for Sulphur Dust:

In conclusion, in-field risk for non-target arthropods is unacceptable and further refinements are still needed for the representative use of Sulphur Dust on grapevine. Further refinement are requested to address the in-field risk for foliage-dwelling predator.
No off-field risk assessment could be performed due to the lack of relevant drift values related to dustable powder product such as Sulphur Dust in order to estimate a reliable exposure of non-target arthropods living in the vicinity of treated fields. The off-field risk assessment is therefore considered as not-finalized.

2.9.1.6 Summary of product exposure and risk assessment for non-target soil meso- and macrofauna

- **Exposure and Risk assessment for earthworm and for other non-target soil meso- and macrofauna for 'Sulfur 80% WG'**

Exposure

The risk assessment for soil dwelling organisms was carried out considering the worst-case application scenarios for 'Sulfur 80% WG' resulting in the maximum PEC_{soil}, *i.e.* multiple spray applications of
- 10× 10 kg a.s./ha with a 7-day interval to grapes,
- 4x 8 kg a.s./ha with a 7-day interval to cereals.

TER calculations

For the tests with *Eisenia fetida* and *Folsomia candida*, reliable EC_{10} values which are lower than the NOEC values have been determined. These endpoints are then to be used in the risk assessment. For *Hypoaspis aculeifer*, the TER values were calculated using the NOEC derived from the study.

The TER values for earthworms and other soil macroorganisms are as follows:

Table 112: TER_{LT} value for earthworms (Tier-1) and other soil meso- and macrofauna

Species, test item	**EC_{10}/NOEC (mg a.s./kg dw)**	**$PEC_{soil, max}$ (mg a.s./kg dw)**	**TER_{LT} (criterion TER ≥ 5)**
Critical intended use: Grapevine (10× 10.0 kg a.s./ha, BBCH 05-81)			
Eisenia fetida	728.9 *	58.667	12.4
Folsomia candida	142.6 *	58.667	**2.4**
Hypoaspis aculeifer	984 **	58.667	16.8
Critical intended use: Cereals (4× 8.0 kg a.s./ha, BBCH 15-69)			
Eisenia fetida	728.9 *	38.400	19.0
Folsomia candida	142.6 *	38.400	**3.7**
Hypoaspis aculeifer	984 **	38.400	25.6

* EC_{10}; ** NOEC

As outlined in the table above, the TER_{LT} values are above the trigger value of 5 for long-term exposure of *Eisenia fetida* and *Hypoaspis aculeifer*. For the exposure of *Folsomia candida* the TER_{LT} using the EC_{10} value is below the trigger of 5 for both intended GAP uses in grapevine and cereals.

An acceptable long-term risk is indicated for the soil meso- and macrofauna except *Folsomia candida*. Thus, a higher tier test is required for *Folsomia candida* and the applicant has already indicated that such test will be conducted.

Risk assessment conclusions for 'Sulfur 80% WG'

Tier-1 TER calculations indicate an acceptable risk for earthworms and other non-target soil organisms except for *Folsomia candida* in consideration of the application scenario leading to maximum soil load.

For *Folsomia candida* an acceptable risk cannot be concluded based on the Tier-1 standard test. Thus, a higher tier test with *Folsomia candida* will be conducted. As the higher tier test is not yet available, a higher tier risk assessment cannot be proposed and the risk assessment for soil meso- and macrofauna cannot be finalised.

- **Exposure and Risk assessment for earthworm and for other non-target soil meso- and macrofauna for 'Sulphur Dust'**

First-tier risk assessment

Table 113: First-tier assessment of the acute and chronic risk for earthworms due to the use of Sulphur Dust in grapevine.

Intended use	Grapevine		
Product/active substance	Sulphur Dust / sulfur		
Acute effects on earthworms			
Chronic effects on earthworms			
Species	EC_{10} (mg a.s./kg dw)	$PEC_{soil\ initial}$ (mg a.s./kg dw)	TER_{LT} (criterion TER ≥ 5)
Eisenia fetida	728.9	197	**3.7**

TER values shown in bold fall below the relevant trigger.

The long-term TER value for earthworm is below the trigger value of 5, indicating that for Sulphur Dust based on Tier I, the absence of unacceptable long-term risk to earthworms cannot be concluded.
Further refinements are needed to address the long-term risk for earthworms. According to the applicant, a higher-tier study is planned. Until this test will be available, the long-term risk for earthworms is considered unacceptable when Sulphur Dust is applied according to the proposed used rates.

Risk assessment for other non-target soil meso- and macrofauna (other than earthworms)

Table 114: First-tier assessment of chronic risk for other non-target soil organisms than earthworms (meso- and macrofauna) due to the use of Sulphur Dust in grapevine.

Intended use	Grapevine		
Chronic effects on other soil macro- and mesofauna			
Product/active substance	NOEC/EC_{10} (mg a.s./kg dw)	$PEC_{soil\ initial}$ (mg a.s./kg dw)	TER_{LT} (criterion TER ≥ 5)
Folsomia candida	142.6	197	**0.72**
Hypoaspis aculeifer	984	197	**4.99**

TER values shown in bold fall below the relevant trigger.

The TER_{LT} value for *H. aculeifer* resulting from exposure to Sulphur Dust used on grapevine is below the trigger of 5, indicating that the product may pose a long-term risk for *H. aculeifer* when applied according to the proposed use rates. However, considering that the TER calculated for *H. aculeifer* is very close to the trigger value (TER = 4.99) and the fact that no significant effects were evidenced both on mortality and reproduction in the laboratory study performed with *Hypoaspis aculeifer* (KCP2 10.4.2.2/02 Rossini, L., 2017), it is assumed that the exact NOEC is higher than 984 mg a.s./kg dw. Therefore, it can be concluded that the product poses an acceptable long-term risk for *H. aculeifer* when applied according to the proposed use rates.

The TER_{LT} value for *F. candida* resulting from exposure to Sulphur Dust used on grapevine is below the trigger of 5, indicating that the product poses a long-term risk for *F. candida* when applied according to the proposed use rates.
Further refinements are needed to address the long-term risk for collembola. According to the applicant, a higher-tier study is planned. Until this test will be available, the long-term risk for collembola is considered unacceptable when Sulphur Dust is applied according to the proposed used rates.

Risk assessment conclusions for 'Sulphur Dust'.

Tier-1 TER calculations indicate an acceptable risk for *Hypoaspis aculeifer*. Concerning, earthworms and *Folsomia candida* an unacceptable long-term risk has been identified based on the Tier-1 standard tests. Further refinements are therefore deemed required. According to the applicant, higher-tier studies are planned for earthworms and collembola.

2.9.1.7 Summary of product exposure and risk assessment for soil micro-organisms

- **Risk assessment for Soil Nitrogen Transformation for 'Sulfur 80% WG'**

The predicted environmental concentration of sulfur in soil (PEC) were calculated in consideration of the worst-case application pattern of the representative GAP, *i.e.* multiple spray applications of :

- 10× 10 kg a.s./ha with a 7-day interval to grapes,
- 4x 8 kg a.s./ha with a 7-day interval to cereals.

Table 115: Risk assessment for soil microorganisms due to the use of 'Sulfur 80% WG' in grapevine and cereals

Product/active substance	**Max. conc. with effects ≤ 25 % on N-transformation (mg/kg dw)**	**PEC_{soil} (mg a.s./kg dw)**	**Risk acceptable?**
Critical intended use: **Grapevine (10× 10.0 kg a.s./ha, BBCH 05-81)**			
Sulfur (applied as Sulfur 80% WG)	106.4	58.667	Acceptable risk is indicated, since the NOEC exceeds the max. exposure level
Sulfur (applied as Sulphur Dust)	394.0		
Critical intended use: **Cereals (4× 8.0 kg a.s./ha, BBCH 15-69)**			
Sulfur (applied as Sulfur 80% WG)	106.4	38.4	Acceptable risk is indicated, since the NOEC exceeds the max. exposure level
Sulfur (applied as Sulphur Dust)	394.0		

Risk assessment conclusions for Sulfur 80% WG

Effects within a range of ±25 % compared to the control were observed at exposure levels which exceed the maximum exposure levels in soil calculated in consideration of the worst-case application scenario, *i.e.* 10× 10 kg a.s./ha applied to vineyard and 4x 8 kg a.s./ha applied to cereals. Thus, an acceptable risk for soil microorganisms is indicated for the representative GAP uses of 'Sulfur 80% WG'.

- **Risk assessment for Soil Nitrogen Transformation for 'Sulphur Dust'**

Table 116: Assessment of the risk for effects on soil micro-organisms due to the use of Sulphur Dust in grapevine

Intended use	Grapevine		
N-mineralisation			
Product/active substance	NOEC (mg a.s./kg dw)	$PEC_{soil\ initial}$ (mg a.s/kg dw)	Risk acceptable?
Sulphur Dust / sulfur	394	197	Yes
C-mineralisation			
Product/active substance	NOEC (mg a.s./kg dw)	$PEC_{soil\ initial}$ (mg a.s/kg dw)	Risk acceptable?
Sulphur Dust / sulfur	394	197	Yes

Sulphur Dust had-no significant effect on soil micro-organisms at 400 mg prod/kg. This is 2 times higher than the maximum PEC_S of 197 mg a.s/kg following the worst-case application to grape. This supports the conclusion that under field conditions, use of Sulphur Dust at the proposed rates poses no unacceptable risk to non-target soil micro-organisms.

Risk assessment conclusions for Sulphur Dust

Effects within a range of ±25 % compared to the control were observed at exposure levels which exceed the maximum exposure levels in soil calculated in consideration of the application scenario. Thus, an acceptable risk for soil microorganisms is indicated for the representative GAP uses of 'Sulphur Dust'.

2.9.1.8 Summary of product exposure and risk assessment for non-target terrestrial plants

- **Risk assessment for terrestrial non-target higher plants for 'Sulfur 80% WG'**

Table 117: Risk assessment for terrestrial non-target plants based on the results of the seedling emergence test

Intended use	Grapevine (10× 10.0 kg a.s./ha, BBCH 05-81)		
Active substance **Application rate (kg a.s./ha)**	Sulfur 10× 10.0		
Test system (species tested)	**Lowest ER_{50} [mg a.s./kg $soil_{dw}$]**	**Max. PEC_{soil} after single application at max. rate [mg a.s./kg $soil_{dw}$]**	**Risk for fungicides according to SANCO/10329/2002 recommendations**
Seedling emergence test, (*Daucus carota, Brassica napus, Solanum lycopersicum, Cucumis sativum, Pisum sativum, Beta vulgaris, Zea mays, Allium cepa, Avena sativa, Lolium perenne*)	> 1000	13.3*	Acceptable risk is indicated, since the lowest ER_{50} exceeds the max. PEC_{soil} after single application at the max. rate of 'Sulfur 80% WG' with a sufficient margin of safety
Intended use	Cereals (4× 8.0 kg a.s./ha, BBCH 15-69)		
Active substance **Application rate (kg a.s./ha)**	Sulfur 4× 8.0		
Test system (species tested)	**Lowest ER_{50} [mg a.s./kg $soil_{dw}$]**	**Max. PEC_{soil} after single application at max. rate [mg a.s./kg $soil_{dw}$]**	**Risk for fungicides according to SANCO/10329/2002 recommendations**
Seedling emergence test, (*Daucus carota, Brassica napus, Solanum lycopersicum, Cucumis sativum, Pisum sativum, Beta vulgaris, Zea mays, Allium cepa, Avena sativa, Lolium perenne*)	> 1000	10.7*	Acceptable risk is indicated, since the lowest ER_{50} exceeds the max. PEC_{soil} after single application at the max. rate of 'Sulfur 80% WG' with a sufficient margin of safety

* calculated for a soil depth of 5 cm and 1.5 g/cm^3 bulk density

In addition, in the vegetative vigour test considered as supportive information (KCP 10.6.1/01; Oberwalder, C. & Schmidt, O., 2000), no significant effects on phytotoxicity and plant weight of overall

six species could be observed at the maximum test rate of 31.5 kg prod./ha equivalent to 25.2 kg a.s./ha. This ER_{50} is higher than the maximum application rate of 10 kg a.s./ha requested for use on vineyard and covers the use requested for cereals. Even if not considered fully valid because of a study report insufficiently detailed, this study shows that sulfur did not exhibit herbicidal activity toward non-target terrestrial plants when applied at rate above the requested ones in the present RAR.

Risk assessment conclusions for 'Sulfur 80% WG'

Based on a screening risk assessment recommended for fungicides, safe uses (with respect to an acceptable risk for terrestrial non-target plants) can be identified for 'Sulfur 80 % WG'. No mitigation measures need to be applied.

- **Risk assessment for terrestrial non-target higher plants for 'Sulphur dust'**

Table 118: Tier I assessment of the risk for non-target plants due to the use of Sulphur Dust in grapevine

Intended use	Grapevine		
Active substance/product	sulfur / Sulphur Dust		
Application rate (g/ha)	5 × 29550		
Test species	**Lowest ER_{50} [mg a.s./kg $soil_{dw}$]**	**Max. PEC soil after single application at max rate [mg a.s./kg $soil_{dw}$]**	**Risk for fungicides according to SANCO/10329/2002 recommendations**
Tomato, cucumber, pea, sugar beet, oats, perennial ryegrass, onion, corn, oilseed rape and carrot	> 1000	39.4	Acceptable risk is indicated, since the lowest ER_{50} exceeds the max. PEC soil after single application at the max rate of Sulphur Dust with a sufficient margin of safety

The study performed by Oberwalder, C. & Schmidt, O., 2000 (KCP2 10.6.2/01) is not considered fully valid because of a study report insufficiently detailed. However, in this study shows no significant effects on phytotoxicity and plant weight of overall six species could be observed at the maximum test rate of 31.5 kg prod./ha equivalent to 25.2 kg a.s./ha indicating that sulfur did not exhibit herbicidal activity toward non-target terrestrial plants up to and including this application rate. This ER_{50} is lower than the maximum application rate of 29.55 kg a.s./ha requested for use on vineyard. However, considering the worst case drift value for grapevine (late stage of development), i.e. 8.02%, a TER value above the trigger value of 5 could be calculated demonstrating an acceptable risk without the need of mitigation measure. Thus, RMS considered that it is possible to conclude to an acceptable risk for vegetative vigour.

Risk assessment conclusions for 'Sulphur Dust'

Based on a screening risk assessment recommended for fungicides, safe uses (with respect to an acceptable risk for terrestrial non-target plants) can be identified for Sulphur Dust. No mitigation measures need to be applied.

2.10 ENDOCRINE DISRUPTING PROPERTIES

An assessment of the endocrine disrupting properties of the active substance sulfur in line with the EFSA/ECHA guidance for the identification of endocrine disruptors (2018) has been conducted.

2.10.1 Gather all relevant information

Regarding the mammalian toxicology area, data have been collected from the available repeated-dose toxicity studies in mammals available in the RAR. A systematic literature review was performed according to the EFSA Guidance (2011). Relevant databases were searched for literature on sulfur using different descriptive terms, such as tradenames, CAS number, IUPAC name, and other terms. The search included, but was not restricted to, search terms related to endocrine disruption (please refer to Vol 3B6.10). No relevant study for the ED assessment was retrieved from the literature review. Sulfur has not been tested as part of the US EDSP nor under the US EPA'S ToxCast programme.

Data were gathered in the Excel template provided as Appendix E to the EFSA/ECHA guidance (2018). The table provided by the applicant served as a basis for the RMS assessment but was modified to take into account RMS assessment of the studies assessed in the RAR. According to this template each study was given a unique identification number (Study ID Matrix) that is important for its identification in the data-matrix and Lines of Evidence (LoE) spreadsheets of the Excel.

A summary of all studies considered for the mammalian toxicology, including the Study ID Matrix is outlined in the following table.

Outline of dataset considered for mammalian toxicology assessment:

Type of toxicity	Study type	Study ID Matrix
Repeated dose toxicity studies in mammals	Repeated dose 28-day dermal toxicity study in rat *(Malleshappa, 2006)*	1
	Repeated dose 28-day dermal toxicity study in rat *(Zimmerman, 2009)*	2
	Repeated dose 28-day oral (gavage) toxicity study in rat *(Ramesh, 2005)*	3
	Repeated dose 90-day oral (gavage) toxicity study in rat *(Zimmerman, 2009)*	4
	Repeated dose 90-day oral (gavage) toxicity study in rat *(Malleshappa, 2006)*	5

2.10.2 ED assessment for humans

2.10.2.1 ED assessment for T-modality

2.10.2.1.1 **Have T-mediated parameters been sufficiently investigated?**

	Sufficiently investigated
T-mediated parameters	**No**. The database is limited for sulfur and T-mediated parameters have been investigated in the following studies: - OECD TG 407 - ID: 3 - OECD TG 408 - ID: 4, 5 In accordance with OECD TG in force at the time the studies were conducted, only thyroid histopathology was investigated in these studies; thyroid weight was not measured in any available study and thyroid hormone measurement was not performed. It is noteworthy that OECD TG 409, 451-3, 416/443 are not available for sulfur and are not considered necessary (please refer to relevant sections of Volume 3CA B6). Therefore, the database for investigating thyroid adversity is limited and it is considered that T-mediated parameters have not been sufficiently investigated.

2.10.2.1.2 **Lines of evidence for adverse effects and endocrine activity related to T-modality**

Sulphur **Volume 1 – Level 2**

Study ID Matrix	Effect classification	Effect target	Species	Duration of exposure	Duration unit	Route of administration	Lowest Effect dose	Dose unit	Effect direction	Observed effect (positive and negative)	Assessment of each line of evidence	Assessment on the integrated line of evidence	Modality
3	EATS-mediated	Thyroid histopathology	Rat	28	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d	No treatment-related effect on T-mediated parameters in the 28-d dermal rat studies and in the 28-d and 90-d oral rat studies up to 1000 mg/kg bw/d	No evidence of T-mediated adversity	T
4			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
5			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
2	Sensitive to, but not diagnostic of, EATS	Adrenals histopathology	Rat	28	Days	Dermal		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d	No treatment-related effect on sensitive to, but not diagnostic of, EATS parameters in the 28-d dermal rat studies and in the 28-d and 90-d oral rat studies up to 1000 mg/kg bw/d		
3			Rat	28	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
4			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
5			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
1		Adrenals weight	Rat	28	Days	Dermal		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
2			Rat	28	Days	Dermal		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
3			Rat	28	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
4			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
5			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
2		Brain histopathology examination	Rat	28	Days	Dermal		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
3			Rat	28	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
4			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
5			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
2		Brain weight	Rat	28	Days	Dermal		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
3			Rat	28	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
4			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
5			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
4		Pituitary histopathology	Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
5			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
4	Target organ toxicity	Aorta histopathology	Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d	No evidence of target organ toxicity in the 28-d dermal rat studies and in the 28-d and 90-d oral rat studies up to 1000 mg/kg bw/d. Evidence of local skin effects in one of the	Evidence of systemic toxicity in one of the two available 90-d oral rat toxicity study.	N
5			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
3		Bone marrow histopathology	Rat	28	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
4			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			

Sulphur **Volume 1 – Level 2**

Study ID Matrix	Effect classification	Effect target	Species	Duration of exposure	Duration unit	Route of administration	Lowest Effect dose	Dose unit	Effect direction	Observed effect (positive and negative)	Assessment of each line of evidence	Assessment on the integrated line of evidence	Modality
5			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d	two available 28-d dermal toxicity studies.	Evidence of local skin effects in one of the two available 28-d dermal rat toxicity studies.	
2		Heart histopathology	Rat	28	Days	Dermal		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
3			Rat	28	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
4			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
5			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
2		Heart weight	Rat	28	Days	Dermal		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
3			Rat	28	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
4			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
5			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
1		Kidney histopathology	Rat	28	Days	Dermal		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
2			Rat	28	Days	Dermal		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
3			Rat	28	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
4			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
5			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
1		Kidney weight	Rat	28	Days	Dermal		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
2			Rat	28	Days	Dermal		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
3			Rat	28	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
4			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
5			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
1		Liver histopathology	Rat	28	Days	Dermal		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
2			Rat	28	Days	Dermal		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
3			Rat	28	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
4			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
5			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
1		Liver weight	Rat	28	Days	Dermal		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
2			Rat	28	Days	Dermal		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
3			Rat	28	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			

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Study ID Matrix	Effect classification	Effect target	Species	Duration of exposure	Duration unit	Route of administration	Lowest Effect dose	Dose unit	Effect direction	Observed effect (positive and negative)	Assessment of each line of evidence	Assessment on the integrated line of evidence	Modality
4			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
5			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
3		Lung histopathology	Rat	28	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
4			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
5			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
3		Lymph nodes histopathology	Rat	28	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
4			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
5			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
4		Oesophagus histopathology	Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
5			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
4		Pancreas histopathology	Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
5			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
3		Peripheral nerve histopathology	Rat	28	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
4			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
5			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
4		Salivary glands histopathology	Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
5			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
1		Skin histopathology	Rat	28	Days	Dermal	1000	mg/kg bw/day	Increase	Hyperkeratosis of the treated skin in both sexes, hyperkeratosis of the untreated skin in females, at 1000 mg/kg bw/d (local NOAEL = 400 mg/kg bw/d)			
2			Rat	28	Days	Dermal		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
4			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
5			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
3		Small and large intestines histopathology	Rat	28	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
4			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
5			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
3		Spinal cord histopathology	Rat	28	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
4			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			

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Study ID Matrix	Effect classification	Effect target	Species	Duration of exposure	Duration unit	Route of administration	Lowest Effect dose	Dose unit	Effect direction	Observed effect (positive and negative)	Assessment of each line of evidence	Assessment on the integrated line of evidence	Modality
5			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
2		Spleen histopathology	Rat	28	Days	Dermal		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
3			Rat	28	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
4			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
5			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
2		Spleen weight	Rat	28	Days	Dermal		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
3			Rat	28	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
4			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
5			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
3		Stomach histopathology	Rat	28	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
4			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
5			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
2		Thymus histopathology	Rat	28	Days	Dermal		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
3			Rat	28	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
4			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
5			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
2		Thymus weight	Rat	28	Days	Dermal		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
3			Rat	28	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
4			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
5			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
3		Trachea histopathology	Rat	28	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
4			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
5			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
3		Urinary bladder histopathology	Rat	28	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
4			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
5			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
1		Body weight	Rat	28	Days	Dermal		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			

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Study ID Matrix	Effect classification	Effect target	Species	Duration of exposure	Duration unit	Route of administration	Lowest Effect dose	Dose unit	Effect direction	Observed effect (positive and negative)	Assessment of each line of evidence	Assessment on the integrated line of evidence	Modality
2	Systemic toxicity		Rat	28	Days	Dermal		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d	Effects on body weight parameters and food consumption in one of the two available 90-d oral toxicity studies at 1000 mg/kg bw/d		
3			Rat	28	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
4			Rat	90	Days	Oral	1000	mg/kg bw/day	Decrease	Decreased body weight (SS, -7% during the treatment period, -10% during the recovery period) and body weight gain (SS, -12% Days 0-93) in males at 1000 mg/kg bw/d			
5			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
1		Clinical chemistry and haematology	Rat	28	Days	Dermal		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
2			Rat	28	Days	Dermal		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
3			Rat	28	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
4			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
5			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
1		Clinical signs	Rat	28	Days	Dermal		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
2			Rat	28	Days	Dermal		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
3			Rat	28	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
4			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
5			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
1		Food consumption	Rat	28	Days	Dermal		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
2			Rat	28	Days	Dermal		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
3			Rat	28	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
4			Rat	90	Days	Oral	1000	mg/kg bw/day	Decrease	Decreased food consumption in males at 1000 mg/kg bw/d (SS, up to 10% compared to controls)			
5			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
1		Mortality	Rat	28	Days	Dermal		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
2			Rat	28	Days	Dermal		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
3			Rat	28	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
4			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
5			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			

Assessment of the integrated lines of evidence and weight of evidence for T-mediated adversity and endocrine activity:

WoE for T-mediated adversity:

- Thyroid histopathology was investigated in the 28-day oral toxicity study and in both 90-day oral toxicity studies. No adverse changes were observed.

WoE for T-mediated endocrine activity:

- No data available.

2.10.2.1.3 Initial analysis of the evidence and identification of relevant scenario for the ED assessment of T-modality

Selection of relevant scenario:

Adversity based on T-mediated parameters	Positive mechanistic OECD CF level 2/3 Test	Scenario	Next step of the assessment	Scenario selected
No (sufficiently investigated)	Yes/No	1a	Conclude: ED criteria not met because there is no "**T-mediated**" adversity	
Yes (sufficiently investigated)	Yes/No	1b	Perform MoA analysis	
No (not sufficiently investigated)	Yes	2a (i)	Perform MoA analysis (additional information may be needed for the analysis)	
No (not sufficiently investigated)	No (sufficiently investigated)	2a (ii)	Conclude: ED criteria not met because no **T-mediated endocrine activity** observed	
No (not sufficiently investigated)	No (not sufficiently investigated)	2a (iii)	Generate missing level 2 and 3 information. Alternatively, generate missing "EATS-mediated" parameters. Depending on the outcome move to corresponding scenario	**X**
Yes (not sufficiently investigated)	Yes/No	2b	Perform MoA analysis	

2.10.2.1.4 Conclusion of the assessment of T-modality

No T-mediated adversity was observed in the available insufficient dataset. Based on scenario 2a (iii), the endocrine activity was not sufficiently investigated for the T-modality and according to the guidance, additional information would be needed.
Nevertheless, it is considered that the waivers for long-term/carcinogenicity study, reproductive toxicity studies and setting of toxicological reference values could also apply for endocrine disrupting potential. Sulfur is generally regarded as safe for human exposure given the wide range of background exposure, its low acute and short-term toxicity and its non-genotoxic potential. In addition, it is an essential element needed at a high dose level. Therefore, it was considered unnecessary to require additional information to conclude on ED properties of sulfur.

2.10.2.2 ED assessment for EAS-modalities

2.10.2.2.1 Have EAS-mediated parameters been sufficiently investigated?

	Sufficiently investigated

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EAS-mediated parameters	**No**, based on the lack of the following studies: - OECD TG 443 - OECD TG 416, test protocol according to latest version of January 2001 A reproductive toxicity study is not available for sulfur.

2.2.2 - Lines of evidence for adverse effects and endocrine activity related to EAS-modalities

Study ID Matrix	Effect classification	Effect target	Species	Duration of exposure	Duration unit	Route of administration	Lowest Effect dose	Dose unit	Effect direction	Observed effect (positive and negative)	Assessment of each line of evidence	Assessment on the integrated line of evidence	Modality
3	EATS-mediated	Coagulating gland histopathology	Rat	28	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d	No treatment-related effect on EAS-mediated parameters in the 28-d dermal rat studies and in the 28-d and 90-d oral rat studies up to 1000 mg/kg bw/d	No evidence of EAS-mediated adversity	EAS
5			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
3		Epididymis histopathology	Rat	28	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
4			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
5			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
3		Epididymis weight	Rat	28	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
4			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
5			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
4		Mammary gland histopathology (female)	Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
5			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
2		Ovary histopathology	Rat	28	Days	Dermal		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
3			Rat	28	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
4			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
5			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
2		Ovary weight	Rat	28	Days	Dermal		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
3			Rat	28	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
4			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
5			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
3		Prostate histopathology (with seminal vesicles and coagulating glands)	Rat	28	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
4			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
5			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
3		Seminal vesicles histopathology	Rat	28	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
4			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
5			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
2			Rat	28	Days	Dermal		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			

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Study ID Matrix	Effect classification	Effect target	Species	Duration of exposure	Duration unit	Route of administration	Lowest Effect dose	Dose unit	Effect direction	Observed effect (positive and negative)	Assessment of each line of evidence	Assessment on the integrated line of evidence	Modality
3		Testis histopathology	Rat	28	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
4			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
5			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
1		Testis weight	Rat	28	Days	Dermal		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
2			Rat	28	Days	Dermal		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
3			Rat	28	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
4			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
5			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
1		Uterus histopathology (with cervix)	Rat	28	Days	Dermal		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
3			Rat	28	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
4			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
5			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
4		Uterus weight (with cervix)	Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
5			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
4		Vagina histopathology	Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
2	Sensitive to, but not diagnostic of, EATS	Adrenals histopathology	Rat	28	Days	Dermal		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d	No treatment-related effect on sensitive to, but not diagnostic of, EATS parameters in the 28-d dermal rat studies and in the 28-d and 90-d oral rat studies up to 1000 mg/kg bw/d		
3			Rat	28	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
4			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
5			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
1		Adrenals weight	Rat	28	Days	Dermal		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
2			Rat	28	Days	Dermal		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
3			Rat	28	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
4			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
5			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
2		Brain histopathology examination	Rat	28	Days	Dermal		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
3			Rat	28	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			

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Study ID Matrix	Effect classification	Effect target	Species	Duration of exposure	Duration unit	Route of administration	Lowest Effect dose	Dose unit	Effect direction	Observed effect (positive and negative)	Assessment of each line of evidence	Assessment on the integrated line of evidence	Modality
4			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
5			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
2		Brain weight	Rat	28	Days	Dermal		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
3			Rat	28	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
4			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
5			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
4		Pituitary histopathology	Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
5			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
4	Target organ toxicity	Aorta histopathology	Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d	No evidence of target organ toxicity in the 28-d dermal rat studies and in the 28-d and 90-d oral rat studies up to 1000 mg/kg bw/d. Evidence of local skin effects in one of the two available 28-d dermal toxicity studies.	Evidence of systemic toxicity in one of the two available 90-d oral rat toxicity study. Evidence of local skin effects in one of the two available 28-d dermal rat toxicity studies.	N
5			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
3		Bone marrow histopathology	Rat	28	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
4			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
5			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
2		Heart histopathology	Rat	28	Days	Dermal		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
3			Rat	28	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
4			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
5			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
2		Heart weight	Rat	28	Days	Dermal		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
3			Rat	28	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
4			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
5			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
1		Kidney histopathology	Rat	28	Days	Dermal		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
2			Rat	28	Days	Dermal		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
3			Rat	28	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
4			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
5			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
1		Kidney weight	Rat	28	Days	Dermal		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			

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Study ID Matrix	Effect classification	Effect target	Species	Duration of exposure	Duration unit	Route of administration	Lowest Effect dose	Dose unit	Effect direction	Observed effect (positive and negative)	Assessment of each line of evidence	Assessment on the integrated line of evidence	Modality
2			Rat	28	Days	Dermal		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
3			Rat	28	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
4			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
5			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
1		Liver histopathology	Rat	28	Days	Dermal		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
2			Rat	28	Days	Dermal		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
3			Rat	28	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
4			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
5			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
1		Liver weight	Rat	28	Days	Dermal		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
2			Rat	28	Days	Dermal		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
3			Rat	28	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
4			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
5			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
3		Lung histopathology	Rat	28	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
4			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
5			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
3		Lymph nodes histopathology	Rat	28	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
4			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
5			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
4		Oesophagus histopathology	Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
5			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
4		Pancreas histopathology	Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
5			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
3		Peripheral nerve histopathology	Rat	28	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
4			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
5			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			

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Study ID Matrix	Effect classification	Effect target	Species	Duration of exposure	Duration unit	Route of administration	Lowest Effect dose	Dose unit	Effect direction	Observed effect (positive and negative)	Assessment of each line of evidence	Assessment on the integrated line of evidence	Modality
4		Salivary glands histopathology	Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
5			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
1		Skin histopathology	Rat	28	Days	Dermal	1000	mg/kg bw/day	Increase	Hyperkeratosis of the treated skin in both sexes, hyperkeratosis of the untreated skin in females, at 1000 mg/kg bw/d (local NOAEL = 400 mg/kg bw/d)			
2			Rat	28	Days	Dermal		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
4			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
5			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
3		Small and large intestines histopathology	Rat	28	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
4			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
5			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
3		Spinal cord histopathology	Rat	28	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
4			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
5			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
2		Spleen histopathology	Rat	28	Days	Dermal		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
3			Rat	28	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
4			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
5			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
2		Spleen weight	Rat	28	Days	Dermal		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
3			Rat	28	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
4			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
5			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
3		Stomach histopathology	Rat	28	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
4			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
5			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
2		Thymus histopathology	Rat	28	Days	Dermal		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
3			Rat	28	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
4			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			

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Study ID Matrix	Effect classification	Effect target	Species	Duration of exposure	Duration unit	Route of administration	Lowest Effect dose	Dose unit	Effect direction	Observed effect (positive and negative)	Assessment of each line of evidence	Assessment on the integrated line of evidence	Modality
5			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
2		Thymus weight	Rat	28	Days	Dermal		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
3			Rat	28	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
4			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
5			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
3		Trachea histopathology	Rat	28	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
4			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
5			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
3		Urinary bladder histopathology	Rat	28	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
4			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
5			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
1	Systemic toxicity	Body weight	Rat	28	Days	Dermal		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d	Effects on body weight parameters and food consumption in one of the two available 90-d oral toxicity studies at 1000 mg/kg bw/d		
2			Rat	28	Days	Dermal		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
3			Rat	28	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
4			Rat	90	Days	Oral	1000	mg/kg bw/day	Decrease	Decreased body weight (SS, -7% during the treatment period, -10% during the recovery period) and body weight gain (SS, -12% Days 0-93) in males at 1000 mg/kg bw/d			
5			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
1		Clinical chemistry and haematology	Rat	28	Days	Dermal		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
2			Rat	28	Days	Dermal		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
3			Rat	28	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
4			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
5			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
1		Clinical signs	Rat	28	Days	Dermal		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
2			Rat	28	Days	Dermal		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
3			Rat	28	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
4			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			

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Study ID Matrix	Effect classification	Effect target	Species	Duration of exposure	Duration unit	Route of administration	Lowest Effect dose	Dose unit	Effect direction	Observed effect (positive and negative)	Assessment of each line of evidence	Assessment on the integrated line of evidence	Modality
5			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
1		Food consumption	Rat	28	Days	Dermal		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
2			Rat	28	Days	Dermal		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
3			Rat	28	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
4			Rat	90	Days	Oral	1000	mg/kg bw/day	Decrease	Decreased food consumption in males at 1000 mg/kg bw/d (SS, up to 10% compared to controls)			
5			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
1		Mortality	Rat	28	Days	Dermal		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
2			Rat	28	Days	Dermal		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
3			Rat	28	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
4			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			
5			Rat	90	Days	Oral		mg/kg bw/day	No effect	No treatment-related effect up to 1000 mg/kg bw/d			

Assessment of the integrated lines of evidence and weight of evidence for EAS-mediated adversity and endocrine activity:

WoE for EAS-mediated adversity:

- There is no EAS-mediated adversity observed in the available dataset.

WoE for EAS-mediated endocrine activity:

- No data available.

2.10.2.2.2 Initial analysis of the evidence and identification of relevant scenario for the ED assessment of EAS-modalities

Selection of relevant scenario:

Adversity based on EAS-mediated parameters	Positive mechanistic OECD CF level 2/3 Test	Scenario	Next step of the assessment	Scenario selected
No (sufficiently investigated)	Yes/No	1a	Conclude: ED criteria not met because there is no "**EAS-mediated**" adversity	
Yes (sufficiently investigated)	Yes/No	1b	Perform MoA analysis	
No (not sufficiently investigated)	Yes	2a (i)	Perform MoA analysis (additional information may be needed for the analysis)	
No (not sufficiently investigated)	No (sufficiently investigated)	2a (ii)	Conclude: ED criteria not met because no **EAS-mediated endocrine activity** observed	
No (not sufficiently investigated)	No (not sufficiently investigated)	2a (iii)	Generate missing level 2 and 3 information. Alternatively, generate missing "EATS-mediated" parameters. Depending on the outcome move to corresponding scenario	**X**
Yes (not sufficiently investigated)	Yes/No	2b	Perform MoA analysis	

2.10.2.2.3 Conclusion of the assessment of EAS-modalities

No EAS-mediated adversity was observed in the available insufficient dataset. Based on scenario 2a (iii), the endocrine activity was not sufficiently investigated for the EAS-modalities and according to the guidance, additional information would be needed.
Nevertheless, it is considered that the waivers for long-term/carcinogenicity study, reproductive toxicity studies and setting of toxicological reference values could also apply for endocrine disrupting potential. Sulfur is generally regarded as safe for human exposure given the wide range of background exposure, its low acute and short-term toxicity and its non-genotoxic potential. In addition, it is an essential element needed at a high dose level. Therefore, it was considered unnecessary to require additional information to conclude on ED properties of sulfur.

2.10.2.3 Overall conclusion on the ED assessment for humans

For T-modality and for EAS-modalities, no EATS-mediated adversity was observed in the available insufficient dataset. Based on scenario 2a (iii), the endocrine activity was not sufficiently investigated for EATS-modalities and according to the guidance, additional information would be needed.
Nevertheless, it is considered that the waivers for long-term/carcinogenicity study, reproductive toxicity studies and setting of toxicological reference values could also apply for endocrine disrupting potential.

Sulfur is generally regarded as safe for human exposure given the wide range of background exposure, its low acute and short-term toxicity and its non-genotoxic potential. In addition, it is an essential element needed at a high dose level. Therefore, it was considered unnecessary to require additional information to conclude on ED properties of sulfur.

Based on a weight of evidence, taking into account the limited database, the known toxicological properties of sulfur and its wide range of background exposure and considering that sulfur is an essential element needed at a high dose level, it can be concluded that sulfur is not an endocrine disruptor in humans.

2.10.3 ED assessement for non-target organisms

Information on potential ED properties of sulfur was gathered, evaluated, and subjected to a WoE approach according to the ECHA/EFSA ED guidance. The WoE approach was conducted in order to check whether properties of sulfur meet the criteria set out in the Commission Regulation (EU) No 2018/605 pursuant to the PPPR.

According to the criteria, a substance shall be considered as having endocrine-disrupting properties if:

(a) it shows an adverse effect in an intact organism or its progeny, which is a change in the morphology, physiology, growth, development, reproduction, or, life span of an organism, system, or (sub)population that results in an impairment of functional capacity, an impairment of the capacity to compensate for additional stress, or an increase in the susceptibility to other influences;

No adverse effects were observed for any EATS-mediated parameter or parameters sensitive to, but not diagnostic of, EATS-related effects in intact organisms upon exposure to sulfur.

(b) it has an endocrine mode of action, i.e. it alters the function(s) of the endocrine system;

Although, endocrine activity of sulfur was not specifically addressed, the available information provided by the parameters investigated indicate that there is no evidence for an endocrine mode of action of sulfur.

(c) the adverse effect is a consequence of the endocrine mode of action.

Absence of adverse effects on 'EATS' parameters in combination with lack of an endocrine MoA renders the question for causality obsolete for the assessment of sulfur.

Sulfur does not meet the criteria of a substance having endocrine-disrupting properties, since there is no evidence for any endocrine-related adversity of sulfur in (eco-)toxicological study reports or in literature from the public domain. Thus, the tripartite definition of a substance having endocrine-disrupting properties cannot be met.

According to the ECHA/EFSA ED guidance, EATS-mediated adversity has not been sufficiently investigated for human health and mammals. This is based on the fact that for a sufficient investigation for estrogen-, androgen-, and steroidogenesis-related adversity, OECD CF level 5 (OECD TG 443 or 416) studies are missing. Moreover, for a sufficient investigation of the thyroid-related adversity OECD CF level 4 (OECD TG 409 and 451-3) and OECD CF level 5 studies are required (OECD TG 443 or 416). The absence of these studies is justified in the EFSA conclusion (2008): "No long-term toxicity and carcinogenicity studies were performed, as sulfur is generally regarded as safe for human exposure given the wide range of background exposure, its low acute and short-term toxicity and its non-genotoxic potential. In addition, it is an essential element needed at a high dose level. Therefore, it was considered unnecessary to require long-term and carcinogenicity [and reproductive toxicity studies; as specified in 2.6 (p. 9-10)] studies with sulfur." However, according to the ECHA/EFSA ED guidance, a lack of these studies (and associated information on the EATS-parameters) would lead, in the absence of positive effects and absence of information on endocrine activity, to scenario 2a(iii) (Figure 2 and Table 1). Consequently, OECD level 2 and 3 information should be generated to investigate potential endocrine activity of sulfur, or the studies listed above should be generated to further investigate EATS-related

adversity. The same is true for the non-target organism assessment lacking the required studies for a sufficient investigation of estrogen, androgen-, and steroidogenesis-related adversity (OECD TG 240 or US EPA TG OPPTS 850.1500) and thyroid-related adversity (OECD TG 241). However, in consideration of the absence of any EATS-related adverse effects in the variety of endocrine-sensitive organs tested in the different mammalian toxicology studies, the fact that sulfur is generally regarded as safe for human exposure and its role as an essential element, the information on EATS-related adversity in mammals can be considered as sufficient. This would lead to scenario 1a (Table 1), which would lead to the conclusion that endocrine activity has not to be investigated and that sulfur can be concluded to be a substance with no endocrine-disrupting properties because there is no 'EATS-mediated' adversity.

In conclusion, based on the weight of evidence, sulfur is considered to have no endocrine-disrupting properties according to the criteria set out in Commission Regulation (EU) No 2018/605 pursuant to the PPPR.

3.1 - Lines of evidence for adverse effects and endocrine activity related to EATS-modalities for non-target organisms

Study ID Matrix	Effect classification	Effect target	Species	Duration of exposure	Duration unit	Route of administration	Lowest Effect dose	Dose unit	Effect direction	Observed effect (positive and negative)	Assessment of each line of evidence	Assessment on the integrated line of evidence	Modality
1	Sensitive to, but not diagnostic of, EATS	Behaviour (fish)	Oncorhynchus mykiss (formerly Salmo gairdneri)	28	days	Uptake from water	32	mg/L water	Increase	Increase of fish with slow motility 2/6 at highest concentration, no effect in control 0/10	No statistical significance, effect might be due to turbidity of the medium, general mortality	No indication for substance-related effects on the hormonal system.	
1	Sensitive to, but not diagnostic of, EATS	Length (fish)	Oncorhynchus mykiss (formerly Salmo gairdneri)	28	days	Uptake from water	32	mg/L water	No effect				
1	Sensitive to, but not diagnostic of, EATS	Body weight (fish)	Oncorhynchus mykiss (formerly Salmo gairdneri)	28	days	Uptake from water	3.2	mg/L water	Decrease	Fishes in vessels 3.2, 10, 32 and 100 mg/L in average less weight than control	No statistical significance	No indication for substance-related effects on the hormonal system.	
1	Systemic toxicity	Mortality	Oncorhynchus mykiss (formerly Salmo gairdneri)	28	days	Uptake from water	32	mg/L water	Increase	At highest concentration 4/10 fish dead, 0/10 in the control	Statistical significance with 95% probability	No indication for substance-related effects on the hormonal system.	

Overall conclusions for non-target organisms

With regard to the assessment of the endocrine disruption potential of sulfur for humans according to the ECHA/EFSA guidance (2018), a standard data package on sulfur is not available.

RMS agrees with applicant conclusion. Indeed, sulfur is considered ubiquitous in the environment and is also essential for animal and plant functions (constituent of amino acids, etc.). It is characterized by no or low toxicity toward vertebrates observed in the available toxicity studies. In addition, no EATS-related adverse effects was identified in the mammamlian toxicology studies nor in the ecotoxicological section.

Sulfur is of poor solubility in water (water solubility of sulfur =16 µg/L (20 C) proposed as new endpoint in the present RAR, see Volume 3 CA B2 (B.2.5), Rigamonti, E. (2018) (KCA 2.5/03)) therefore not bioavailable to fish and amphibians.
Therefore, an assessment strictly following the scheme provided in the Guidance for the identification of endocrine disruptors (EFSA, 2018) is not considered necessary by RMS.

In addition, according to the Guidance for the identification of endocrine disruptors (EFSA, 2018): “There may be cases in which due to the knowledge on the physico-chemical and (eco)toxicological properties of the substance an ED assessment does not appear scientifically necessary or testing for this purpose not technically possible (BP Regulation1, Annex IV or PPP Regulation 2, Annex, Point 1.5).”

RMS therefore, considers that sulfur is not expected to have endocrine disruption properties and that no further investigation through generation of new studies is considered necessary for non-target organisms due to the physico-chemical properties of the substance (i.e. very poor solubility in water) and its use as food supplement.

Overall, by considering that the substance is:

i- used as food additive and nutrient;

ii- is poorly soluble in water and therefore the test could be difficult to perform with the active substance;

It is considered that the ED assessment can be waived for non-target organisms.

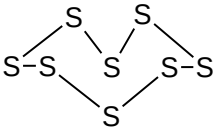
2.11 PROPOSED HARMONISED CLASSIFICATION AND LABELLING ACCORDING TO THE CLP CRITERIA *[SECTIONS 1-6 OF THE CLH REPORT]*

2.11.1 Identity of the substance [section 1 of the CLH report]

2.11.1.1 Name and other identifiers of the substance

Table 119: Substance identity and information related to molecular and structural formula of the substance

Sulphur **Volume 1 – Level 2**

Name(s) in the IUPAC nomenclature or other international chemical name(s)	Sulfur
Other names (usual name, trade name, abbreviation)	Sulphur
ISO common name (if available and appropriate)	Sulfur Sulphur
EC number (if available and appropriate)	231-722-6
EC name (if available and appropriate)	Sulfur
CAS number (if available)	7704-34-9
Other identity code (if available)	CIPAC No. 18
Molecular formula	S_8
Structural formula	
SMILES notation (if available)	-
Molecular weight or molecular weight range	32.064 g/mol (S) 256.512 g/mol (S_8)
Information on optical activity and typical ratio of (stereo) isomers (if applicable and appropriate)	Not applicable
Description of the manufacturing process and identity of the source (for UVCB substances only)	Confidential information, please refer to Vol. 4
Degree of purity (%) (if relevant for the entry in Annex VI)	≥ 990 g/kg

2.11.1.2 Composition of the substance

Table 120: Constituents (non-confidential information)

Constituent (Name and numerical identifier)	**Concentration range (% w/w minimum and maximum in multi-constituent substances)**	**Current CLH in Annex VI Table 3.1 (CLP)**	**Current self-classification and labelling (CLP)**
Sulphur (CAS n° 7704-34-9)	≥ 99.0	Skin Irrit. 2; H315	Skin Irrit. 2; H315

The substance is mono-constituent

Table 121: Impurities (non-confidential information) if relevant for the classification of the substance

Impurity (Name and numerical identifier)	**Concentration range (% w/w minimum and maximum)**	**Current CLH in Annex VI Table 3.1 (CLP)**	**Current self-classification and labelling (CLP)**	**The impurity contributes to the classification and labelling**
-	-	-	-	-

Table 122: Additives (non-confidential information) if relevant for the classification of the substance

Additive (Name and numerical identifier)	**Function**	**Concentration range (% w/w minimum and maximum)**	**Current CLH in Annex VI Table 3.1 (CLP)**	**Current self-classification and labelling (CLP)**	**The additive contributes to the classification and labelling**
-	-	-	-	-	

Table 123: Test substances (non-confidential information)

Identification of test substance	**Purity**	**Impurities and additives (identity, %, classification if available)**	**Other information**	**The study(ies) in which the test substance is used**
-	-	-	-	-

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2.11.2 Proposed harmonized classification and labelling

2.11.2.1 Proposed harmonised classification and labelling according to the CLP criteria

Table 124: Proposed harmonised classification and labelling according to the CLP criteria

	Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors	Notes
					Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard statement Code(s)	Suppl. Hazard statement Code(s)		
Current Annex VI entry	016-094-00-1	sulfur	231-722-6	7704-34-9	Skin Irrit. 2	H315	GHS07 Wng	H315			
Dossier submitters proposal	016-094-00-1	sulfur	231-722-6	7704-34-9	**Retain:** Skin Irrit. 2 **Add:** Eye Irrit. 2 STOT SE 3	**Retain:** H315 **Add:** H319 H335	**Retain:** GHS07 Wng	**Retain:** H315 **Add:** H319 H335			
Resulting Annex VI entry if agreed by RAC and COM	016-094-00-1	sulfur	231-722-6	7704-34-9	Skin Irrit. 2 Eye Irrit. 2 STOT SE 3	H315 H319 H335	GHS07 Wng	H315 H319 H335			

2.11.2.2 Additional hazard statements / labelling

None.

Table 125: Reason for not proposing harmonised classification and status under CLH public consultation

Hazard class	Reason for no classification	Within the scope of CLH public consultation
Explosives	Data conclusive but not sufficient for classification	Yes
Flammable gases (including chemically unstable gases)	Hazard class not applicable	No
Oxidising gases	Hazard class not applicable	No
Gases under pressure	Hazard class not applicable	No
Flammable liquids	Hazard class not applicable	No
Flammable solids	Data conclusive but not sufficient for classification	Yes
Self-reactive substances	Data conclusive but not sufficient for classification	Yes
Pyrophoric liquids	Hazard class not applicable	No
Pyrophoric solids	Data conclusive but not sufficient for classification	Yes
Self-heating substances	Data conclusive but not sufficient for classification	Yes
Substances which in contact with water emit flammable gases	Data conclusive but not sufficient for classification	Yes
Oxidising liquids	Hazard class not applicable	No
Oxidising solids	Data conclusive but not sufficient for classification	Yes
Organic peroxides	Data conclusive but not sufficient for classification	Yes
Corrosive to metals	Data conclusive but not sufficient for classification	Yes
Acute toxicity via oral route	Data conclusive but not sufficient for classification	Yes
Acute toxicity via dermal route	Data conclusive but not sufficient for classification	Yes
Acute toxicity via inhalation route	Data conclusive but not sufficient for classification	Yes
Skin corrosion/irritation	Harmonised classification: Skin Irrit. 2 H315	Yes
Serious eye damage/eye irritation	Harmonised classification proposed: Eye Irrit. 2 H319	Yes
Respiratory sensitisation	Data lacking	No
Skin sensitisation	Data conclusive but not sufficient for classification	Yes
Germ cell mutagenicity	Data conclusive but not sufficient for classification	Yes
Carcinogenicity	Data conclusive but not sufficient for classification	Yes
Reproductive toxicity	Data conclusive but not sufficient for classification	Yes
Specific target organ toxicity-single exposure	Harmonised classification proposed: STOT SE 3 H335	Yes
Specific target organ toxicity-repeated exposure	Data conclusive but not sufficient for classification	Yes
Aspiration hazard	Hazard class not applicable	No

Hazard class	Reason for no classification	Within the scope of CLH public consultation
Hazardous to the aquatic environment	Data conclusive but not sufficient for classification	Yes
Hazardous to the ozone layer	Data lacking	No

2.11.3 History of the previous classification and labelling

The harmonised classification and labelling of Sulphur has been considered previously in the EU (ATP01). The existing entry in Annex VI of CLP Regulation (EU) 1272/2008 is: Skin Irrit. 2, H315: Causes skin irritation.
In the framework of the renewal assessment of Sulphur under Regulation (EC) 1107/2009, RMS proposed to reconsider the current harmonised classification of the active substance by retaining the current classification and adding Eye Irrit. 2, H319: Causes serious eye irritation and STOT SE 3, H 335: May cause respiratory irritation. Therefore, in this context, a targeted CLH proposal is presented in this document using the common agreed template for DAR/RAR/CLH report.

RAC general comment

Sulfur (or sulphur) is regulated under the Plant Protection Products, Classification, Labelling and Packaging and REACH regulations. The present opinion is based on the information provided in the classification proposal prepared in relation to the pesticide re-evaluation under regulation 1107/2009.

Sulfur is used as fungicide against mildew in wine and in cereal crops. It also has an acaricidal function.

The pesticide active substance sulfur (pure and technical grade) is a yellow solid with a purity of 990 mg/kg. Formulations on the market include powders, granules and flakes. The classification proposal is based on studies carried out on sulfur technical or on a formulation called Sulphur Dust, which contains 985 mg/kg sulfur, which is used as a representative formulation by one of the two applicant groups under PPPR. The other applicant group has included an 80% Wettable Granule in their re-evaluation dossier.

Sulfur is registered in the EU Observatory for nanomaterials (EUON) as the substance is included in the French nano-inventory. Sulfur is not registered under REACH as a nanomaterial, and the substance is not included in the Belgian nanomaterials inventory. No information specific to the nanoform of sulfur is available in the classification dossier or in the REACH registration. During the RAC evaluation process, the applicant under the PPPR argued in a submitted document that pesticide formulations of sulfur would not fall under the definition of nanoparticles according to EU nanomaterial definition, as it did not meet the condition for 50% or more of the particles being in the size range of 1-100 nm.

The substance has a solubility in water of 16 µg/L and the solubility in organic solvents ranges from 0.17 g/L in methanol to ~14 g/L in toluene and dichloromethane.

2.11.4 Identified uses

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Sulphur is a fungicide and acaricide active substance used for many years in Europe on various crop. For more details, please refer above on chapter, 1.6.1 Details of representative uses.

2.11.5 Data sources

The data source is the dossier submitted by the applicant and supporting the Annex I Renewal of the active substance Sulphur under Regulation EC 1107/2009.

2.12 RELEVANCE OF METABOLITES IN GROUNDWATER

Not applicable to inorganic compounds.

2.13 CONSIDERATION OF ISOMERIC COMPOSITION IN THE RISK ASSESSMENT

Not applicable, as the substance does not have isomers.

2.14 RESIDUE DEFINITIONS

2.14.1 Definition of residues for exposure/risk assessment

Food of plant origin: elemental sulphur

Food of animal origin: none

Soil: sulfur

Groundwater: sulfur and sulfates

Surface water: sulfur and sulfates

Sediment: sulfur and sulfates

Air: sulfur (free and particulate)

2.14.2 Definition of residues for monitoring

Food of plant origin: none

Food of animal origin: none

Soil: none

Groundwater: none

Surface water: none

Sediment: none

Air: sulfur

Level 3

SULPHUR

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

3.1.1.1 Article 4				
		Yes	No	
i)	It is considered that Article 4 of Regulation (EC) No 1107/2009 is complied with. Specifically the RMS considers that authorisation in at least one Member State is expected to be possible for at least one plant protection product containing the active substance for at least one of the representative uses.	X		RMS considers that sulphur can be renewed and that authorizations of PPP can be granted in at least one Member States provided that additional data are submitted. Risk assessment cannot be finalised for the PPP Sulphur Dust for the environment and non target organisms, and for the PPP Sulfur 80% WG for non target organisms. Please refer to Level 2, points 2.8 and 2.9
3.1.1.2 Submission of further information				
		Yes	No	
i)	It is considered that a complete dossier has been submitted	X		RMS considers that a complete dossier was submitted. However, please refer to Table 3.1.4.
ii)	It is considered that in the absence of a full dossier the active substance may be approved even though certain information is still to be submitted because: (a) the data requirements have been amended or refined after the submission of the dossier; or (b) the information is considered to be confirmatory in nature, as required to increase confidence in the decision.			
3.1.1.3 Restrictions on approval				
		Yes	No	
	It is considered that in line with Article 6 of Regulation (EC) No 1107/2009 approval should be subject to conditions and restrictions.		X	
3.1.1.4 Criteria for the approval of an active substance				
Dossier				
		Yes	No	

	It is considered the dossier contains the information needed to establish, where relevant, Acceptable Daily Intake (ADI), Acceptable Operator Exposure Level (AOEL) and Acute Reference Dose (ARfD).			Not relevant. Due to the low toxicity of Sulphur, no toxicological reference value has been established. Please refer to Level 2, point 2.6
	It is considered that the dossier contains the information necessary to carry out a risk assessment and for enforcement purposes (relevant for substances for which one or more representative uses includes use on feed or food crops or leads indirectly to residues in food or feed). In particular it is considered that the dossier: (a) permits any residue of concern to be defined; (b) reliably predicts the residues in food and feed, including succeeding crops (c) reliably predicts, where relevant, the corresponding residue level reflecting the effects of processing and/or mixing; (d) permits a maximum residue level to be defined and to be determined by appropriate methods in general use for the commodity and, where appropriate, for products of animal origin where the commodity or parts of it is fed to animals; (e) permits, where relevant, concentration or dilution factors due to processing and/or mixing to be defined.	X		In the framework of the renewal, it is proposed to maintain sulphur in the Annex IV of regulation 396/2005/EC Please refer to Level 2, point 2.7
	It is considered that the dossier submitted is sufficient to permit, where relevant, an estimate of the fate and distribution of the active substance in the environment, and its impact on non-target species.	X		See level 2, Points 2.8 and 2.9
Efficacy				
		Yes	No	
	It is considered that it has been established for one or more representative uses that the plant protection product, consequent on application consistent with good plant protection practice and having regard to realistic conditions of use is sufficiently effective.	X		The efficacy was not assessed for the renewal process of sulphur. Sulphur based products are currently registered on the representative uses in some MS. Sulphur based products will be re-assessed following the renewal of sulphur.
Relevance of metabolites				
		Yes	No	
	It is considered that the documentation submitted is sufficient to permit the establishment of the toxicological, ecotoxicological or environmental relevance of metabolites.	X		Not applicable to inorganic compounds.
Composition				

		Yes	No	
	It is considered that the specification defines the minimum degree of purity, the identity and maximum content of impurities and, where relevant, of isomers/diastereo-isomers and additives, and the content of impurities of toxicological, ecotoxicological or environmental concern within acceptable limits.	X		Sufficient information has been presented by the notifiers to support the declared technical specification, with respect to the minimum purity of the active substance, the identity and the maximum level of impurities in the technical material.
	It is considered that the specification is in compliance with the relevant Food and Agriculture Organisation specification, where such specification exists.	X		No FAO specifications are set for this active substance
	It is considered for reasons of protection of human or animal health or the environment, stricter specifications than that provided for by the FAO specification should be adopted	X		Among impurities that were quantified in all the batches, mercury, cadmium, arsenic, lead and nickel are considered relevant impurities due to their toxicological properties. Specifications are therefore proposed for these impurities.
Methods of analysis				
		Yes	No	
	It is considered that the methods of analysis of the active substance, safener or synergist as manufactured and of determination of impurities of toxicological, ecotoxicological or environmental concern or which are present in quantities greater than 1 g/kg in the active substance, safener or synergist as manufactured, have been validated and shown to be sufficiently specific, correctly calibrated, accurate and precise.	X		All the methods developed for the determination of the active substance in the technical material are validated. These methods are based on HPLC-UV technique or by iodometric titration (CIPAC method). Mercury, arsenic, Cadmium, Lead and Nickel are considered as relevant impurities; fully validated methods are available for their determination in the technical substance.
	It is considered that the methods of residue analysis for the active substance and relevant metabolites in plant, animal and environmental matrices and drinking water, as appropriate, shall have been validated and shown to be sufficiently sensitive with respect to the levels of concern.	X		No residue definition has been set for plant, animal and environmental matrices, therefore no method for monitoring is necessary. However, without monitoring data showing that the background levels of sulphur in air are not significantly increased by the use in agriculture or viticulture, a monitoring method for the determination of sulphur residues in air should be provided. Residues of active substance in air should be defined and should include the parent (Sulfur itself).
	It is confirmed that the evaluation has been carried out in accordance with the uniform principles for evaluation and authorisation of plant protection products referred to in Article 29(6) of Regulation 1107/2009.	X		
Impact on human health				

Impact on human health - ADI, AOEL, ARfD				
		Yes	No	
	It is confirmed that (where relevant) an ADI, AOEL and ARfD 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.	X		As agreed for the first approval of the active substance (EFSA, 2008), considering that sulfur is an essential element needed at high dose levels, the wide background exposure levels of sulfur, the low additional burden originating from crop protection uses of sulfur as well as the toxicological properties of sulfur, setting of toxicological reference values is not required. Instead, non-dietary exposure might be assessed against the average sulfur background level (24 mg/kg bw/day).
Impact on human health – proposed genotoxicity classification				
		Yes	No	
	It is considered that, on the basis of assessment of higher tier genotoxicity testing carried out in accordance with the data requirements and other available data and information, including a review of the scientific literature, reviewed by the Authority, **the substance SHOULD BE classified or proposed for classification**, in accordance with the provisions of Regulation (EC) No 1272/2008, **as mutagen category 1A or 1B.**		X	Based on the available data, sulfur can be considered as devoid of genotoxic potential (provided that the ongoing *in vitro* mammalian cell gene mutation test confirms this conclusion).
Impact on human health – proposed carcinogenicity classification				
		Yes	No	
i)	It is considered that, on the basis of assessment of the carcinogenicity testing carried out in accordance with the data requirements for the active substances, safener or synergist and other available data and information, including a review of the scientific literature, reviewed by the Authority, **the substance SHOULD BE classified or proposed for classification**, in accordance with the provisions of Regulation (EC) No 1272/2008, **as carcinogen category 1A or 1B.**		X	As agreed for the first approval of the active substance (EFSA, 2008), sulfur is generally regarded as safe for human exposure given the wide range of background exposure, its low acute and short-term toxicity and its non-genotoxic potential. In addition, it is an essential element needed at a high dose level. Therefore, it was considered unnecessary to require carcinogenicity toxicity studies with sulfur.
ii)	Linked to above classification proposal. It is considered that exposure of humans to the active substance, safener or synergist in a plant protection product, under realistic proposed conditions of use, is negligible, that is, the product is used in closed systems or in other conditions excluding contact with humans and where residues of the active substance, safener or synergist concerned on food and feed do not exceed the default value set in accordance with Article 18(1)(b) of Regulation (EC) No 396/2005.			Not relevant

Impact on human health – proposed reproductive toxicity classification				
		Yes	No	
i)	It is considered that, on the basis of assessment of the reproductive toxicity testing carried out in accordance with the data requirements for the active substances, safeners or synergists and other available data and information, including a review of the scientific literature, reviewed by the Authority, **the substance SHOULD BE classified or proposed for classification**, in accordance with the provisions of Regulation (EC) No 1272/2008, **as toxic for reproduction category 1A or 1B.**		X	As agreed for the first approval of the active substance (EFSA, 2008), sulfur is generally regarded as safe for human exposure given the wide range of background exposure, its low acute and short-term toxicity and its non-genotoxic potential. In addition, it is an essential element needed at a high dose level. Therefore, it was considered unnecessary to require reproductive toxicity studies with sulfur.
ii)	Linked to above classification proposal. It is considered that exposure of humans to the active substance, safener or synergist in a plant protection product, under realistic proposed conditions of use, is negligible, that is, the product is used in closed systems or in other conditions excluding contact with humans and where residues of the active substance, safener or synergist concerned on food and feed do not exceed the default value set in accordance with Article 18(1)(b) of Regulation (EC) No 396/2005.			Not relevant
Impact on human health – proposed endocrine disrupting properties classification				
		Yes	No	
i)	It is considered that **the substance SHOULD BE identified as having endocrine disrupting properties** in accordance with the provisions of point 3.6.5 in Annex II of Regulation (EC) No 1107/2009		X	An assessment of the endocrine disrupting properties has been conducted according to EFSA/ECHA Guidance document (2018). For T-modality and for EAS-modalities, no EATS-mediated adversity was observed in the available insufficient dataset. Based on scenario 2a (iii), the endocrine activity was not sufficiently investigated for EATS-modalities and according to the guidance, additional information would be needed. Nevertheless, it is considered that the waivers for long-term/carcinogenicity study, reproductive toxicity studies and setting of toxicological reference values could also apply for endocrine disrupting potential. Sulfur is generally regarded as safe for human exposure given the wide range of background exposure, its low acute and short-term toxicity and its non-genotoxic potential. In addition, it is an essential element needed at a high dose level. Therefore, it was considered unnecessary to require additional information to conclude on ED properties of sulfur.

				Based on a weight of evidence, taking into account the limited database, the known toxicological properties of sulfur and its wide range of background exposure and considering that sulfur is an essential element needed at a high dose level, it can be concluded that sulfur is not an endocrine disruptor in humans.
ii)	Linked to above identification proposal. It is considered that exposure of humans to the active substance, safener or synergist in a plant protection product, under realistic proposed conditions of use, is negligible, that is, the product is used in closed systems or in other conditions excluding contact with humans and where residues of the active substance, safener or synergist concerned on food and feed do not exceed the default value set in accordance with Article 18(1)(b) of Regulation (EC) No 396/2005.			Not relevant
Fate and behaviour in the environment				
Persistent organic pollutant (POP)				
		Yes	No	
	It is considered that the active substance **FULFILS** the criteria of a persistent organic pollutant (POP) as laid out in Regulation 1107/2009 Annex II Section 3.7.1.		X	No degradation data available. Sulphur is not expected to be persistent in elemental form due to its dissipation in all environmental compartments. Sulfur readily undergoes degradation through oxidative or reductive processes under aerobic or anaerobic conditions by specific microbial organisms to sulfate ions (SO_4^{2-}) or sulfides (-S-), respectively, both of which in turn are abundant in nature.
Persistent, bioaccumulative and toxic substance (PBT)				
		Yes	No	
	It is considered that the active substance **FULFILS** the criteria of a persistent, bioaccumulative and toxic (PBT) substance as laid out in Regulation 1107/2009 Annex II Section 3.7.2.		X	No degradation data available. Sulphur is not expected to be persistent in elemental form due to its dissipation in all environmental compartments. Sulfur readily undergoes degradation through oxidative or reductive processes under aerobic or anaerobic conditions by specific microbial organisms to sulfate ions (SO_4^{2-}) or sulfides (-S-), respectively, both of which in turn are abundant in nature.
Very persistent and very bioaccumulative substance (vPvB).				
		Yes	No	
	It is considered that the active substance **FULFILS** the criteria of a a very persistent and very bioaccumulative substance (vPvB) as laid out in Regulation 1107/2009 Annex II Section 3.7.3.		X	No degradation data available. Sulphur is not expected to be persistent in elemental form due to its dissipation in all environmental compartments. Sulfur readily undergoes degradation through oxidative

				or reductive processes under aerobic or anaerobic conditions by specific microbial organisms to sulfate ions (SO_4^{2-}) or sulfides (-S-), respectively, both of which in turn are abundant in nature.
Ecotoxicology				
		Yes	No	
i	It is considered that the risk assessment demonstrates risks to be acceptable in accordance with the criteria laid down in the uniform principles for evaluation and authorisation of plant protection products referred to in Article 29(6) under realistic proposed conditions of use of a plant protection product containing the active substance, safener or synergist. The RMS is content that the assessment takes into account the severity of effects, the uncertainty of the data, and the number of organism groups which the active substance, safener or synergist is expected to affect adversely by the intended use.	X		An acceptable overall risk for birds is indicated for the representative GAP uses of 'Sulfur 80% WG'. For 'Sulphur dust', further refinements are needed for granivorous, insectivorous, omnivorous and frugivorous birds. An acceptable overall risk for mammals is indicated for the representative GAP uses of 'Sulfur 80% WG' and 'Sulphur Dust'. A risk for aquatic organisms (fish, aquatic invertebrates, algae and sediment dwelling organisms) has been identified for all representative uses and all representative products. The risks to bees are acceptable for both representative products. For non-target arthropods, the in-field risk for non-target arthropods is unacceptable and further refinements are still needed for the representative use of 'Sulfur 80% WG' and 'Sulphur Dust'. The off-field risk for terrestrial non-target arthropods is acceptable for the representative use of 'Sulfur 80% WG' on cereals and grapevine with implementation of mitigations measures. The off-field risk for terrestrial non-target arthropods is not finalized for the representative use of 'Sulphur Dust'. For the representative uses of 'Sulfur 80% WG' an acceptable long-term risk is indicated for the soil meso- and macrofauna except *Folsomia candida*. A higher-tier risk assessment is required. For the representative uses of 'Sulphur Dust' an acceptable long-term risk is indicated for *Hypoaspis aculeifer* whereas further refinements are needed for earthworms and collembola. The risk for soil micro-organisms is acceptable for both representative products.

				The risk for terrestrial plants is acceptable without mitigation for both representative products.
ii	It is considered that the substance **SHOULD BE identified as having endocrine disrupting properties** that may cause adverse effects on non-target organisms in accordance with the provisions of point 3.8.2 in Annex II of Regulation (EC) No 1107/2009.		X	RMS considers that sulfur is not expected to have endocrine disruption properties and that no further investigation through generation of new studies is considered necessary for non-target organisms due to the physico-chemical properties of the substance (i.e. very poor solubility in water) and its use as food supplement. Overall, by considering that the substance is: i- used as food additive and nutrient; ii- is poorly soluble in water and therefore the test could be difficult to perform with the active substance; It is considered that the ED assessment can be waived.
iii	Linked to the consideration of the endocrine properties immediately above. It is considered that the exposure of non-target organisms to the active substance in a plant protection product under realistic proposed conditions of use is negligible.			Not relevant.
iv	It is considered that it is established following an appropriate risk assessment on the basis of Community or internationally agreed test guidelines, that the use under the proposed conditions of use of plant protection products containing this active substance, safener or synergist: — will result in a negligible exposure of honeybees, or — has no unacceptable acute or chronic effects on colony survival and development, taking into account effects on honeybee larvae and honeybee behaviour.	X		The acute and chronic risk for bees is considered acceptable for all intended uses.
Residue definition				
		Yes	No	
	It is considered that, where relevant, a residue definition can be established for the purposes of risk assessment and for enforcement purposes.	X		Not relevant for monitoring.

				For plant, it is proposed to consider the parent compound elemental sulphur (S_8) alone as the residue definition for risk assessment because a large part of the applied product do not penetrate into the organism and is stable at the leaf surface. For animals, because elemental sulphur is metabolised in sulphate and organic sulphur after ingestion by livestock's, and because external traces of parental compound are not of matter, it is proposed not to set any residue definition in livestock's.
Fate and behaviour concerning groundwater				
		Yes	No	
	It is considered that it has been established for one or more representative uses, that consequently after application of the plant protection product consistent with realistic conditions on use, the predicted concentration of the active substance or of metabolites, degradation or reaction products in groundwater complies with the respective criteria of the uniform principles for evaluation and authorisation of plant protection products referred to in Article 29(6) of Regulation 1107/2009.	X		Sulfur is not of concern for the contamination of groundwater, but the potential for groundwater contamination for sulfates needed to be addressed, as they are highly mobile in soil. For SULFUR 80% WG product, no exceedance of the trigger value of 250 mg/L for sulfates is expected according to the intended uses, when no background concentration in soil of sulphur/sulfate or background concentration of sulfate in groundwater is considered. *For SULPHUR DUST product,* an exceedance of the trigger value of 250 mg/L cannot be excluded for sulfates for some weather/Soil scenarios. No background concentration in soil of sulphur/sulfate or background concentration of sulfate in groundwater was considered.

3.1.2 Proposal – Candidate for substitution

Candidate for substitution				
		Yes	No	
	It is considered that the active substance shall be approved as a candidate for substitution		X	Sulphur does not meet the criteria to be considered as a candidate for substitution (as below): *—its ADI, ARfD or AOEL is significantly lower than those of the majority of the approved active substances within groups of substances/use categories,* **NO** *— it meets two of the criteria to be considered as a PBT substance* **NO**

				— there are reasons for concern linked to the nature of the critical effects (such as developmental neurotoxic or immunotoxic effects) which, in combination with the use/exposure patterns, amount to situations of use that could still cause concern, for example, high potential of risk to groundwater; even with very restrictive risk management measures (such as extensive personal protective equipment or very large buffer zones), **NO** *— it contains a significant proportion of non-active isomers,* **NO** *— it is or is to be classified, in accordance with the provisions of Regulation (EC) No 1272/2008, as carcinogen category 1A or 1B, if the substance has not been excluded in accordance with the criteria laid down in point 3.6.3,* **NO** *— it is or is to be classified, in accordance with the provisions of Regulation (EC) No 1272/2008, as toxic for reproduction category 1A or 1B if the substance has not been excluded in accordance with the criteria laid down in point 3.6.4,* **NO** *— if, on the basis of the assessment of Community or internationally agreed test guidelines or other available data and information, reviewed by the Authority, it is considered to have endocrine disrupting properties that may cause adverse effects in humans if the substance has not been excluded in accordance with the criteria laid down in point 3.6.5.]* **NO**

3.1.3 Proposal – Low risk active substance

Low-risk active substances				
		Yes	No	
	It is considered that the active substance **shall be considered of low risk.** If the active substance is not a micro-organism, in particular it is considered that: (a) the substance **should NOT be classified or proposed for classification** in accordance to Regulation (EC) No 1272/2008 as any of the following: — carcinogenic category 1A, 1B or 2, — mutagenic category 1A, 1B or 2, — toxic to reproduction category 1A, 1B or 2, — skin sensitiser category 1, — serious damage to eye category 1, — respiratory sensitiser category 1, — acute toxicity category 1, 2 or 3, — specific Target Organ Toxicant, category 1 or 2, — toxic to aquatic life of acute and chronic category 1 on the basis of appropriate standard tests, — explosive, — skin corrosive, category 1A, 1B or 1C; (b) it has **not been identified as priority substance under Directive 2000/60/EC**; (c) it is **not deemed to be an endocrine disruptor** in accordance to Annex II of Regulation (EC) No 1107/2009; (d) it **has no neurotoxic or immunotoxic effects**; (e) it **is not persistent** (half-life in soil is more than 60 days) or its **bio-concentration factor is lower than 100**.	X		For aquatic environment, due to the low toxicity and the low water solubility of sulfur, no classification is proposed neither for the active substance nor for both products. Sulfur is generally regarded as safe for human exposure given the wide range of background exposure, its low acute and short-term toxicity and its non-genotoxic potential. In addition, it is an essential element needed at a high dose level. Sulfur is classified as a skin irritant category 2 according to Regulation (EC) No 1272/2008. The RMS also considers that classifications as eye irritant category 2 and STOT SE category 3 for respiratory tract irritation are warranted. No other classification is deemed necessary. Sulfur is not an endocrine disruptor in humans according to Annex II of Regulation (EC) No 1107/2009.

	(f) it is a **semiochemical** and verifies points (a) to (d). Paragraph (e) doesn't apply to naturally occurring active substances. If the active substance is a micro-organism, in particular it is considered that at strain level the micro-organism has not demonstrated multiple resistance to anti-microbials used in human or veterinary medicine. If the active substance is a baculovirus, in particular it has not demonstrated adverse effects on non-target insects.			

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

Data gap	Relevance in relation to representative use(s)	Study status		
		No confirmation that study available or on-going.	Study on-going and anticipated date of completion	Study available but not peer-reviewed
3.1.4.1 Identity of the active substance or formulation				
None				
3.1.4.2 Physical and chemical properties of the active substance and physical, chemical and technical properties of the formulation				
None				
3.1.4.3 Data on uses and efficacy				
None				
3.1.4.4 Data on handling, storage, transport, packaging and labelling				
None				
3.1.4.5 Methods of analysis				
No analytical method for the determination of sulphur residues in air was provided.	The absence of such a method precludes monitoring data to be generated to demonstrate that the increase in exposure is not significant compared to the background level of the substance S_8. This method should be able to determine distinctively sulphur residues in the vapour phase and sulphur particles in air. The LOQ of	X		

	this analytical method should be sufficently low, e.g. ≤ 0.1 µg/m^3, and be specific to elemental sulphur at oxidation state 0.			
3.1.4.6 Toxicology and metabolism				
In vitro mammalian cell gene mutation test with sulfur	Relevant for all representative uses		X (October 2020)	
Determination of the inhalable, thoracic and alveolar dust fractions of 'Sulphur Dust'	Relevant for DP formulation		X (Q2 2020)	
In vitro dermal absorption study with sulfur in 'Sulfur 80% WG' formulations on human skin	Relevant for WG formulations		X (October 2020)	
3.1.4.7 Residue data				
None				
3.1.4.8 Environmental fate and behaviour				
More information/data on the extrapolation of the drift % value (BBA, 2000) to foliar dust applications should be provided. Specific data on the drift value for the application of dustable powder formulation could help for conducting a robust environmental risk assessment.	For dustable powder formulation	X		
Information/data on the soil concentration of elemental sulfur should be provided by the notifiers in order to assess the impact of of the applied amounts of elemental sulfur following the use of sulphur on the soil concentration.	Relevant for all intended uses	X		
Information on the natural buffering capacity of soils in Europe to neutralize acid inputs from sulfate ions potentially formed following the use of sulfur and on the possible adverse effects on non-target terrstrial organisms.	Relevant for all intended uses	X		

Information on the natural buffering capacity of surface water bodies in Europe to neutralize acid inputs from sulfate ions potentially formed following the use of sulfur and on the possible adverse effects on non-target aquatic organisms.	Relevant for all intended uses	X		
Monitoring data on sulphur residues in air compartment. Please also refer to data gap identified above under Point 3.1.4.5.	Relevant for all intended uses	X		
3.1.4.9 Ecotoxicology				
Bee larval development for sulfur	Relevant for all intended uses		X	
Earthworm higher-tier field study with Sulphur	For dustable powder product		X	
Collembolian higher-tier study with Sulphur	Relevant for all intended uses		X	

3.1.5 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)**
Risk to non-target arthropods.	All representative uses.
Risk to earthworms	Use on grapevine for the representative product Sulphur Dust
Risk to collembola	All representative uses.
Risk to aquatic organisms	All representative uses.
Risk to granivorous, insectivorous, omnivorous and frugivorous birds	Use on grapevine for the representative product Sulphur Dust

3.1.6 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 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	-

3.1.7 Overview table of the concerns identified for each representative use considered

(If a particular condition proposed to be taken into account to manage an identified risk, as listed in 3.3.1, has been evaluated as being effective, then 'risk identified' is not indicated in this table.)
All columns are grey as the material tested in the toxicological studies has not been demonstrated to be representative of the technical specification.

Representative use		Use "Grapevine" (Sulfur 80% WG)	Use "Cereals" (Sulfur 80% WG)	Use "Grapevine" (Sulphur Dust)
Operator risk	Risk identified			
	Assessment not finalised			
Worker risk	Risk identified			
	Assessment not finalised			
Bystander risk	Risk identified			
	Assessment not finalised			
Consumer risk	Risk identified			
	Assessment not finalised			
Risk to wild non target terrestrial vertebrates	Risk identified			
	Assessment not finalised			X
Risk to wild non target terrestrial organisms other than vertebrates	Risk identified			
	Assessment not finalised	X	X	X
Risk to aquatic organisms	Risk identified			
	Assessment not finalised	X	X	X
Groundwater exposure active substance	Legal parametric value breached			
	Assessment not finalised			
Groundwater exposure metabolites	Legal parametric value breached			
	Parametric value of 10µg/L[(a)] breached			
	Assessment not finalised			X (based on the provisional PECgw) 2/7
Comments/Remarks				

The superscript numbers in this table relate to the numbered points indicated within chapter 3.1.5 and 3.1.6. Where there is no superscript number, see level 2 for more explanation.

(a): Value for non relevant metabolites prescribed in SANCO/221/2000-rev 10-final, European Commission, 2003

3.1.8 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**
The need for a subchronic toxicity study by inhalation route is proposed to be discussed between Member States during the expert meeting	No repeated-dose inhalation toxicity study is available on sulfur. Nevertheless, taking into account the results of the newly submitted epidemiological study (Raanan 2017 – please refer to Vol 3 CA B6.9.4), the RMS considered that this could be a justification for conducting a repeat dose inhalation toxicity study with sulfur. It is also noteworthy that many of the plant protection products are in the form of a very fine powder (90% of particles <53µm; 10% of the particles < 5.7µm) applied as powder/dust, which could raise concern related to non-dietary exposure. Furthermore, it was demonstrated from the exposure study (Garofani S., 2010a) that inhalation represents the major part of systemic exposure of bystander/resident, particularly in children (please refer to Vol 3CP Sulphur Dust B6). Please refer to Vol 1 Level 2.6.3.1.1.

3.1.9 Critical issues on which the Co RMS did not agree with the assessment by the RMS

Points on which the co-rapporteur Member State did not agree with the assessment by the rapporteur member state. Only the points relevant for the decision making process should be listed.

Issue on which Co-RMS disagrees with RMS	**Opinion of Co-RMS**	**Opinion of RMS**
In vivo genotoxicity	We agree that repeated micronucleus assay in mouse bone marrow should not be required due to questionable exposure of target tissue. However, in order to demonstrate the lack of genotoxic potential of sulphur in vivo an in vivo genotoxicity study at site of first contact would be the most appropriate.	Two *in vivo* micronucleus assays are available on sulfur: one with sulfur technical by oral route and one with sulfur dust by intraperitoneal injection. They were both performed under GLP according to OECD TG 474. Although some deviations according to current OECD TG 474 (2016) were noted, the studies were compliant with OECD TG 474 (1997) and could be considered acceptable. Under the conditions of these studies, no statistically significant increase in the number of micronuclei was noted at the limit dose of 2000 mg/kg bw. Nevertheless, the reliability of the negative results were questionable as

		the bone marrow was not demonstrated to be exposed in these studies. In the absence of ADME studies and of systemic toxicity observed in the toxicity studies available on sulfur, lines of evidence of bone marrow exposure could not be gathered. Nevertheless, as sulfur is an essential element of low toxicity needed at a high dose level and retrieved in dietary items/food consumptions, as no genotoxicity concern was raised for sulfur despite its long history of use (including pharmaceutical uses) and as the available genotoxicity assays showed negative results (pending results of the *in vitro* mammalian cell gene mutation assay to be submitted later), the RMS considered that the concern on genotoxicity is very low and that further data are not required. Overall, sulfur can be considered as devoid of genotoxic potential.

3.2 PROPOSED DECISION

It is proposed that:

Sulphur can be renewed under Regulation (EC) No 1107/2009 as a low risk active substance provided that additional data are submitted to finalise the risk assessment for environment and non target organisms (refer to 3.1.4).

It is considered that the following is specified in Part A of the Commission Implementing Regulation for the approval of the active substance:

None.

It is considered that the following be specified in Part B of the Commission Implementing Regulation as areas requiring particular attention from Member States when evaluating applications for product authorisation(s):

- the risk to birds (Grapevine for dustable powder products),
- the risk to wild non target terrestrial organisms other than vertebrates,
- the risk to aquatic organisms,
- the risk to groundwater,
- the specification of the technical material

It is considered that it should be specified that conditions of use shall include risk mitigation measures, where appropriate.

It is proposed that the Member States concerned shall request the submission of confirmatory information:
(a) where new data requirements are established during the evaluation process, or
(b) as a result of new scientific and technical knowledge, or
(c) to increase confidence in the decision.

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

Proposed condition/risk mitigation measure	Relevance in relation to representative use(s)
Mitigation measures for non-target arthropods (Sulfur 80% WG): - An acceptable off-field risk can be concluded for the use in cereals with consideration of an unsprayed buffer zone of 5 meters.	For the representative use on cereals of the representative product 'Sulfur 80% WG'.
Mitigation measures for non-target arthropods (Sulfur 80% WG): - For the early application of 'Sulfur 80% WG' in grapevine an acceptable off-field risk is reached with consideration of an unsprayed buffer zone of 10 meter.	For the representative use on grapevine of the representative product 'Sulfur 80% WG'.
Mitigation measures for non-target arthropods (Sulfur 80% WG): - For the late application of 'Sulfur 80% WG' in grapevine an acceptable off-field risk is reach with consideration of an unsprayed buffer zone of 20 meters.	For the representative use on grapevine of the representative product 'Sulfur 80% WG'.

3.4 APPENDICES

GUIDANCE DOCUMENTS USED IN THIS ASSESSEMENT

General

SANCO/2012/11251 rev. 4 [Guidance Document on the renewal of approval of active substances to be assessed in compliance with Regulation (EU) No 844/2012 (the Renewal Regulation)]

Section identity, physical chemical and analytical methods

Section physico chemical properties

Manual on development and use of FAO and WHO specifications for pesticides - third revision of the First Edition, WHO, Rome 2016
Chemicals Regulation Directorate, DATA REQUIREMENTS HANDBOOK, (Version 2.2, June 2012)
Technical monograph N°17, 2nd edition, Guidelines for Specifying the Shelf Life of Plant Protection Products, June 2009
Evaluation Manual for the Authorisation of plant protection products and biocides according to Regulation (EC) No 1107/2009, EU part, Plant Protection Products, Chapter 2 Physical and chemical properties, version 2.0; January 2014, Board
Guidance ST/SG/AC 10/11/Rev.5 for the safety properties
CLP regulation 1272/2008
Regulation (UE) N°283/2013 (1st March 2013) setting out data requirements for active substances, 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
Regulation (UE) N°284/2013 (1st March 2013) setting out data requirements for plant protection products, 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

Section analytical methods

SANCO/3030/99 rev.4: Technical Material and preparations: guidance for generating and reporting methods of analysis in support of pre- and post-registration data requirements for Annex II (part A, Section 4) and Annex III (part A, Section 5) of Directive 91/414
SANCO/3029/99 rev .4: Residues: guidance for generating and reporting methods of analysis in support of pre-registration data requirements for Annex II (part A, section 4) and Annex III (part A, Section 5) of directive 91/414
SANCO/825/00 rev.8.1: Guidance document on pesticide residues analytical methods

Section Data on application and efficacy

SANCO/2012/11251 rev. 4 [Guidance Document on the renewal of approval of active substances to be assessed in compliance with Regulation (EU) No 844/2012 (the Renewal Regulation)], point 4.6 Substance efficacy.

Section Toxicology

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

EFSA (European Food Safety Authority), 2014. Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products. EFSA Journal 2014;12(10):3874, 55 pp., doi:10.2903/j.efsa.2014.3874

EFSA (European Food Safety Authority) Scientific Committee, Benford D, Halldorsson T, Jeger MJ, Knutsen HK, More S, Naegeli H, Noteborn H, Ockleford C, Ricci A, Rychen G, Schlatter JR, Silano V, Solecki R, Turck D, Younes M, Craig P, Hart A, Von Goetz N, Koutsoumanis K, Mortensen A, Ossendorp B, Martino L, Merten C, Mosbach-Schulz O and Hardy A, 2018. Guidance on Uncertainty Analysis in Scientific Assessments. EFSA Journal

2018;16(1):5123, 39 pp. https://doi.org/ 10.2903/j.efsa.2018.5123

ECHA (European Chemicals Agency) and EFSA (European Food Safety Authority) with the technical support of the Joint Research Centre (JRC), Andersson N, Arena M, Auteri D, Barmaz S, Grignard E, Kienzler A, Lepper P, Lostia AM, Munn S, Parra Morte JM, Pellizzato F, Tarazona J, Terron A and Van der Linden S, 2018. Guidance for the identification of endocrine disruptors in the context of Regulations (EU) No 528/2012 and (EC) No 1107/2009. EFSA Journal 2018;16(6):5311, 135 pp. https://doi.org/10.2903/j.efsa.2018.5311. ECHA-18-G-01-EN

International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, ICH Harmonised Guideline – Guideline for Elemental Impurities Q3D (R1), March 2019

Section Residue and consumer risk assessment

SANCO/11188/2013 - Rev. 2, 14 September 2015; Guidance document on criteria for the inclusion of active substances into Annex IV of Regulation (EC) N° 396/2005.

OECD, 2009. OECD Guidelines for the testing of chemicals – Crop field trial. No 509, Paris 2009

Doc SANCO/221/2000- rev.10, 25 February 2003- Guidance document on the assessment of the relevance of metabolites in groundwater-

Section fate and behavior in environment

European Commission (2014) - 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 3, 613 pp.

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 (1997) - Soil persistence models and EU Registration - The Final Report of the Soil Modelling Workgroup of FOCUS (Forum for the Co-ordination of Pesticide Fate Models and their Use) – 29 February 1997.

FOCUS (2001) - FOCUS Surface Water Scenarios in the EU Evaluation Process under 91/414/EEC. Report of the FOCUS Working Group on Surface Water Scenarios, EC Document Reference SANCO/4802/2001-rev.1. 221 pp.

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.

FOCUS (2008) - Pesticides in Air: Considerations for Exposure Assessment. Report of the FOCUS Working Group on Pesticides in Air, EC Document Reference SANCO/10553/2006 Rev 2 June 2008. 327 pp.

FOCUS (2014a) - Generic guidance for Tier 1 FOCUS groundwater assessments. Version 2.2, May 2014.

FOCUS (2014b) - Generic Guidance for Estimating Persistence and Degradation Kinetics from Environmental Fate Studies on Pesticides in EU Registration, version 1.1

FOCUS (2015) - Generic guidance for FOCUS surface water Scenarios, Version: 1.4, Date: May 2015

SANCO (2003) Guidance document on the assessment of the relevance of metabolites in groundwater of substances regulated under Council directive 91/414/EEC. Sanco/221/2000-rev.10-final, 25 February 2003.

Section ecotoxicology

EFSA (2009) - Guidance Document on Risk Assessment for Birds and Mammals on request from EFSA (EFSA Journal 2009; 7(12): 1438).

EFSA (2013) - Guidance document on tiered risk assessment for plant protection products for aquatic organisms in edge-of-field surface waters in the context of Regulation (EC) No 1107/2009", (EFSA Journal 2013; 11(7):3290)

SANCO (2002) - Guidance Document on Terrestrial Ecotoxicology", as provided by the Commission Services (SANCO/10329/2002 rev 2 (final), October 17, 2002).

EFSA (2013) - EFSA Guidance Document on the risk assessment of plant protection products on bees (*Apis mellifera, Bombus* spp.) and solitary bees, Journal 2013; 11(7):3295.

ESCORT 2 guidance document (Candolfi et al. 2001), Guidance document on regulatory testing and risk assessment procedures for plant protection products with non-target arthropods.

3.5 REFERENCE LIST

Regulation (EU) No 844/2012 of 18 September 2012 setting out the provisions necessary for the implementation of the renewal procedure for active substances, as provided for in Regulation (EC) No 1107/2009 of the European Parliament and of the Council concerning the placing of plant protection products on the market

SANCO/2012/11251 rev. 4 [Guidance Document on the renewal of approval of active substances to be assessed in compliance with Regulation (EU) No 844/2012 (the Renewal Regulation)]

Regulation (EC) No 1107/2009 of the European Parliament and of the Council of 21 October 2009 concerning the placing of plant protection products on the market and repealing Council Directives 79/117/EEC and 91/414/EEC

Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006

Regulation (EU) No 2016/183 of 11 February 2016 amending Implementing Regulation (EU) No 686/2012 allocating to Member States, for the purposes of the renewal procedure, the evaluation of the active substances whose approval expires by 31 December 2018 at the latest

Regulation (EC) No 2229/2004 of 3 December 2004 laying down further detailed rules for the implementation of the fourth stage of the programme of work referred to in Article 8(2) of Council Directive 91/414/EEC

Regulation (EC) No 1095/2007 of 20 September 2007 amending Regulation (EC) No 1490/2002 laying down further detailed rules for the implementation of the third stage of the programme of work referred to in Article 8(2) of Council Directive 91/414/EEC and Regulation (EC) No 2229/2004 laying down further detailed rules for the implementation of the fourth stage of the programme of work referred to in Article 8(2) of Council Directive 91/414/EEC

EFSA (European Food Safety Authority), 2008 ; Conclusion regarding the peer review of the pesticide risk assessment of the active substance sulphur. doi: 10.2903/j.efsa.2009.221r

Review report for the active substance sulphur Finalised in the Standing Committee on the Food Chain and Animal Health at its meeting on 13 March 2009 in view of the inclusion of sulphur in Annex I of Directive 91/414/EEC; Sulphur SANCO/2676/08 – final, dated 22 October 2009

Directive 91/414/EEC of 15 July 1991 concerning the placing of plant protection products on the market

Directive 2009/70/EC of 25 June 2009 amending Council Directive 91/414/EEC to include difenacoum, didecyldimethylammonium chloride and sulphur as active substances

Review report for the active substance sulphur Finalised in the Standing Committee on the Food Chain and Animal Health at its meeting on 13 March 2009 in view of the inclusion of sulphur in Annex I of Directive 91/414/EEC; Sulphur SANCO/2676/08 – final, dated 13 July 2012

Regulation (EU) 2017/555 of 24 March 2017 amending Implementing Regulation (EU) No 540/2011 as regards the extension of the approval periods of several active substances listed in Part B of the Annex to Implementing Regulation (EU) No 686/2012 (AIR IV renewal programme)

Regulation (EU) No 459/2010 of 27 May 2010 amending Annexes II, III and IV to Regulation (EC) No 396/2005 of the European Parliament and of the Council as regards maximum residue levels for certain pesticides in or on certain products

Regulation (EC) No 396/2005 of the European Parliament and of the Council of 23 February 2005 on maximum residue levels of pesticides in or on food and feed of plant and animal origin and amending Council Directive 91/414/EEC

Section identity, physical chemical and analytical methods

None

Section data on application and efficacy

None

Section toxicology

None

Section residue and consumer risk assessment

None

Section fate and behavior in environment

None

Section ecotoxicology

None

Additional references
Study report for Gene Mutation Assay in Chinese Hamster V79 Cells in vitro (V79/HPRT), Report/Study Number: 1992500, 2020